ABSTRACT

Sensitivity and Specificity of Malignant Melanoma, Squamous Cell Carcinoma, and Basal Cell Carcinoma in a General Dermatological Practice

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Introduction. Incidence of melanoma and non-melanoma skin cancer is increasing worldwide. Melanoma is the sixth most common cancer in the United States, making skin cancer a significant public health issue.

Background and goal. The goal of this study was to provide estimates for sensitivity (P(T+|D+)), specificity (P(T-|D-)), and likelihood ratios (P(T+|D+)/P(T+|D-)) for a positive test and (P(T-|D+)/P(T-|D-)) for negative test of clinical diagnosis compared with pathology reports for malignant melanoma (MM), squamous cell carcinoma (SCC) , basal cell carcinoma (BCC), and benign lesions. This retrospective cohort study collected data on 595 patients with 2,973 lesions in a Central Texas dermatology clinic, randomly selecting patients seen by the dermatology clinic between 1995 and 2011. The ascertation of disease was documented on the pathology report and served as the "gold standard."

Hypotheses. Major hypotheses were that the percentage of agreement beyond that expected by chance between the clinicians' diagnosis and the pathological gold

standard were 0.10, 0.10, 0.30, and 0.40 for MM, SCC, BCC and benign lesions respectively.

Results. For MM, the resulting estimates were: (a) 0.1739 (95% C.I. 0.0495, 0.3878), for sensitivity; (b) 0.9952 (95% C.I. 0.9920, 0.9974) for specificity; and (c) the likelihood ratios for a positive and negative test result were 36.23 and 0.83, respectively. For SCC, the resulting estimates were (a) 0.0833 (95% C.I. 0.0312, 0.1726) for sensitivity; (b) 0.9976 (95% C.I. 0.9950, 0.9990); and (c) the likelihood ratios for a positive and negative test result were 34.71 and 0.92, respectively. For BCC, the resulting estimates were: (a) 0.2178 (95% C.I. 0.1630, 0.2812) for sensitivity; (b) 0.9910 (95% C.I. 0.9867, 0.9941) for specificity; and (c) the likelihood ratios for a positive and negative test result were 24.20 and 0.79, respectively. For benign lesions, the resulting estimates were (a) 0.4942 (95% C.I. 0.4715, 0.5169) for sensitivity; (b) 0.9305 (95% C.I. 0.9135, 0.9450) for specificity; and (c) the likelihood ratios for a positive and negative test result were 7.11 and 0.54, respectively. Estimates for the kappa statistic (95% confidence intervals) were 0.1896 (0.0261, 0.3532), 0.1898 (0.0899, 0.2896), 0.3308 (0.2608, 0.3532), and 0.3585 (0.3319, 0.3850) for MM, SCC, BCC, and benign lesions, respectively.

Conclusions. Over-biopsying lesions and fear of missing malignancy have a significant impact on the sensitivity and specificity of clinical diagnosis, leading to lowered accuracy. These results challenge clinicians to continue to work toward improving their diagnostic skills concerning MM, SCC, BCC, and benign lesions.

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SENSITIVITY AND SPECIFICITY OF MALIGANANT MELANOMA, SQUAMOUS CELL CARCINOMA, AND BASAL CELL CARCINOMA IN A GENERAL DERMATOLOGICAL PRACTICE

A Thesis Submitted to the Faculty of

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CHAPTER ONE

Introduction

Types of Skin Cancer

There are three major types of skin cancer: basal cell carcinoma, squamous cell carcinoma and malignant melanoma[159,203]. Basal cell carcinoma and squamous cell carcinoma are considered non-melanoma skin cancers[58,159]. Both are more common than melanoma, easier to treat, and are associated with lower rates of mortality. Non-melanoma skin cancers are also known as keratinocytic skin cancer and arise from the keratinocytes in the epithelial strata of the skin. Melanoma is a rare form of skin cancer[203]. However, it is important to detect it early; early detection of melanoma is associated with higher rates of survival[25, 40, 77, 78, 93, 132, 193, 203]. (See glossary for definitions of terms.)

Early melanomas tend to be thinner. More progressed melanomas tend to be thicker; the thicker the tumor, the deeper into the skin it has penetrated, making it more likely to metastasize into the blood stream and lymphatic system[86]. Primary non-melanoma skin cancer puts a patient a risk for subsequent non-melanoma skin cancers and melanoma, making detection of non-melanoma skin cancer of great importance as well[175].

The three types of skin cancers can be classified as "in situ," meaning that the tumor has yet to metastasize or invade tissue beyond the original tumor location. The cancerous cells have remained in place, confined to the tumor itself. Invasive melanoma is a tumor that has invaded the skin underlying the tumor, exhibiting vertical growth.

Additionally, there are sub-types of non-melanoma and melanoma skin cancers. Superficial basal cell carcinoma usually presents itself as an atrophic, scaly lesion appearing mainly on the trunk[85,128]. Bowen's Disease is squamous cell carcinoma in situ[128]. Lentigo maligna melanoma is a specific type of melanoma that arises from lentigo maligna[258].

Epidemiology

Non-melanoma skin cancers are the most common of all human cancers and are the most common types of skin malignancy in populations of European ancestry[58,159]. Basal cell carcinoma is more common than squamous cell carcinoma[159]. The incidence of all three types of skin cancer, malignant melanoma, squamous cell carcinoma, and basal cell carcinoma, has risen worldwide in recent years[58]. The incidence of non-melanoma skin cancer has had an average annual increase between 3% and 8% in populations of European origin in Australia, Europe, and the United States[58]. Rogers et al. (2010) estimate an age-adjusted non-melanoma skin cancer rate increase of 109%, going from 71.8 per 100,000 persons in 1972 to 150.4 per 100,000 persons in 1999[208]. Between 1979 and 1993, there has been a 235% increase in females and a 350% increase in males for squamous cell carcinomas, with an 80% increase in basal cell carcinomas for both genders[208]. In the United States, incidence rates for melanoma have risen an average of 4.6% annually between 1975 and 1985 and 2.7% annually between 1986 and 2007[203]. According to Erdei et al. (2010), average annual increases of melanoma rates between 3% and 7% have been seen worldwide[86].

Melanoma is the sixth most common cancer in the United States, comprising 4% of all cancers. The cumulative lifetime risk of melanoma is 1 in 58[203]. An estimated

68,130 invasive melanomas were diagnosed in 2010, with an additional 46,770 melanomas in situ diagnosed in the same year[203]. Between 900,000 and 1,200,00 cases of non-melanoma skin cancer cases occur each year[208].

Precursors

Both non-melanoma and melanoma skin cancers have precursors. Precursors are pre-existing skin lesions from which a skin cancer arises. Squamous cell carcinomas often arise from actinic keratoses[159]. Actinic keratoses are dry, rough, scaly patches of skin that result from prolonged exposure to ultra violet radiation and are considered to be actinic damage. Lentigo maligna is a precursor to lentigo maligna melanoma, a subtype of melanoma that makes up approximately 10-40% of all melanoma cases[258]. Clinically atypical nevi, which often are later histopathologically confirmed dysplastic nevi, can be precursors for melanoma. Nevus is the medical term for benign skin tumors, or moles in layman's terms. Some researchers argue that melanomas are more likely to arise de novo, making atypical nevi irrelevant in terms of acting as a precursor. However, a history of atypical nevi is a strong predictor of melanoma, even if melanoma does not arise from pre-existing lesions[26,131,139,223,238].

Risk Factors

The strongest risk factor for non-melanoma skin cancer is ultra violet (UV) radiation exposure; UV radiation has a particularly strong correlation with the development of squamous cell carcinoma[159]. Consistent sun exposure caused by living in a sunny climate closer to the equator is more associated with squamous cell carcinoma, while intermittent sun exposure and childhood sun exposure is more associated with basal

cell carcinoma[159]. History of sun exposure and tanning bed use are both significant contributors to UV exposure.

Risk factors for malignant melanoma include history of sun burns, number of moles, number of atypical moles, male gender, older age, personal history of melanoma, family history of melanoma, personal history of non-melanoma skin cancer, fair skin color, light hair color, light eye color, and tendency to freckle[85,109,258].

Diagnosis and Grading

Diagnosis of a skin cancer usually begins with a clinician examining the lesion without any aids. A patient either presents the lesion as the chief complaint or the clinician finds the lesion during the physical exam. The clinician can then examine the lesion with the aid of magnifiers, dermoscopy, or a number of other technologies used in the diagnosis process[83,133,175,188,203,221,251,256]. If the lesion is suspect and the patient's history and physical exam are such that the clinician feels that the lesion may be malignant, the clinician gives a clinical diagnosis and biopsies the lesion. The standard of care is to send the biopsy to either a general histopathologist or specialized dermatopathologist to have the clinical diagnosis confirmed or revised. The pathological diagnosis is considered the gold standard, the ultimate determination of the presence or absence of the disease[78,92,203,263].

The pathologist will not only classify the lesion, but will also note the degree of dysplasia, grade the lesion, and record if any of the margins are positive for the tumor. Grading of dysplasia is very important in determining whether the lesion could turn into a malignant tumor and if the lesion needs to be excised. Mild dysplasia does not call for concern if the lesion is completely excised. If the lesion is graded as having moderate to

severe dysplasia, clinicians will often reexamine the patient's other suspect lesions. Additionally, if the lesion had not been completely excised the first time, the lesion will have to be re-excised using wider and/or deeper margins. Grading of dysplasia has been studied by pathologists, using inter-rater reliability and has been shown to not be very consistent overall, which is problematic for both the pathological community and the clinicians in their determination of the most appropriate treatment for their patients[92,223].

Staging of melanoma is a more precise system, with two different classification systems used to stage melanoma. Breslow thickness and Clark's level are both measurements of how far the tumor has penetrated the skin and are used in staging of melanoma[258]. Melanoma is graded as in situ (Stage 0), Stage 1, Stage 2, Stage 3, and Stage 4. The prognosis is very good if the melanoma is in situ, with a 98% five-year survival rate. However, if the patient has Stage 4 melanoma, the five-year survival rate is only 15%[10].

Treatment

Excision is the gold standard of treatment for all three types of skin cancer[194,221]. Excision is also referred to as a biopsy. Biopsying methods include superficial shave biopsy, saucerization (deep shave biopsy or scoop shave biopsy), incisional biopsy (punch biopsy or scalpel biopsy), and excisional biopsy[241]. Superficial shave biopsy is the most commonly used, due to its quick execution, low cost, ease of care and low morbidity[241]. Biopsy itself has few risks, with scarring, bleeding and infection being the most common. Clinicians have expressed concern that incisional biopsy may lead to micrometastasis; however, the type of biopsy employed in treatment has not been shown

to have any significant impact on survival after stratifying across potential confounders[190,241].

For an excisional biopsy, it is recommended to allow 4 mm between the lesion and the edge of the excision, in order to completely excise the cancer[71]. Incomplete excision occurs when a clinician or surgeon does not completely excise the lesion, meaning that the lateral and/or the deep margins still contain cancer cells, which is determined by a histopathologist or dermatopathologist. The tumor is still present in situ and must be re-excised. Incomplete excision is measured using re-excision rates[241]. Re-excision rates for basal cell carcinoma have been measured at 1.54%[194] and 3.2%[221]. Squamous cell re-excision rates range from 3.9% to 15.9%[194]. Incomplete excision is not typically an issue for malignant melanoma, as wide margins are used; however, Bakhai et al. (2010) noted that inadequate margins during the first surgical procedure can be considered incomplete excision and calls for a re-excision with wider margins[20]. Incomplete excision is correlated with higher recurrence rates. Studies have reported recurrence rates of 25%, 38%, 39% and 41%[221] of basal cell carcinoma in incompletely excised lesions.

Other types of treatment for basal cell carcinoma and squamous cell carcinoma include cautery, carbon dioxide laser, Mohs' micrographic surgery, photodynamic therapy, radiotherapy, and topical chemotherapy[159,241]. Mohs' micrographic surgery is often employed to treat melanoma. Mohs' surgery is a type of surgery that allows the complete removal of the tumor while sparing the surrounding healthy tissue[128]. Actinic damage, especially actinic keratoses, is commonly treated with liquid nitrogen, tretinoins, and topical chemotherapy[159]. Primary, non-metastasized melanoma must be treated with surgical excision[203].

Morbidity Associated with Skin Biopsy

Biopsying lesions that appear to be clinically benign creates unnecessary morbidity[151]. It has been suggested that morbidity can be a deterrent to biopsying lesions[87]. However, the morbidity from skin biopsy is minor. Bleeding, bruising, scarring, infection, and allergic reaction to topical antibiotic are associated with skin biopsy[166]. Pain, local reaction to anesthetic, and healing issues related to keloiding and chronic medical conditions that affect the skin's ability to heal have been noted[209]. Biopsy holds few risks for the patient. As our study does not address surgical excision of pathohistologically confirmed skin cancers, the issue of metastases and micrometastases as a result of surgical excision of melanoma will not be addressed. Kim et al. (2010) notes in his study concerning terror management theory that skin biopsies "remind the patient of cancer," which may alter their behavior when considering the possibility of their own death[136]. Kim et al. (2010) did address psychological morbidity that may accompany skin biopsies, but its results focused on a greater compliance of patients that received skin biopsies, which may have some effect on future behavior and measures taken to prevent future skin cancers in patients who undergo a skin biopsy[136].

Thesis Research Purpose and Goals

The purpose of this thesis is to is to estimate the sensitivity (P(T+|D+)), specificity (P(T-|D-), and the likelihood ratios (LRs) of clinical diagnosis for three skin cancers – basal cell carcinoma, squamous cell carcinoma, and malignant melanoma – within a dermatological practice. The goal is to determine a clinician's ability to diagnose a disease. The clinical diagnosis is considered a medical test, and determining its accuracy is of great importance in the proper treatment of disease. In dermatology, the

gold standard by which the clinician's diagnosis is measured is the pathology report[78,92,203,260]. The scientific literature on which the goals and hypotheses are based focuses on the following issues: (1) accuracy in clinical diagnosis (sensitivity, specificity, likelihood ratios, clinical accuracy, and positive and negative predictive values); and (2) pathophysiology, epidemiology, and treatment of the three skin cancers. The thesis will address the gap in the literature concerning the lack of studies of clinical diagnostic accuracy in general dermatological practices in the United States with the aim of providing estimates generalizable to other similar populations.

CHAPTER TWO

Review of Literature

Importance of Clinical Diagnosis

Early diagnosis is of utmost importance in the management of skin cancer[40,93,193]. An early diagnosis will significantly improve the prognoses of both melanoma[25,132,203,241] and non-melanoma[77, 175] skin cancer patients. Recognition of malignant lesions is influenced by a clinician's training, experience, and skill[188,260]. Patient characteristics, such as gender, age, occupation, and family history of skin cancer, may have an influence on a clinician's diagnosis[41,64,101,135,168].

The increasing incidence of both melanoma and non-melanoma skin cancers worldwide make diagnostic clinical accuracy of rising importance[41, 81, 86, 119, 159, 161, 208, 231]. Melanoma's incidence is increasing faster than any other cancer in the United States, [86, 203] with the possible exception being non-melanoma skin cancer. However, it is difficult to estimate the incidence rate of non-melanoma skin cancer, due to it generally not being included in cancer registries[77]. The estimated incidence of new cases of melanoma is over 110,000 cases for 2010 in the United States[203]. The estimated incidence of new cases of non-melanoma skin cancer is 1,000,000 cases per year in the United Kingdom[159] and an estimated 99,000 to 1,200,000 new cases per year in the United States[203]. Basal cell carcinoma is the most common skin cancer comprising 75% of all skin cancers, followed by squamous cell carcinoma making up 20% and melanoma constituting only 5% of all skin cancers[159,182]. However, more than 75% of skin cancer deaths are due to melanoma, making it the most lethal skin cancer[11].

The gold standard for diagnosis of skin lesions is the pathological analysis[78,92,203,260]. The pathological analysis is not a perfect gold standard[92,202]; however, it is the final determination of whether a patient has skin cancer or not. The discrepancy of histological diagnostic criteria between different dermatopathologists illustrates this point, as well as the less than perfect inter-rater reliability between pathologists. One way to improve the accuracy of the pathological analysis is to send the skin biopsies to a dermatopathologist rather than a general pathologist[120].

Although there are many guidelines[203] and new technologies to aid in the diagnosis of a skin lesion[133,175,251,256], *the choice of which lesions to examine and biopsy is still a function of clinical decision making and clinical diagnosis*; the choice depends on the clinician's skill and experience for naked eye examination[83,188,203,241].

Measures of Accuracy for Clinical Diagnosis

Sensitivity, specificity, positive predictive value and negative predictive value are all measures of accuracy for clinical testing. Sensitivity (P(T+|D+)) is the proportion of those individuals who have the disease as is determined by the pathology report that were correctly given the clinical diagnosis of having the disease, i.e. that is, P (positive clinical diagnosis | positive pathological report)[105, 202, 265]. Specificity (P(T-|D-)) is the proportion of those patients who are pathologically ascertained to be disease-free and are correctly given the clinical diagnosis of being disease-free, i.e. that is, P (negative clinical diagnosis | negative pathological report)[105,202,265]. Positive predictive value is the proportion of pathology-report disease among those with a positive diagnosis – that is, P (positive pathology report | positive clinical diagnosis), or P (disease | positive clinical diagnosis)[105, 202, 265]. 1 –predictive value negative is also of concern for physicians and

patients alike – that is, P(disease | negative clinical diagnosis). Clinical accuracy is the proportion of correctly diagnosed cases. Using the table below, sensitivity = A/(A+C); specificity = D/(B+D); and positive predictive value = A/(A+B)[105,202,265].

1 –predictive value negative = C/(C+D). Clinical (diagnostic) accuracy = (A+D)/(A+B+C+D).

Table 1: Clinical Diagnosis versus Pathology Report

Clinical Diagnosis	Pathology Report Diseased	Pathology Report Non-diseased
Positive	A = Number of individuals diseased and positive	B = Number of individuals disease-free and positive
Negative	C = Number of individuals diseased and negative	D = Number of individuals disease-free and negative
Totals	A+C = Total number of diseased individuals	B+D = Total number of disease-free individuals

Adapted from *Studying a Study and Testing a Test*, Riegelman and Hirsch, 1989[202].

Sensitivity and specificity are measurements of accuracy of a test that are mathematically independent of the prevalence of disease[202]. Sensitivity and specificity are both functions of the clinician's observations, experience, and decision-making skills in regards to taking the history and in performing the physical exam on the patient. Prevalence is the pretest probability in clinical medicine, while P(disease | positive clinical diagnosis) and P(disease | negative clinical diagnosis) are the posttest probabilities[202].

Sensitivity and specificity are both conditional probabilities that estimate an association of the test with the presence or absence of disease. Previously determined sensitivities and specificities are used in the clinical diagnosis of the next patient. The P(D+|T+) and P(D+|T-) are conditional probabilities that are directly impacted by prevalence; it would be incorrect to use these measures from previous studies in the

diagnosis of individual patients outside of the study's population. P(D+|T+) and P(D+|T-) are not generalizable in such a manner. However, sensitivity, P(T+|D+) and specificity, P(T-|D-), are both mathematically prevalence-free measures of the ability of a test to correctly diagnose a patient.

Conditional probabilities, such as sensitivity, can be denoted in several ways, depending on the field. Clinical medicine tends to use the term sensitivity. The proportion of all individuals who have the disease (as ascertained by the pathological analysis) and were given, correctly, the clinical diagnosis of disease is another way of stating sensitivity. The following are other useful notations: P(T+|D+) – that is probability that the test is positive given that the disease is positive; P(data | hyp) – that is the probability of the data given the disease hypothesis; and, $P(y|\theta)$ – that is the probability of the data y given the hypothesis theta.

Measures of Agreement for Clinical Diagnosis

Inter-observer agreement and intra-observer agreement are a major concern in clinical diagnosis[202]. Many studies have been conducted that research the inter-observer agreement for both clinicians and dermatopathologists[27,212]. The findings support the idea that medical care will differ between physicians as medical knowledge, skill, and expertise varies. The *kappa* statistic is used to measure inter-observer agreement beyond what would happen solely due to chance[216]. The kappa statistic is not only used for inter-rater reliability. It can also be used as a measure of how good a clinician is at diagnosing lesions when comparing diagnosis with pathological analysis. Kappa compares the clinician's diagnoses with what might be expected from chance alone and calculates how

much of the disease they are picking up beyond chance. (See Methods Chapter for explanation of the kappa statistic.)

Clinical Diagnosis versus Histopathological Diagnosis

The clinical diagnosis is the diagnosis given by a clinician after taking the patient's history and performing a physical exam[216]. The clinical diagnosis is itself a type of test[202,216]. Many consider taking specimens and ordering imaging to be clinical tests; however, these are actually paraclinical tests. C*linical tests* are the clinical variables from the history and physical exam[202]. The standard by which the clinical test is compared is the pathology report[120,203]. In dermatology, the biopsy pathology report is the gold standard[81,92,120,203,260].

Studies have shown significant variability between dermatologists, both in diagnosis and grading of dysplasia; the *kappa* statistic has been estimated at 0.28 for such studies, showing low inter-rater reliability[237]. This means that there was only 28% agreement beyond the agreement that is expected by chance alone. Statisticians usually consider a *kappa* value of 0.21 to 0.40 to be fair agreement; 0.41 to 0.60 to be moderate agreement; 0.61 to 0.80 to be substantial agreement; and 0.81 to 1.0 to be excellent agreement[252]. The *kappa* statistic can range from being -1.0 to 1.0, with 0.0 being agreement due only to chance, 1.0 being perfect agreement, and negative values indicating agreement less than that due solely to chance[252].

The difference in ascertaining cancer between specialized dermatopathologists and general histopathologists is significant as well[120]. Positive predictive values were used as a means of comparing the general histopathologists to the specialized dermatopathologists, using the dermatopathologist's results as the gold standard. The

results showed a PPV of 92.8% for basal cell carcinoma, 72.6% for squamous cell carcinoma, 82.6% for actinic keratosis, 91.3% for malignant melanoma, and 93.3% for common nevi[120]. The most significant discrepancy was between actinic keratosis and squamous cell carcinoma, with dermatopathologists reclassifying 27.4% of squamous cell carcinomas as actinic keratoses and 10.9% of actinic keratoses as squamous cell carcinomas[120]. The results show that variability is found not only between clinicians, but also between histopathologists and dermatopathologists.

Total Skin Exam

Total Skin Exam (TSE) is a full body cutaneous exam performed by a clinician who is qualified to diagnose skin lesions[203]. Total skin exam is also known as Full-Body Skin Examination (FBSE). The total skin exam has a sensitivity of 93.3% and a specificity of 97.8% for melanoma when performed by dermatologists[203]. The total skin exam is an effective way to monitor those who are high risk for skin cancer. Dermatologist-initiated FBSE (i.e., not in response to a patient's complaint) finds more than half of melanomas (56.3%) in a general-practice dermatological clinic[132]. Full-Body Skin Exams performed by dermatologists have been shown to be significantly associated with finding early melanomas, which are thinner and easier to treat than those melanomas with higher Breslow thickness[78,97,104,132,203].

Breslow thickness is a tool of prognosis for melanoma; it is a measurement of how deeply the melanoma has penetrated the tissue. Breslow thickness is determined by excision of the lesion[258]. Alternatively, Clarke's Level may be used as another prognostic factor for melanoma. However, instead of being measured in millimeters like

Breslow thickness, Clarke's Level is determined in relation to other skin structures. Both prognostic tools are used in diagnostic staging of melanoma[162].

Initially, melanoma spreads superficially[203]. This is commonly known as melanoma in situ. When a melanoma starts to become thicker and penetrate the underlying layers of skin, dermatologists classify this as invasive melanoma or cutaneous melanoma. Patient-detected melanomas tend to be thicker than those first found by dermatologists[132]. Melanomas found by dermatologists have an average Breslow thickness of 0.33 mm, while those that were a part of the patient's chief complaint have an average thickness of 0.55 mm[132].

Sensitivities, Specificities and Positive Predictive Values for Diagnosis of Melanoma

Diagnosing melanoma is extremely important to dermatologists and general practitioners alike. Melanoma is the least common of skin cancers[130], composing only 1% of skin malignancies; however, it causes 60% of skin cancer deaths[233]. The table below lists the sensitivities, specificities, and positive predictive values for several studies that have been conducted to evaluate dermatologists' ability to correctly diagnose malignant melanoma (MM).

Table 2: Melanoma Sensitivity, Specificity, Prevalence, Positive Predictive Value and 1 – Negative Predictive Value

Author	Country	Year	Lesions	MM Sens	MM Spec	MM Prev	MM P(D+|T+)	MM P(D+|T-)
Heal[119]	Australia	2008	NS	0.381	NS	NS	0.388	NS
Osbourne[132]	United Kingdom	2003	NS	0.79	0.970	NS	0.59	0.012
Carli[46]	Italy	2004	97	0.867	0.954	NS	0.137	0.001
Green[104]	Australia	1998	100	0.790	0.96	NS	NS	NS
Morton[177]	United Kingdom	1998	1999	0.88	0.98	0.014	0.76	0.008
Ek[84]	Australia	2005	2582	0.478	0.128	0.009	0.306	0.005
Grin[105]	United States	1990	13878	0.808	0.992	0.015	0.730	0.005
Wolf[265]	Austria	1998	44258	0.701	0.994	0.012	0.607	0.006

MM Sens = malignant melanoma sensitivity; MM Spec = malignant melanoma specificity; MM Prev = malignant melanoma prevalence; MM P(D+|T+) = malignant melanoma positive predictive value; MM P(D+|T-) = 1 - predictive value negative for melanoma; NS = not specified

The median of these sensitivity estimates is 0.79, with all but two studies ranging between 0.701 and 0.88. The median for specificity is 0.97, with all of the study estimates of specificity at 0.95 or above. The positive predictive value varies greatly, of course, since predictive values are prevalence dependent.

Sensitivities, Specificities and Positive Predictive Values for Diagnosis of Squamous Cell Carcinoma

The clinical diagnosis of squamous cell carcinoma has one of the lowest sensitivities and specificities among both specialists and non-specialists. This is largely due to the controversy between pathologists in regards to what constitutes an early squamous cell carcinoma. This issue is discussed later as a contributing factor to the difficulty clinicians have in diagnosing a lesion. Few studies have been conducted determining dermatologists' sensitivity and specificity. Sensitivities reported for squamous cell carcinoma include 56.3%[84], 41.3%[119], and 70%[104]. The only specificity reported is 0.88 (Green et al. 1988)[104].

Table 3: Squamous Cell Carcinoma Sensitivity, Specificity, Positive Predictive Value and 1 – Negative Predictive Value

Author	Country	Year	Lesions	Patients	SCC Sens	SCC Spec	SCC P(D+|T+)	SCC P(D+|T-)
Heal[119]	Australia	2008	NS	8694	0.414	NS	0.494	NS
Green[104]	Australia	1998	100	2095	0.7	0.878	0.389	0.038
Ek[84]	Australia	2005	2582	1223	0.563	0.791	0.403	0.122

SCC Sens = squamous cell carcinoma sensitivity; SCC Spec = squamous cell carcinoma specificity; SCC P(D+|T+)= squamous cell carcinoma positive predictive value

Sensitivities, Specificities and Positive Predictive Values for Diagnosis of Basal Cell Carcinoma

Few studies have investigated the sensitivity and specificity of basal cell carcinoma diagnosis. This could be due to the fact that the malignancy is often treated without histological confirmation. However, one might make the conjecture that, due to its high incidence and ease of treatment, knowing the clinical diagnostic accuracy of basal cell carcinoma may not be the priority of researchers. Listed below are three Australian studies and their findings.

Table 4: Basal Cell Carcinoma Sensitivity, Specificity, Positive Predictive Value, and 1 – Negative Predictive Value

Author	Country	Year	Lesions	Patients	BCC Sens	BCC Spec	BCC P(D+|T+)	BCC P(D+|T-)
Heal[119]	Australia	2008	NS	8694	0.639	NS	0.727	NS
Green[104]	Australia	1998	100	2095	0.978	0.454	0.595	0.038
Ek[84]	Australia	2005	2582	1223	0.889	0.565	0.645	0.148

BCC Sens = basal cell carcinoma sensitivity; BCC Spec = basal cell carcinoma specificity; BCC P(D+|T+)= basal cell carcinoma positive predictive value

Existing Guidelines

There are three major existing guidelines for clinical diagnosis of melanoma. These are the ABCD criteria, the "ugly duckling sign," and Glasgow 7-Point Checklist[203].

The ABCD criteria were initially developed by the New York University School of Medicine Department of Dermatology to recognize early melanomas. The acronym ABCD stands for Asymmetry, Border irregularity, Color variegation, and Diameter greater than 6 mm. E was later added to the acronym and stands for Evolving. However, few melanomas are characterized by all five characteristics. There is even a subset of melanomas that fail to meet any of the criteria. Conversely, there are numerous non-melanoma skin cancers and benign lesions that meet the criteria, rendering the criteria insensitive and non-specific in a non-specialist's practice. The most notable downfall of the ABCD criteria is the diameter criterion. In 25% of newly diagnosed melanomas, the diameter is less than 6 mm. The sensitivity ranges from 57% to 90% for the ABCD criteria, while the specificity ranges from 59% to 90%[203].

The Glasgow 7-Point Checklist is a more specific form of the ABCD criteria. The three main points are change in size, shape and color. The four minor points are sensory change, diameter of 7 mm or greater, the presence of crusting, inflammation or bleeding. The more complex nature of the Glasgow Checklist makes it a less commonly used set of criteria for diagnosing melanoma[203].

The "ugly duckling sign" is a highly sensitive technique that compares a rather atypical nevus or lesion with the surrounding nevi. Rather than having a predetermined, specific set of criteria determining what is an atypical nevus, the clinician compares the

suspect lesion to the nevi surrounding it. If it "looks different from all its neighbors," it is a good candidate for melanoma[203].

The three sets of guidelines have been combined with algorithms for use with new technologies and are not solely used for Naked Eye Examination in Total Skin Examination. Dermoscopy is one of these new technologies. Dermoscopy is non-invasive technique that allows for greater magnification of the skin. By applying liquid between the dermatoscope and the skin and by the use of polarized light, the epidermis and superficial dermis become translucent, allowing for visualization of epidermal structures[203,241,251]. This can lead to higher sensitivity and specificity[237,251]. For example, dermoscopy can be combined with any of the following algorithms to improve sensitivity and specificity: pattern analysis, ABCD rule of dermoscopy; 7-point checklist, CASH (Color, Architecture, Symmetry and Homogeneity), Menzies method, and 3 point rule[203,251]. The 7-point checklist criteria are atypical pigment network, blue-whitish veil, atypical vascular pattern, irregular streaks, irregular pigmentation, irregular dots/globules, and regression structures[15,241]. The algorithm for the 7-point checklist is as follows:

1. Odds ratios are assigned to each of the 7 points on the checklist using multivariate analysis.
2. 7-point criteria given an odds ratio greater than 5 are assigned a score of 2 points. 7-point criteria given an odds ratio less than 5 are assigned a score of 1 point.
3. Any lesion having a score of 3 or greater should be diagnosed as melanoma and excised for further pathohistological evaluation. Any lesion having a score less than 3 can be considered a non-melanoma[15].

Risk Factors for Skin Cancer

There are an abundance of studies addressing possible risk factors for both melanoma and non-melanoma skin cancers. These include: gender, age, hair color, eye color, skin color (skin type), freckling, ability to tan, tendency to burn, number of severe (blistering) sunburns, time spent outdoors, sun protective behavior, tanning bed history, family history of skin cancer, personal history of non-melanoma and melanoma skin cancers, personal history of other cancers, immunosuppression, presence of atypical (dysplastic) nevi, number of common nevi, and anatomical location of suspect lesion[41,64,97,101,130,135,168,196,201,213]. The presence of one or more of these risk factors or the degree to which the individual is affected has the potential to influence the clinician's diagnosis and decision to biopsy a particular lesion. The only crude odds ratios that were significant in Kiiski et al. (2010) were age over 65, blonde or red hair color, and the tendency to sunburn, respectively 1.48 (1.21-1.80), 1.23 (1.00-1.52), 1.98 (1.31-3.01) and 1.65 (1.32-2.07) with 95% confidence intervals[135].

What Really is Influencing the Clinician's Diagnosis?

Gachon et al. (2005) undertook a study to determine if the aforementioned guidelines were at the forefront of the clinician's mind during the decision-making process[23,24]. Dermatologists have a much higher sensitivity than general practitioners and other specialties[93,97]. Therefore, to heighten the non-dermatologists' awareness of the dermatological decision-making process and to give insight to current dermatologists on how to hone their skills, the recognition process was thoroughly examined. Gachon et al. (2005) split the recognition process into three categories: overall pattern recognition (OPR), analytic criteria recognition (ACR), and differential recognition (DR)[93]. Overall

pattern recognition stems from the ability of an individual to recognize an object after developing her own recognition from past images. Analytic criteria recognition is based on using standardized criteria and definitions to recognize an object, while differential recognition is dependent on the ability to recognize when an object does not adhere to a general pattern. In the diagnosis of melanoma, OPR is born out of a clinician's experience and intuition from specialized training. ACR is equivalent to the use of the ABCD criteria. The "ugly duckling" sign exemplifies differential recognition[93].

The results from Gachon et al. (2005) showed that OPR was the strongest influence, with overall complexity and irregularity of the lesion being the most significant contributing factors to the diagnosis and the strongest predictors of a true positive. DR was the second most influential, with the "ugly duckling sign" in the clinical diagnosis being a strong predictor of melanoma[93]. This demonstrates that the dermatologist's clinical opinion of the lesion has a stronger influence on both the diagnosis and the accuracy than a list of criteria. This would logically lead to the conclusion that either the criteria were lacking or pattern recognition should be the focus in training. This undergirds the evidence for the need for specialists in the treatment of skin cancer and bolsters the argument that explicit comparisons of sensitivity and specificity should be the priority in assessing improvement. Even when considering implementing new technologies to aid in the diagnosis of melanoma, such criteria are still used. Hence, pattern recognition should be emphasized in the training, not solely the criteria. However, there are professionals in the field who believe that clinical accuracy is determined by not only clinical skills, but also largely by prevalence[104].

Some studies reveal that the physical examination plays a greater role in diagnosis than the patient history. The hypothesis is that the appearance of the lesion during the

physical examination is more important than the patient's history in determining whether or not the lesion is considered malignant and whether or not a biopsy is ordered. Hallock (Hallock 1996 and Hallock and Lutz 1998) is a strong proponent of this view[111,112]. However, a number of studies have shown that past skin malignancies are a good predictor for future skin malignancies; one-fifth of all skin malignancy will develop a new lesion within the following year[112]. Past melanoma and non-melanoma skin cancers are good predictors of melanoma[85,163,183]. Additionally, family history is a strong predictor for melanoma[64,85,183,219,262]. This would suggest that in order to practice the highest standard of medicine it is absolutely essential to see a suspicious lesion through the lens of the patient's personal and family history.

Disagreement among Dermatopathologists: Impossible Clinical Decisions

Two prominent disagreements have arisen in dermatopathology. The first concerns the issue of dysplastic nevi. There is much debate as to whether dysplastic nevi are benign melanocytic lesions, a risk factor for melanoma, or a precursor to melanoma[223]. Early melanoma and atypical melanocytic pigmented lesions are very difficult to distinguish – both clinically and histopathologically[26,27,131,139,215,238,242]. The debate among dermatopathologists and pathologists has not reached a conclusive decision. Thus, the clinical diagnosis may correspond to one dermatopatholist's diagnosis, while being completely different from another dermatopathologist's conclusion regarding the biopsy. This lends itself to lower clinical sensitivity and specificity. Furthermore, depending on the opinions of a particular pathologist, the recommended treatment may differ.

The second issue surrounds the issue of actinic (or solar) keratosis and its relationship to squamous cell carcinoma. Many believe that actinic keratoses are simply precursors to squamous cell carcinoma. Madan et al. (2010) notes that 1-10% of actinic keratoses will become squamous cell carcinomas over a 10-year period; however, the author considers that estimate to be quite low[159]. Some dermatopathologists put the pathologic diagnosis as actinic keratosis, but recommend treatment of the lesion as if it were an early squamous cell carcinoma. Others believe that not all actinic keratoses left in situ will become squamous cell carcinomas. However, due to squamous cell carcinomas being a faster growing and more metastatic cancer than basal cell carcinomas, it is important that a conclusion be reached on the best protocol for treatment when it comes to actinic keratoses and squamous cell carcinomas.

These issues are significant, as no concrete definitions have been assigned to pathologically describe the conditions. Therefore, no definite clinical definition or parameters can be assigned to a certain diagnosis. Lack of clarity is incredibly important when it comes to treatment. A dermatologist must decide whether to treat a pathological diagnosis of actinic keratosis as if it were an early squamous cell carcinoma and excise the lesion surgically if any residual portion of the lesion remains or to watch and wait while leaving the lesion in situ.

Conservative Measures: Biopsy All or Watch and Wait?

There is a general tendency in the dermatology field to biopsy or excise all moles that appear to look abnormal, "just in case" the lesion might turn out to be malignant[84]. This tendency to biopsy is a conservative measure on the physician's part. Many lesions that appear to be benign, such as a seborrheic keratosis, turn out to actually be

malignant[125,187]. However, this process of "over-biopsying" may be due to the fear of missing early melanomas and coming up against a malpractice case in court for failing to biopsy a malignant lesion. Physicians are especially careful to keep meticulous notes of all atypical nevi in patient records. However, the increasing incidence of both non-melanoma skin cancer and melanoma may encourage clinicians to perform more biopsies. Additionally, physicians perform biopsies for cosmetic and functional purposes or simply to reassure the patient[59]. This leads to a high number of skin biopsies being handled by dermatopathologists and pathologists alike. Investigators have researched whether it is necessary to have a pathologist screen every biopsy, especially with those that the clinician was firm in their diagnosis. Parslew and Rhodes (1997) showed that, while the majority of the lesions would not need a dermatopatholgist, the sensitivity and specificity were not perfect. The noted missed melanomas were the reason for continued pathology use[187]. The fear of false negatives will plague the dermatological community until clinicians greatly improve their clinical diagnostic skills, at the cost of a lower specificity.

Types of Studies

There are three main types of studies that have to do with the issue of clinical diagnosis. The first type is a prevalence study. The results determine what the prevalence of the disease is within a particular population. The sample size of this type of study must be very substantial in order to give a representative picture of the disease prevalence. The estimate of the prevalence can then be used as the prior probability for diagnosis of a patient. The second type is a diagnostic accuracy study. These are studies whose results center on sensitivity, specificity, and likelihood ratios. The sample size is

typically smaller than in prevalence studies. These statistics (sensitivity and specificity) can then be used in the diagnosis of the next patient. The third type of study – diagnosis – is a case study. The sample size of the study is only one – the patient (or lesion, in a dermatology case) of interest.

The Gap

The literature has several studies noting the clinical diagnostic accuracy for melanoma. However, the majority of the findings are not generalizable, as the parameters of the study are very specific or the health care settings are very different than those found in the United States. Furthermore, findings in homogenous populations of European countries or Australia and New Zealand concerning risks or prevalence are applied with less assurance to the very heterogeneous American population, even if the population is mainly of European descent. Latitude is a key component of prevalence as well.

Another recent trend in the literature is to compare the diagnostic ability of general practitioners with dermatologists, which has shed light on diagnostic sensitivity and specificity among dermatologists; the main purpose of such studies has been not to determine accuracy and precision of clinical diagnosis but rather to demonstrate the need for the skills of specialists[20,40,182,220]. Additionally, not many studies have been conducted that estimate the clinical accuracy of diagnosis of all three skin cancers and benign lesions.

Therefore, the purpose of this study is to perform a retrospective cohort study in a general dermatological practice to determine the sensitivities and specificities, the "likelihoods," for melanoma, squamous cell carcinoma, basal cell carcinoma, and benign

lesions. By examining all four types of lesions, a better estimate of clinical accuracy can be ascertained for the particular practice. Furthermore, the findings could be generalized to practices with common characteristics. By estimating the sensitivities, specificities, and likelihood ratios of each clinician, we can determine if the findings are clinically useful and if these clinical diagnoses can be used within the clinical setting to go forward with treatment prior to receiving the pathology report. In addition, sensitivities and specificities for basal cell carcinoma and squamous cell carcinoma would shed light on an otherwise little researched arena. Patient age, gender, ethnicity, lesion location, family history, personal history and sun exposure history will all be recorded in order to stratify across potential confounders and to identify modification and confounding.

CHAPTER THREE

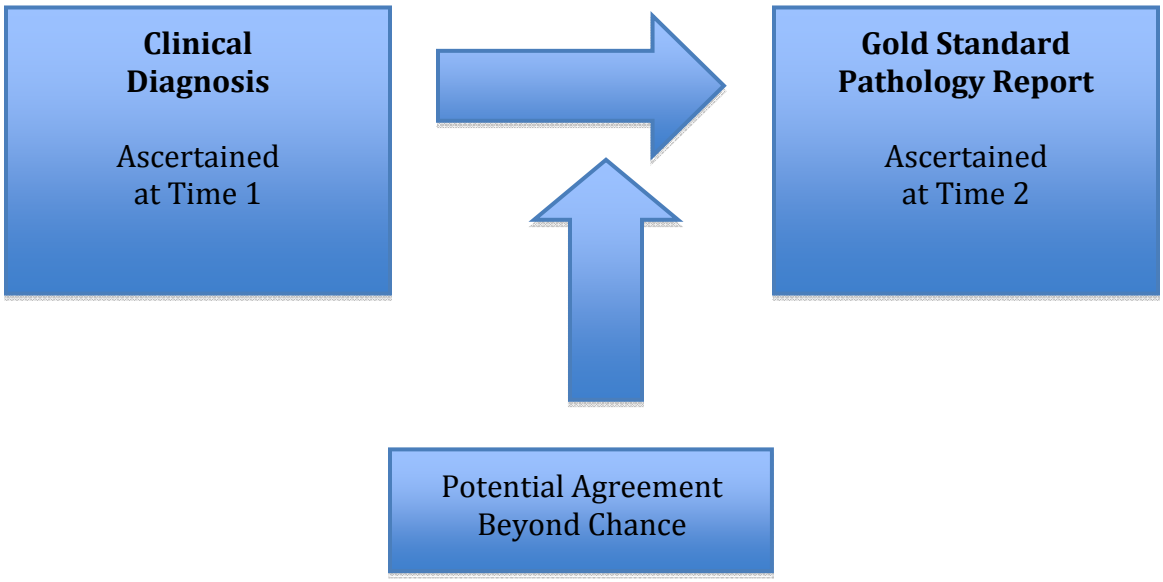
Hypothesis

Research Question

"What are the sensitivity, specificity, and likelihood ratios of a clinical diagnoses of malignant melanoma, squamous cell carcinoma, basal cell carcinoma, and benign lesions in a dermatological practice?"

Study Design:

Retrospective Cohort Study Design



Estimation Goal

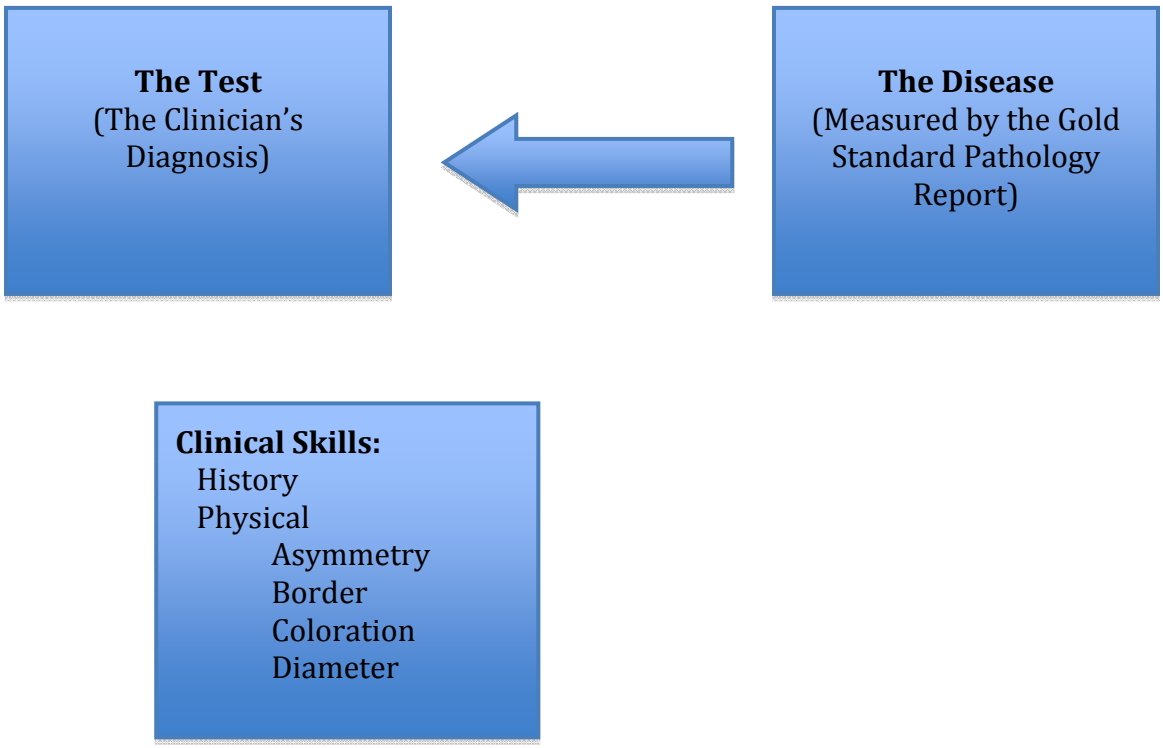
The primary goal of this research is to estimate the sensitivity, specificity, and likelihood ratios of malignant melanoma, squamous cell carcinoma, basal cell carcinoma, and benign lesions – both point and interval estimates – by comparing the clinical

diagnoses to the gold standard of the pathological report from the clinical data in the medical records of a community-based general dermatology practice.

A secondary goal is to test the scientific hypothesis that the agreement between clinical diagnosis and the gold standard of the pathology report will be at least 10%, 10%, 30%, and 40% beyond what would be expected by chance as estimated by the Kappa statistic for malignant melanoma, squamous cell carcinoma, basal cell carcinoma, and benign lesions, respectively.

Assumed Causal Model:

Impact of the Disease Process on History and Physical



The causal model assumes that the disease (or disease process) impacts both the physical signs and the patient's history.

CHAPTER FOUR

Methods

Participants

The patients included in the study were patients seen at a private dermatological practice who had biopsies performed at any point during their treatment by the physicians in the practice. Patients of all ages were included in the study. Both genders were included in the study. Biopsies included both benign and malignant lesions, as determined by the pathological diagnosis. Biopsies performed between 1995 and 2011 were included.

The patients excluded from the study were those patients who did not have a biopsy performed. This was due to the fact that a clinical diagnosis cannot be appraised as true or false without a pathology report. Additional exclusion criteria were those patients who were not seen at the practice within the past three years, as these patients' files are stored off-site, and those patients who were not of European descent (also known as white). The exclusion of ethnicities other than persons of European-American descent was due to the extremely small number of such patients seen at the clinic. Additionally, lesions examined with the dermatoscope were excluded from the study, as dermoscopy has been found to affect sensitivity and specificity in some studies[19,151,203]. Overall, 47.7% of the patients were excluded from the study.

Source of Data

The data was abstracted from patient records at a private dermatological practice in Central Texas. The practice consists of two clinicians, both of whom are board-certified by the American Board of Dermatology. Two dermatolopathology firms examined the biopsies: one based in Houston with four dermatopathologists and one based in Dallas with thirteen dermatopathologists. The dermatopathologists were not blinded to the clinical diagnosis given by the physician, the clinical description of the lesion, or the patient characteristics (age, gender, individual history of melanoma or non-melanoma skin cancer, family history of melanoma and non-melanoma skin cancer, and chronic exposures). The data to be abstracted were selected by taking a sample of the clinic's medial records using a table of random numbers to sample each section of patient files, which were ordered alphabetically by last name.

Time Frame for Data Collection

The data initially were collected at the appointment; this initial set of data consisted of the patient's history and physical exam, as well as the clinician's diagnosis for the biopsied lesions. The second set of data consisted of the pathological diagnosis made by a dermatopathologist; the pathological diagnosis was considered the "gold standard" by which the presence or absence of disease was determined. The pathology reports were received by the clinic within a week of the biopsy date. These biopsies took place between the years 1995 and 2011. These dates encompass the time period that the clinicians were in private practice and used the aforementioned dermatopathology firms, thus giving consistency to the data.

All the data was abstracted from the medical record between March 7 and August 1, 2011. Two undergraduate students abstracted all the data, under the direction of both physicians and an epidemiologist.

Experimental Design

This study is a retrospective cohort study, as the data was abstracted in 2011 after its initial clinical collection in 1995 to 2011. The study is considered a cohort study rather than a cross-sectional study due to the fact that the patients were seen by clinicians and clinical diagnoses were made before independent pathological assessments were made on the biopsies. If one is inclined to consider the study architecture as a cross-sectional study, it is pertinent to note that the clinician's diagnosis preceded any information from the pathology report and was, therefore, blinded.

Measurements

The measurements taken for each patient were abstracted from the patient's records. The patient's records included a history filled out by the patient at the beginning of her treatment, the clinician's notes from each appointment, and the pathology report for the patient's biopsies. The data abstractor gave an identification number to each biopsy. The last three digits denoted the biopsy in the order it appeared within the patient's file (the most recent biopsy being numbered one); the digits preceding the last three were a patient identification number assigned by the data abstractor. This identification number did not pertain to the clinic patient identification number in any way. Thus, no identifying patient characteristics were abstracted. The study was approved by the Baylor University Institutional Review Board (IRB).

The data abstractor then recorded the gender of the patient, the ethnicity of the patient, tanning bed history, family history of skin cancer and personal history of skin cancer. The entirety of this information was found within the clinician's notes and patient file. Additionally, the data abstractor recorded whether or not the patient had atypical nevi. This was found both in the SOAP notes and on the pathology report as the clinician's diagnosis for the biopsy.

The data abstractor then started with the most recent pathology report. The biopsy date was recorded as month, day, and year. The biopsy (slice) identifier was recorded; this was the letter found in front of the biopsy on pathology reports having more than one biopsy. The clinical diagnosis and pathological diagnosis were recorded, which were both found on the pathology report. The clinical diagnosis was listed under clinical information, and the pathological diagnosis was listed under diagnosis on the pathology report and was considered the "gold standard." The location of each lesion was recorded. The age of the patient at the time of the biopsy was calculated. A code for the clinician who gave the clinical diagnosis and performed the biopsy was entered. The dermatopathology firm and dermatopathologist who read the biopsy and gave the pathological diagnosis were given codes and documented.

All of the following information was recorded on a data form (see Appendix). The data was double entered into Excel spreadsheets. Data clean up was accomplished by importing the two sets of data into SAS and by comparing for discrepancies. Any differences found were corrected by referring back to the original data on the physical data sheets. The data was analyzed using SAS Software, Version 9.2 (SAS Institute, Carey, North Carolina).

Statistical Analysis: Univariate Analysis

The univariate analysis employed descriptive statistics to analyze each variable. Frequencies were used to describe categorical data. Mean, median and mode, along with the standard deviation and standard error, were used to describe continuous data. 95% confidence intervals were calculated.

Categorical variables included: clinical diagnosis, clinical diagnosis classification, pathological diagnosis, pathological diagnosis classification, location of the lesion, gender, clinician, dermatopathology lab, dermatopathologist, presence of atypical nevi, family history of skin cancer, and personal history of skin cancer, atypical nevi, and sun exposure. The sole continuous variable in this study was age.

Statistical Analysis: Bivariate Analysis

The bivariate analysis consisted of estimating: (1) the conditional probabilities of sensitivity and specificity; (2) the likelihood ratios (LRs) of positive and negative clinical diagnoses; and, (3) the kappa statistic. Sensitivity is P(T+|D+), the probability that the test is positive given that the disease is positive. Specificity is P(T-|D-), the probability that the test is negative given that the disease is negative. The test is the clinical diagnosis, while the disease is determined by the "gold standard" pathology report. Sensitivity P(T+|D+) and specificity P(T-|D-) are measures of a test's ability to predict the presence of disease. According to the table below, sensitivity was estimated as sensitivity = A/(A+C); specificity was estimated as specificity = D/(B+D).

Table 5: Clinical Diagnosis vs. Pathological Diagnosis

Clinical Diagnosis	Pathology Report Diseased	Pathology Report Non-diseased
Positive	A = Diseased lesions and positive test	B = Disease-free lesions and positive test
Negative	C = Diseased lesions and negative test	D = Disease-free lesions and negative test
Totals	A+C = Diseased lesions	B+D = Disease-free lesions

The likelihood ratios are the likelihood ratio positive (LR+), which equals P(T+|D+)/P(T+|D-) and the likelihood ratio negative (LR-), which equals P(T-|D+)/P(T-|D-). The purpose of the study is to develop mathematically prevalence-free estimates that will be used in future diagnosis, which is possible by estimating the sensitivity P(T+|D+), specificity P(T-|D-), and likelihood ratios.

Table 6: Table Illustrating Conditional Probabilities

	Disease Positive (D+)	Disease Negative (D-)
Test Positive (T+)	a) P(T+|D+)	b) P(T+|D-)
Test Negative (T-)	c) P(T-|D+)	d) P(T-|D-)

The diagnoses were grouped into basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma (MM), and benign lesions. The first analysis dealt only with those lesions that were considered to be classical lesions (i.e., were given the diagnosis of BCC, SCC, MM and benign). The second analysis dealt with both the classical lesions and the low-grade lesions. This included superficial basal cell carcinoma with the rest of the basal cell carcinomas and keratoacanthomas with the squamous cell carcinomas. (The differentiation between Bowen's Disease and SCC was not clear in the pathology reports and was, therefore, not differentiated in the data collection process.) The third analysis dealt with the precursors in addition to the

classical carcinomas and the low-grade carcinomas. Actinic keratoses were added to squamous cell carcinomas and keratoacanthomas. Atypical nevi were added to malignant melanoma. (It should be noted at this point that malignant melanoma has no true low-grade sub-type due to the high morbidity and mortality associated with the disease. The issues of lentigo maligna and lentigo maligna melanoma are discussed in the review of literature chapter. Furthermore, it should also be noted that there are no established basal cell carcinoma precursors, which have been found to arise de novo[159].) The fourth analysis combined BCC, SCC, and MM, as well as all their respective low-grade carcinomas and precursor lesions to form a general group encompassing all disease and dysplasia. The sensitivities, specificities and likelihood ratios for the non-melanoma skin cancers and melanoma were combined to find a general sensitivity P(T+|D+), specificity P(T-|D-), and likelihood ratios for each group in each analysis. SAS 9.2 (Carey, NC) was used for all analyses.

Table 7: Tiered Analyses

Analysis	Benign	BCC	SCC	MM
1. Only classical carcinomas	Benign lesions only	Basal cell carcinoma only	Squamous cell carcinoma only	Malignant melanoma only
2. Inclusion of low-grade carcinomas	Benign lesions only	Basal cell carcinoma and superficial basal cell carcinoma	Squamous cell carcinoma and keratoacanthoma	Malignant melanoma only
3. Inclusion of low-grade carcinomas and precursor lesions	Benign lesions only	Basal cell carcinoma and superficial basal cell carcinoma	Squamous cell carcinoma, keratoacanthoma, and actinic keratosis	Malignant melanoma and atypical nevi
4. Inclusion of all disease	Benign lesions only	Basal cell carcinoma, superficial basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, actinic keratosis, malignant melanoma, and atypical nevi		

These groupings were created in order to address the discrepancy found in the literature concerning what to consider as BCC, SCC, or MM. Thus, tiered analyses were performed in order to provide sensitivities, specificities and likelihood ratios using the most exclusive to the most inclusive criteria.

Statistical Analysis: Multivariate Analysis

The multivariate analyses focused on the relationship of disease (the pathology report) and the test (the clinician's diagnosis) while adjusting for different patient, clinician, and dermatopathologist variables. Sensitivity P(T+|D+), specificity P(T-|D-), and likelihood ratios were estimated while adjusting for various extraneous factors to identify any variables that were possible confounders or modifiers, with the goal of seeing if the clinicians were significantly more accurate at predicting disease in specific groups.

Kappa Statistic

The kappa statistic is a statistic that measures the amount of agreement between two clinicians or, as is the case for our study, the agreement between the clinician and the dermatopathologist (as is represented by the pathology report). Below is a contingency table with hypothetical data.

Malignant Melanoma Only

		Pathological Diagnosis +		-			
Clinical	+	20	A	10	B	30	0.30
Diagnosis	-	15	C	55	C	70	0.70
		35		65		100	
		0.35		0.65			

The observed agreement is equal to (A+D)/(A+B+C+D). Therefore, (20+55)/(100) = 0.75. However, the kappa statistic measures the agreement beyond chance. Chance is determined by the marginal probabilities. See the table below.

Malignant Melanoma Only

		Pathological Diagnosis +	-	
Clinical	+	0.35(30) = 10.5	0.65(30) = 19.5	30
Diagnosis	-	0.35(70) = 24.5	0.65(70) = 45.5	70
		35	65	100

The agreement solely due to chance is equal to (A+D)/(A+B+C+D), from the table above. Therefore, (10.5+45.5)/(100) = 0.56.

The difference between the observed agreement and the agreement solely due to chance is 0.19 (0.75 – 0.56 = 0.19) and is the actual agreement beyond chance. The

potential agreement beyond chance is equal to 1 – the agreement due to chance. Therefore the potential agreement equals 0.44 (1-0.56). The equation for kappa is: kappa = actual agreement beyond chance / potential agreement beyond chance. Kappa is calculated for the example above: kappa = 0.19/0.44 = 0.43. Thus, 43% of the potential agreement beyond chance was realized. Kappa was estimated in this study comparing the clinical diagnoses and pathology reports for the classical lesions and the benign lesions.

The Use of Sensitivity and Specificity versus Predictive Values

Predictive values are calculated PVP = (A/(A+B)) and PVN = (D/(C+D)), as mentioned above in the Review of Literature Chapter. Predictive values are not a prevalence-free statistical measure. Rather, predictive values change with prevalence[20]. Below are a series of tables that demonstrate this phenomenon. The sensitivity and the specificity remain set at 0.90 and 0.60, respectively.

Table 1 prev = 0.10

9	26	35	PVP =	0.26
1	54	55	PVN =	0.98
10	90	100		

Table 2 prev = 0.20

18	32	50	PVP =	0.36
2	48	50	PVN =	0.96
20	80	100		

Table 3 prev = 0.30

27	28	55	PVP =	0.49
3	42	45	PVN =	0.93
30	70	100		

Table 4 prev = 0.40

36	24	60	PVP =	0.60
4	36	40	PVN =	0.90
40	60	100		

Table 5 prev = 0.50

45	20	65	PVP =	0.69
5	30	35	PVN =	0.86
50	50	100		

Table 6 prev = 0.60

54	16	70	PVP =	0.77
6	24	30	PVN =	0.80
60	40	100		

Table 7 prev = 0.70

63	12	75	PVP =	0.84
7	18	25	PVN =	0.72
70	30	100		

Table 8 prev = 0.80

72	8	80	PVP =	0.90
8	12	20	PVN =	0.60
80	20	100		

Table 9 prev = 0.90

81	4	85	PVP =	0.95
9	6	15	PVN =	0.40
90	10	100		

In the table below, the effect of prevalence can be seen on predictive value positive and predictive value negative.

Table 8: Predictive Values Compared Against Sensitivity and Specificity

Prev	PVP	PVN	sens	spec
0.100	0.257	0.982	0.900	0.600
0.200	0.360	0.960	0.900	0.600
0.300	0.491	0.933	0.900	0.600
0.400	0.600	0.900	0.900	0.600
0.500	0.692	0.857	0.900	0.600
0.600	0.771	0.800	0.900	0.600
0.700	0.840	0.720	0.900	0.600
0.800	0.900	0.600	0.900	0.600
0.900	0.953	0.400	0.900	0.600

As prevalence changes, the predictive values change. Hence, estimates of predictive values from previous studies are not useful for a physician in diagnosing the next individual patient. The clinician needs an estimate of the probability of disease than is specific to the patient.

In summary, the conditional probability of predictive value (PVP or PVN) provides an estimate of the probability of disease, given a test result. This is exactly what a clinician needs as the final estimate of the probability of the disease in diagnosis. Please note that in a Bayesian approach to a diagnostic estimate, the clinician will use (a) an estimate of the prior probability of disease in the individual patient, (b) estimates of the probability of the test results in a diseased population – P(test | disease), and (c) an estimate of the probability of test results in a non-diseased population – P(test | non-disease) – to calculate an estimate of the probability of disease given the current patient's test result – P(disease | specific test result); this final estimate is often called the predictive value of a test, i.e. predictive value of a positive test (PVP) or predictive value of a negative test (PVN). When such estimates are presented in the literature, they estimate the ability of the diagnostic procedure for *that patient or population under study*.

The estimates of PVP and PVN would not be used in the estimation of disease in the next patient.

For diagnosis, as illustrated above, the estimates of PVP and PVN are influenced by prevalence, the proportion of the disease in the study. The clinician needs a mathematically prevalence-free estimate of the ability of the test to predict. The phrase "mathematically prevalence-free" is used to denote that the estimates of sensitivity and specificity may be impacted empirically by prevalence; that is, estimates of sensitivity and specificity may systematically differ using the same diagnostic test in populations of varying prevalence of disease. However, the conditional probabilities of sensitivity and specificity have "taken out" the impact of prevalence by focusing on two separate populations – those with disease and those without disease[1,66,150,181].

CHAPTER FIVE

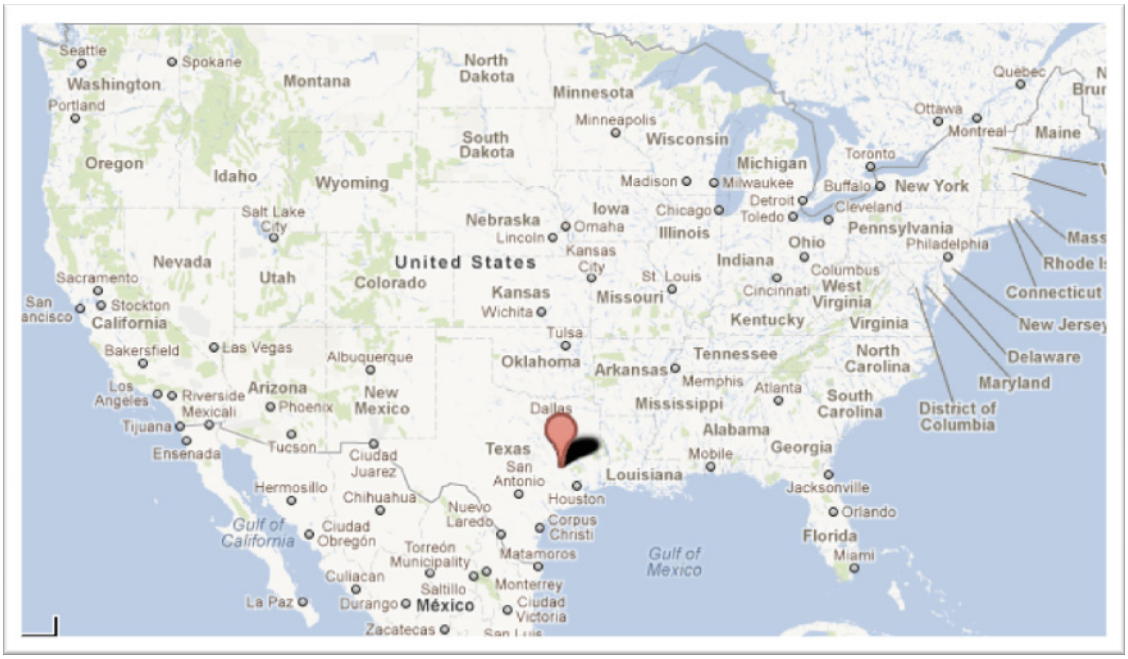
Results

The Clinic and the Participants

The geographical location of the area served by the clinic is approximately 30.6° latitude and -96.4° longitude (see map for general location). It is assumed that the majority of the patients live within 30 miles of the clinic.

The vast majority of patients seen at this clinic are of European ancestry ("white"). The few Hispanics, Asians and African-American patients were excluded from the study, making the sample entirely European-American.

The clinic does not accept Medicare or Medicaid patients. Thus all participants in the study were of a higher socioeconomic status than the general population. All participants had private insurance or were able to pay out-of-pocket for services.



Univariate Analysis

The study consisted of 595 patients with 2,973 lesions. The number of lesions biopsied from each patient ranged from 1 lesion to 150 lesions. The average number of lesions biopsied per patient was 5.

Table 9: Tumors removed per patient

Lesions per Patient	Number of Patients	Percent of patients
1	158	26.6
2	111	18.7
3	77	12.9
4	62	10.4
5	43	7.2
6-10	88	14.8
11-20	39	6.5
>20	17	2.9
Mean = 5	Total = 595	100.0

The patients' ages at the time of the biopsy ranged from 3.75 to 92.75 years old, with the average age at the time of skin biopsy being 48.52 years old.

Table 10: Age at Time of Biopsy

Age Range (years)	Number of Lesions	Percent of Lesions
0-14	43	1.4
15-29	419	14.1
30-39	308	10.4
40-64	1961	66.0
65 and older	242	8.1
Total	2973	100.0

56.58% of the excised lesions were from female patients while 43.42% of the excised lesions were from male patients. 33.5% of the lesions were excised from the head and neck, making it the most common biopsy site. The second most common biopsy site was the mid to lower back with 446 lesions, comprising 15.0% of the total lesions.

Table 11: Topographic Distribution of Skin Lesions

Location	Number of lesions	Percent	Number of benign	Number of premalignant	Number of malignant
Head, neck and scalp	996	33.5	631	171	193
Upper back and shoulders	379	12.7	229	108	42
Mid to lower back	446	15.0	270	160	16
Upper Chest	155	5.2	104	38	12
Mid to lower chest	94	3.2	70	18	6
Trunk, abdomen, and flank	183	6.2	111	65	7
Upper arm	146	4.9	99	33	14
Forearm and hand	150	5.0	93	37	20
Thigh and buttock	246	8.3	173	67	6
Calf, shin and foot	178	6.0	126	36	16
Total	2973	100.0	1906	733	332

Note: Two of the lesions were excluded due to their missing pathological diagnosis.

A more traditional approach to location grouping as is found in the literature (Ek, Hallock, Richmond-Sinclair, Shoaib) is used below to group lesions, using the categories head and neck, trunk, arm, and leg[84,112,201,222]. Our categories are maintained for specificity and comparison.

Table 12: Traditional Locations for Topographical Distribution of Skin Lesions

Location	Number of lesions	Percent of lesions	Traditional Locations	Number of lesions	Percent of lesions
Head, neck and scalp	996	33.5	Head and neck	996	33.5
Upper back and shoulders	379	12.7	Trunk	1257	42.3
Mid to lower back	446	15.0			
Upper Chest	155	5.2			
Mid to lower chest	94	3.2			
Trunk, abdomen, and flank	183	6.2			
Upper arm	146	4.9	Arm	296	9.9
Forearm and hand	150	5.0			
Thigh and buttock	246	8.3	Leg	424	14.3
Calf, shin and foot	178	6.0			
Total	2973	100.0	Total	2973	100.0

Bivariate Analysis

Calculations for the sensitivity, specificity and likelihood ratios are given below in Tables 13-15; the point estimates for sensitivity, 1 – sensitivity, specificity, and 1 – specificity, as well as their respective 95% confidence intervals, are presented.

Pathological Diagnosis

		+	-
Clinical Diagnosis	+	True Positive	False Positive
	-	False Negative	True Negative

Table 13: Sensitivity, Specificity, and Likelihood Ratios of Malignant Melanoma Only

		Pathological Diagnosis +	Pathological Diagnosis -	
Clinical Diagnosis	+	4	14	28
	-	19	2933	2952
		23	2947	2970

Sensitivity = 4/23 = 0.1739

Specificity = 2933/2947 = 0.9952

		Pathological Diagnosis +	Pathological Diagnosis -
Clinical Diagnosis	+	0.1739	0.0048
	-	0.8261	0.9952
		1.0000	1.0000

LR + = 0.1739/0.0048 = 36.23

LR - = 0.8261/0.9952 = 0.8301

Table 14: Sensitivity, Specificity, and Likelihood Ratios of Squamous Cell Carcinoma Only

		Pathological Diagnosis +	Pathological Diagnosis -	
Clinical Diagnosis	+	6	7	13
	-	66	2891	2957
		72	2898	2970

Sensitivity = 6/72 = 0.0833

Specificity = 2891/2898 = 0.9976

		Pathological Diagnosis +	Pathological Diagnosis -
Clinical Diagnosis	+	0.0833	0.0024
	-	0.9167	0.9976
		1.0000	1.0000

LR + = 0.0833/0.0024 = 34.71

LR - = 0.9167/0.9976 = 0.92

Table 15: Sensitivity, Specificity, and Likelihood Ratios of Basal Cell Carcinoma Only

		Pathological Diagnosis +	Pathological Diagnosis -	
Clinical Diagnosis	+	44	25	69
	-	158	2743	2901
		202	2768	2970

Sensitivity = 44/202 = 0.2178

Specificity = 2743/2768 = 0.9910

		Pathological Diagnosis +	Pathological Diagnosis -
Clinical Diagnosis	+	0.2178	0.0090
	-	0.7822	0.9910
		1.0000	1.0000

LR + = 0.2178/0.0090 = 24.20

LR - = 0.7822/0.9910 = 0.79

A Practical but Pivotal Diagnostic Issue

Given the unique context of dermatological medicine in the U.S. (see Discussion and Conclusions Chapter), it is prudent to point out that, for most dermatologists, the key issue is whether or not a lesion is sent off for pathological assessment. Thus, in the minds of many dermatologists, a diagnosis of "Non-Benign" has the practical ramification that the lesion will be thoroughly examined by a pathologist. Whether or not the dermatologist is precise in labeling the lesion may be a secondary issue in day-to-day clinical practice.

In Tables 16-18, the clinical diagnosis of "Non-Benign" is compared in relation to the pathology report for MM, SCC, and BCC. These point estimates for the sensitivity, P(T+|D+), of picking up MM, SCC, and BCC were 0.9130, 0.8488, and 0.9310, respectively. The point estimates for the specificity, P(T-|D-) of correctly labeling non-disease for MM, SCC, and BCC were 0.3441, 0.3478, and 0.3637, respectively.

Table 16: Sensitivity, Specificity, and Likelihood Ratios of Non-Benign Diagnoses Against Pathological Diagnosis of Malignant Melanoma

		Pathological Diagnosis Malignant Melanoma Only		
		+	-	
Clinical	+	21	1933	1954
Diagnosis	-	2	1014	1016
Non-Benign		23	2947	2970

Sensitivity = 21/23 = 0.9130

Specificity = 1014/1933 = 0.3441

		Pathological Diagnosis Malignant Melanoma Only	
		+	-
Clinical	+	0.9130	0.6559
Diagnosis	-	0.0870	0.3441
Non-Benign		1.0000	1.0000

LR + = 0.9130/0.6559 = 1.39

LR - = 0.0870/0.3441 = 0.25

Table 17: Sensitivity, Specificity, and Likelihood Ratios of Non-Benign Diagnoses Against Pathological Diagnosis of Squamous Cell Carcinoma

		Pathological Diagnosis Squamous Cell Carcinoma Only		
		+	-	
Clinical	+	73	1881	1954
Diagnosis	-	13	1003	1016
Non-Benign		86	2884	2970

Sensitivity = 73/86 = 0.8488

Specificity = 1003/2884 = 0.3478

		Pathological Diagnosis Squamous Cell Carcinoma Only	
		+	-
Clinical	+	0.8488	0.6522
Diagnosis	-	0.1512	0.3478
Non-Benign		1.0000	1.0000

LR + = 0.8488/0.6522 = 1.30

LR - = 0.1512/0.3478 = 0.43

Table 18: Sensitivity, Specificity, and Likelihood Ratios of Non-Benign Diagnoses Against Pathological Diagnosis of Basal Cell Carcinoma

		Pathological Diagnosis Basal Cell Carcinoma Only		
		+	-	
Clinical	+	203	1751	1954
Diagnosis	-	15	1001	1016
Non-Benign		218	2752	2970

Sensitivity = 203/218 = 0.9312

Specificity = 1001/2752 = 0.3637

		Pathological Diagnosis Basal Cell Carcinoma Only	
		+	-
Clinical	+	0.9312	0.6363
Diagnosis	-	0.0688	0.3637
Non-Benign		1.0000	1.0000

LR + = 0.9312/0.6363 = 1.46

LR - = 0.0688/0.3637 = 0.19

A summary of the sensitivities, specificities, confidence intervals, and likelihood ratios for all the analyses in this study are found in Tables 19 and 20 below.

Table 19: Sensitivities, Specificities, and Likelihood Ratios for All Levels of the Tiered Analysis

Diagnosis	Common Medical Name	Conditional Probability	Point Estimate	95% Confidence Intervals	Likelihood Ratios
MM	Sensitivity	P(T+|D+)	0.1739	(0.0495, 0.3878)	36.23
	1 - specificity	P(T+|D-)	0.0048	(0.0026, 0.0080)	
	1 – sensitivity	P(T-|D+)	0.8261	(0.6122, 0.9505)	0.83
	Specificity	P(T-|D-)	0.9952	(0.9920, 0.9974)	
MM + Precursors	Sensitivity	P(T+|D+)	0.9214	(0.8960, 0.9423)	3.50
	1 – specificity	P(T+|D-)	0.2631	(0.2456, 0.2811)	
	1 – sensitivity	P(T-|D+)	0.0786	(0.0577, 0.1040)	0.11
	Specificity	P(T-|D-)	0.7369	(0.7189, 0.7544)	
SCC	Sensitivity	P(T+|D+)	0.0833	(0.0312, 0.1726)	34.71
	1 – specificity	P(T+|D-)	0.0024	(0.0010, 0.0050)	
	1 – sensitivity	P(T-|D+)	0.9167	(0.8274, 0.9688)	0.92
	Specificity	P(T-|D-)	0.9976	(0.9950, 0.9990)	
SCC + low grades	Sensitivity	P(T+|D+)	0.1279	(0.0656, 0.2173)	28.42
	1 – specificity	P(T+|D-)	0.0045	(0.0024, 0.0077)	
	1 – sensitivity	P(T-|D+)	0.8721	(0.7827, 0.9344)	0.88
	Specificity	P(T-|D-)	0.9955	(0.9923, 0.9976)	
SCC + low grades + Precursors	Sensitivity	P(T+|D+)	0.0854	(0.0555, 0.1244)	25.88
	1 – specificity	P(T+|D-)	0.0033	(0.0015, 0.0063)	
	1 – sensitivity	P(T-|D+)	0.9146	(0.8756, 0.9445)	0.92
	Specificity	P(T-|D-)	0.9967	(0.9937, 0.9985)	
BCC	Sensitivity	P(T+|D+)	0.2178	(0.1630, 0.2812)	24.20
	1 – specificity	P(T+|D-)	0.0090	(0.0003, 0.0721)	
	1 – sensitivity	P(T-|D+)	0.7822	(0.7188, 0.8370)	0.79
	Specificity	P(T-|D-)	0.9910	(0.9867, 0.9941)	
BCC + low grades	Sensitivity	P(T+|D+)	0.2431	(0.1877, 0.3056)	25.86
	1 – specificity	P(T+|D-)	0.0094	(0.0062, 0.0138)	
	1 – sensitivity	P(T-|D+)	0.7569	(0.6944, 0.8123)	0.76
	Specificity	P(T-|D-)	0.9906	(0.9862, 0.9938)	
All disease	Sensitivity	P(T+|D+)	0.9305	(0.9135, 0.9450)	1.84
	1 – specificity	P(T+|D-)	0.5058	(0.4831, 0.5285)	
	1 – sensitivity	P(T-|D+)	0.0695	(0.0550, 0.0865)	0.14
	Specificity	P(T-|D-)	0.4942	(0.4715, 0.5169)	
Benign Lesions	Sensitivity	P(T+|D+)	0.4942	(0.4715, 0.5169)	7.11
	1 – specificity	P(T+|D-)	0.0695	(0.0550, 0.0865)	
	1 – sensitivity	P(T-|D+)	0.5058	(0.4831, 0.5285)	0.54
	Specificity	P(T-|D-)	0.9305	(0.9135, 0.9450)	

Table 20: Sensitivities, Specificities, and Likelihood Ratios for Non-Benign Diagnoses

Clinical Diagnosis	Pathological Diagnosis	Common Medical Name	Conditional Probability	Point Estimate	95% Confidence Intervals	Likelihood Ratios
Non-Benign	MM*	Sensitivity	P(T+|D+)	0.9130	(0.7196, 0.9893)	1.39
		1 - specificity	P(T+|D-)	0.6559	(0.6385, 0.6731)	
		1 – sensitivity	P(T-|D+)	0.0870	(0.0107, 0.2804)	0.25
		Specificity	P(T-|D-)	0.3441	(0.3269, 0.3615)	
Non-Benign	SCC*	Sensitivity	P(T+|D+)	0.8488	(0.7554, 0.9170)	1.39
		1 - specificity	P(T+|D-)	0.6522	(0.6345, 0.6696)	
		1 – sensitivity	P(T-|D+)	0.1512	(0.0830, 0.2446)	0.25
		Specificity	P(T-|D-)	0.3478	(0.3304, 0.3655)	
Non-Benign	BCC*	Sensitivity	P(T+|D+)	0.9312	(0.8891, 0.9610)	1.39
		1 - specificity	P(T+|D-)	0.6363	(0.6180, 0.6543)	
		1 – sensitivity	P(T-|D+)	0.0688	(0.0390, 0.1109)	0.25
		Specificity	P(T-|D-)	0.3637	(0.3457, 0.3820)	

*The focus of this table is upon the practical clinical issue of missed MM, SCC, and BCC when the clinician diagnoses "Non-Benign."

Multivariate Analysis

The results of the multivariate analysis did not indicate that any of the potential modifying variables tested (gender, family history of skin cancer, individual history of skin cancer, history of atypical nevi, tanning history, and location) had a marked impact of the sensitivity, specificity or likelihood ratios for any of analyses. The one exception was patient history; in general, the estimates for sensitivities were slightly lower among patients with prior individual skin cancer history than those patients without prior individual history. It is inferred that because the clinicians see the chart manifesting

patient history before they see the patient, they tend to send a larger proportion of these lesions for pathological diagnosis, thus slightly decreasing the sensitivity of the clinical diagnosis (data not shown). The differences were not statistically significant. Further studies with more lesions and more patients may reveal confounding or modifying factors in the diagnosis of patients.

Kappa Statistic

Comparing the (a) diagnoses of the clinician with the (b) "gold standard" conclusions of the pathologists for each lesion using the Kappa statistic resulted in the following estimates: the clinicians' ability to diagnose MM, SCC, BCC, and benign lesions was approximately 19%, 19%, 33%, and 36%, respectively, beyond what would be expected by chance. That is, of the potential agreement beyond chance that was available, the percentage of actual agreement between the clinicians' diagnoses and the pathology report is estimated by Kappa (see Table 21). 95% confidence intervals for the point estimates also are provided.

Table 21: Kappa Statistic Results and 95% Confidence Intervals

Analysis	Kappa	Lower Limit	Upper Limit
Clinical diagnosis of MM vs. pathological diagnosis of MM	0.1896	0.0261	0.3532
Clinical diagnosis of SCC vs. pathological diagnosis of SCC	0.1898	0.0899	0.2896
Clinical diagnosis of BCC vs. pathological diagnosis of BCC	0.3308	0.2608	0.3532
Clinical diagnosis of Benign lesion vs. pathological diagnosis of Benign lesion	0.3585	0.3319	0.3850
Clinical diagnosis of Non-Benign vs. pathological diagnosis of Non-Benign	0.3585	0.3319	0.3850

CHAPTER SIX

Discussion and Conclusions

I. *Limitations*

There are four potential threats to sound inference, two are internal to the sample and two are external to the sample. The two internal threats are systematic error and random error. The two external threats are generalization across persons, settings, and times, and construct validity.

A. *Systematic Error*

1. *Sampling Issues*

Sampling issues were explicitly addressed in the methods chapter. In order to minimize any impact of European ethnicity represented in the surnames, each section of patient files alphabetically ordered by last name was sampled using a table of random numbers. A patient file was selected if it met all the inclusion criteria and none of the exclusion criteria. Participants with surnames beginning with K, for example, were not overly sampled.

2. *Not all lesions were biopsied*

Unfortunately, not all of the lesions that were considered suspect were biopsied, especially those that were considered to be premalignant. Actinic keratoses, for instance, are often treated with liquid nitrogen or topical chemotherapeutic creams; these lesions are not included in the estimates of the clinicians' sensitivity and specificity. However,

this problem is inherent to every dermatological study unless a different protocol is put in place. It would not be considered good medical practice to cause more morbidity than necessary by biopsying a lesion that could be treated with less invasive measures.

3. *False Positives*

One significant limitation in our study concerns false negatives. Since a clinician has no reason to biopsy a lesion that (a) appears to be clinical benign, or (b) is not causing discomfort or pain to the patient, or (c) is not suspect due to family or patient history, then there is no way to know if the un-biopsied lesion is indeed benign. Hence, the findings from our study do not represent the true C cell in a contingency table as only biopsied lesions are considered in this study. This is true in the case of any area of medicine or genetics. It is considered wasteful and unnecessary to undergo testing for what appears to be clinically normal. Indeed, by undergoing unnecessary testing, disease is often "created" with false positives. Additionally, depending on the test, the patient could experience unnecessary morbidity.

4. *Not Just the First Lesion*

What could be construed as a major sampling error was that biopsies from all of a patient's visits were included in the study. The clinicians examined many of the patients multiple times. Hence, the physicians had clinical experience with the patient. The study was not designed in such a way that the gathered data only included biopsies taken from the first encounter between the physician and the patient. Rather, it included all biopsies from the patients. A potentially better measurement of the physicians' sensitivity and specificity would have been rendered had the study included only the lesions biopsied

during the patient's first appointment. Conversely, data were not gathered in our study following suspicious lesions over time. Our data are not longitudinal. Therefore, the issue of how a lesion may progress over time and how that affects (a) the clinician's decision to biopsy and (b) clinical diagnostic accuracy was not addressed.

5. *Misclassification*

The physician writes down the diagnosis recorded on the biopsy form sent off to pathology for a portion of the patient visits. For the other portion, the nurse who is assisting the clinician records the diagnosis on the biopsy form. Both physicians will allow the nurses to fill out the biopsy forms. There have been instances during which the nurse does not record the accurate diagnosis. Unless the clinician goes back to the patient file or biopsy report and changes the mistake, there is no way for the researcher to know if such a mistake has occurred. The technique employed to try and identify any incongruent points in the patients' records was the careful examination of the biopsy form against the physicians' notes. This type of error falls under systematic error, as a nurse assists the clinician consistently in filling out the biopsy form for pathology during the patient visit. These misclassification errors systematically lower the sensitivity and specificity.

6. *Pathologists Not Blinded*

One potential confounding factor that we could not address was that the dermatopathologists were not blinded to the clinicians' diagnosis in our study. Hence, it could be argued that the clinical diagnosis had some effect on the pathological diagnosis. Indeed, dermatopathologists often give a pathological diagnosis along with the caveat of

"treat according to clinical findings." We cannot rule out undue effect of the clinical diagnosis on the pathological diagnosis; however, we can make the assertion that because sensitivity and specificity were not perfect, dermatopathologists diagnosed according to pathological findings rather than being influenced by the clinical diagnosis.

7. *Pathology Disagreements*

Another potential confounding factor was that not all dermatopathologists agree on the classification of certain lesions. As not all lesions were assessed by the same dermatopathologist, this could have caused an imbalanced pathohistological account of the lesions due to differing schools of thought to which the dermatopathologists ascribed. The lesions were randomly divided and sent to the two dermatopathology firms. However, one dermatopathologist (Dermatopathologist 1) had a much greater number of pathology reports in our study, as is noted below in the table. This could have potentially influenced the sensitivity and specificity of the clinicians, either by them ascribing to a different school of thought and leading to a decreased sensitivity and specificity or by them conforming to the pattern set by the dermatopathologist and artificially increasing their sensitivity and specificity.

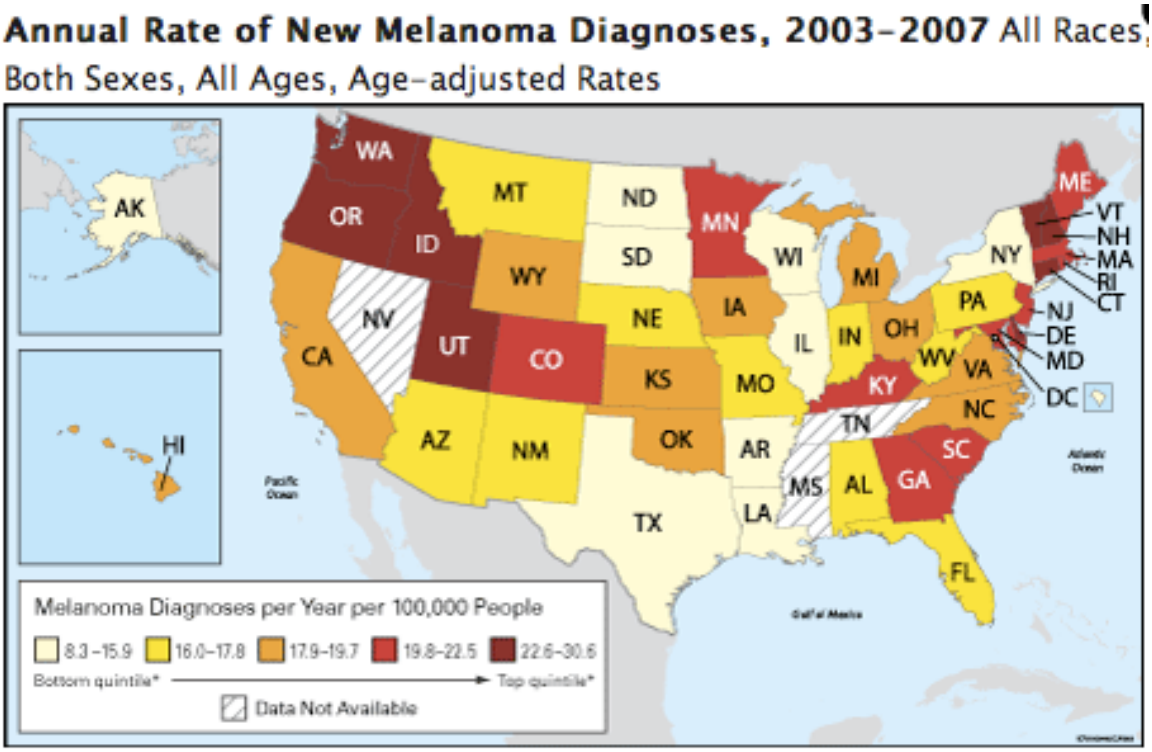
Table 22: Number of Lesions Examined by Each Dermatopathologist

Dermatopathologist	Number of Lesions	Percentage of Lesions
0	9	0.3
1	1660	55.8
2	260	8.7
3	109	3.7
4	20	0.7
5	1	0.0
6	38	1.3
7	193	6.5
8	12	0.4
9	16	0.5
10	106	3.6
11	87	2.9
12	12	0.4
13	67	2.3
14	36	1.2
15	238	8.0
16	58	2.0
17	12	0.4
18	1	0.0
Missing information	38	1.3

8. *Impact of prevalence*

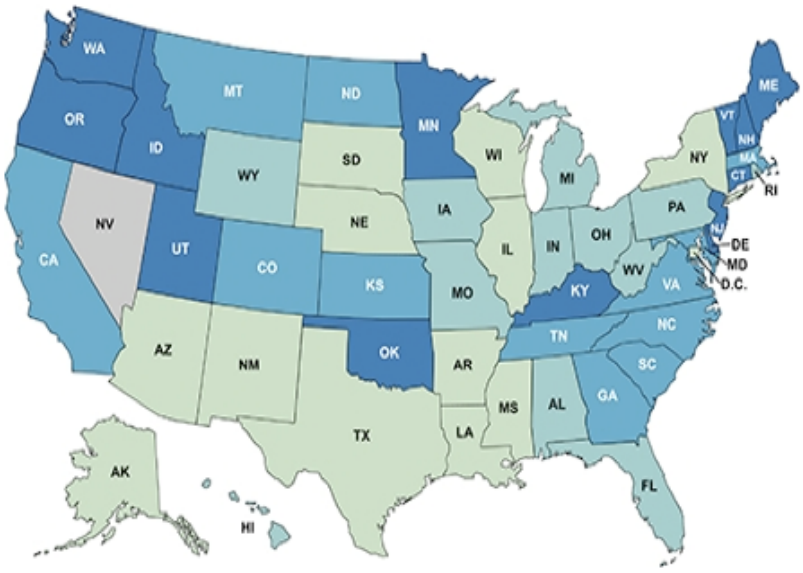
One potential confounder that may seem counter-intuitive to our argument below for the use of sensitivity and specificity as a measure for clinical diagnostic accuracy is that sensitivity and specificity has been shown to increase in areas where a certain disease has a higher prevalence. Therefore, prevalence of basal cell carcinoma, squamous cell carcinoma, and malignant melanoma may be affecting the clinicians' sensitivity and specificity. Indeed, this is a reasonable conjecture, as the more a clinician is exposed to a certain disease (or lesion, as is the case in dermatology), the better she should get at diagnosing that disease (or lesion). Therefore, clinicians in Australia and New Zealand should have higher sensitivities and specificities than those in the United States, as the prevalence of malignant melanoma is higher there. Notice also, that prevalence within

the United States varies from state to state. Below are two maps showing the incidence of malignant melanoma by state. (Note that prevalence is not equivalent to incidence. Rather, prevalence is the number of cases existing in the population, while incidence rate is the number of new cases per unit of person time. Therefore, even though prevalence is not equal to incidence, incidence is a good indicator of prevalence.) Notice that Texas is in the lowest range in both studies.



From the United States Environmental Protection Agency[248]

Melanoma of the Skin Incidence Rates* by State, 2007†



Color on Map	Interval	States
	8.6 to 16.7	Alaska, Arizona, Arkansas, District of Columbia, Illinois, Louisiana, Mississippi, Nebraska, New Mexico, New York, South Dakota, Texas, and Wisconsin
	16.8 to 19.2	Alabama, Florida, Hawaii, Indiana, Iowa, Michigan, Missouri, Ohio, Pennsylvania, Rhode Island, West Virginia, and Wyoming
	19.3 to 22.1	California, Colorado, Georgia, Kansas, Maryland, Massachusetts, Montana, North Carolina, North Dakota, South Carolina, Tennessee, and Virginia
	22.2 to 28.1	Connecticut, Delaware, Idaho, Kentucky, Maine, Minnesota, New Hampshire, New Jersey, Oklahoma, Oregon, Utah, Vermont, and Washington

From the Centers for Disease Control[74]

9. *Adjusting for Potential Confounders*

To address potential confounding and modification, estimates for sensitivity and specificity were adjusted for gender, age, family history, patient history, history of atypical nevi and anatomical location. None of the factors were found to be confounders or modifiers of the estimates, except for the minor impact of the patient's individual history. If a patient had a history of skin cancer, the clinician was slightly more prone to biopsy a lesion – resulting in a slightly lowered estimate of sensitivity.

10. *Immunosuppression*

This study did not gather data concerning immunosuppression, as there was no portion of the patient information sheet that addressed immunosuppression. Indeed, only one patient had immunosuppression noted in the clinical record. Immunosuppression is linked to higher rates of skin cancers, especially in patients with kidney transplants. As the patient files did not include these data, immunosuppression could not be studied. Therefore, this study cannot address any effect of immunosuppression in patients has on the physicians' decisions.

11. *Incomplete Excisions and Re-excision Rates*

This study did not address the issue of not fully excised lesions and re-excision rates, as this was not the focus of the study.

12. *Dermoscopy*

This study did not include any lesions examined by dermoscopy. Some studies have shown dermoscopy to have an impact on sensitivity and specificity[15,151,203,228,251], while others have noted no significant impact[19,45].

13. *Unknown Family or Personal History*

Another limitation in this study was that a number of lesions were associated with unknown family history (N = 1601) or unknown personal history (N = 60). Therefore, this does not present a complete picture of how important a role family history and personal history play in diagnosis of a lesion.

B. *Random Error*

The impacts of random error are addressed in this study explicitly by the calculation of 95% confidence intervals to accompany the point estimates of sensitivity and specificity. Given the design of the study and the sample size, the 95% confidence intervals refer to the fact that, if 100 repeated samples of the same size were taken of the clinic data, 95 of those samples would providence confidence intervals that enclose the true parameter.

Thus, the estimates provided in this study are the result of a sound method. The history of clinical science points to a method that results in plausible estimates. (Is it known that this study is one of the 95 samples that produce intervals that enclose the true parameter? No. That is not known.)

Though the number of lesions in our study was comparable to many studies in the literature, the study would have provided more precise estimates with a larger amount of data.

C. *Generalizability Across Persons, Settings and Times*

Our sample included all those patients seen in the general dermatological practice who had a biopsy between the years 1995 and 2011. Patients of all ages and both genders were included in the sample. Only patients of European descent were included in the study. The patient had to be seen within three years of the time of collection, as those patients who had not been seen within three years had their records stored off-site. As noted above, it is likely that the majority of our population is middle to upper class due to the clinicians not accepting Medicare or Medicaid as forms of payment and is a reflection of that subset of the general population. The approximate latitude and longitude of the

clinic area is listed above and can be used as a measure for environmental factors to which patients were exposed.

D. *Construct Validity*

1. *Categorization of Data*

Determining how to categorize the data was difficult as there are no established, discrete, agreed upon guidelines concerning the classification of particular lesions within the fields of dermatology and, especially, of dermatopathology. The ambiguity and dissonance in diagnosis categorization (i.e., what to consider malignant, what to consider a low-grade skin cancer, what to consider a precursor or premalignant lesion, and what to consider benign) led to several different groupings of lesions in order to satisfy differing schools of thought concerning diagnosis categorization. Thus, the data was analyzed in several ways.

2. *Double Diagnoses*

One of the limitations of our study was that many of the diagnoses were double or triple diagnoses or had the diagnosis of "Rule Out Skin Cancer." These were not exact diagnoses of "Basal Cell Carcinoma," "Squamous Cell Carcinoma," "Malignant Melanoma," etc. that other studies only included. Therefore, several analyses were performed, starting with only specific diagnoses. The multiple diagnoses were analyzing using the most serious diagnosis as the actual diagnosis.

II. *The Context of Diagnosis in Dermatology in the United States*

One of the most eye-opening results was the low sensitivities and specificities for the individual diagnoses. The clinicians were picking up almost all of the disease as a whole (sensitivity = 0.9305); however, they were having very low sensitivities and specificities for each of the three individual skin cancers. *The inference is that the clinicians were very good at detecting disease and dysplasia, but they were not necessarily calling the disease by its precise name.* This could be the case because of how insurance is currently structured regarding dermatology in the United States. Currently, insurance will pay for the biopsy of any lesions that is considered to be suspect and for the biopsy to be examined by a histopathologist or a dermatopathologist. This means that every lesion that a dermatologist biopsies will be sent to pathology, with a result being returned within a few business days.

The significance of this practice is that as long as a lesion is biopsied, a pathologist will examine it to determine if any pathology is present in the lesion. Given this context in dermatology, dermatologists do not need to be exact in their diagnosis. Although several studies have shown that dermatologists are consistently better than general practitioners at clinical diagnosis, these studies are not conducted with the view of how dermatologists can have the best clinical diagnosis possible. Rather, such studies are simply a comparison of dermatologists against other fields. It is reasonable to say that if a clinician is diagnosing skin lesions all day rather than a menagerie of other ailments, she will be better at diagnosing skin lesions. This assumption is bolstered by the fact that dermatologists do their three years of residency only in dermatology. Yet, the fact remains that there is significant room for improvement in the American system.

In Tables 16-18 and in Table 20, the approach taken was to compare the practical diagnosis of "Non-Benign" to the pathology report for MM, SCC, and BCC. These three estimates for sensitivity were relatively high (0.9130, 0.8488, and 0.9312) for MM, SCC, and BCC compared to the sensitivities of clinical diagnoses of MM, SCC, and BCC (0.1739, 0.0833, and 0.2178). In the everyday practice of clinical medicine, the clinical diagnosis of "Non-Benign" ensures that the lesion is sent off for careful pathologic examination. The pathology report will come back in only a few days; thus, this over-arching diagnosis of "Non-Benign" may be accomplishing exactly what the dermatologist was intending.

A comparison to Ek's study in Australia shows a great dissonance in the number of benign lesions biopsies and estimates of sensitivity and specificity. Ek's study had 2,582 lesions, 828 of which were found histopathologically to be benign (32% of the total sample). This study had 2,973 lesions, 1,906 of which were found histopathologically to be benign (64% of the total sample). This is two times as many benign lesions being biopsied as in the Australian study. Ek's study notes a sensitivity of 47.8% for malignant melanoma, while this study found a sensitivity of 17.4%. The ability to pick up malignancy (sensitivity = 0.9305) is comparable to Ek's estimate (sensitivity = 0.975); the particular diagnoses leave room for improvement[84].

The fear of missing melanomas and malpractice suits may fuel many of these unnecessary biopsies, especially considering that missed melanomas are the second most common cause for malpractice claims in the United States, only after misread breast biopsies[250]. However, studies has investigated the effectiveness of examining all lesions versus that of examining just those lesions clinically diagnosed as benign. It was

determined that it was a better practice to have every biopsied lesion examined by a pathologist rather than miss malignancy in a clinically designated benign lesion. This seems to be the general sentiment in the dermatological community[187,250].

Over-biopsying seems to be an undeniable problem[112]. However, researchers have examined whether or not the issue can be addressed by not sending every biopsy off to pathology. Though this would not decrease the morbidity the patient experienced from the biopsy, which is minimal (as is discussed above), it would address the burden that medical insurance currently bears with the great number of skin biopsies that must be processed. Van Dijk (2008) examined the possibility of only pathologically examining the lesions that were clinically diagnosed as malignant or premalignant lesions. The study found that over-diagnosis of nevi was found in 14% of the biopsied lesions (170/1217), and under-diagnosis of melanoma was found in 11% of the biopsied lesion (132/1217) in a study of melanocytic lesions[250]. Baade (2008) found that 53% of lesions diagnosed as "not at all likely to be malignant" composed 20% of the melanomas found in the study[18]. The possibility of missing a melanoma was considered to be too great a risk, and the researchers concluded that it was best to continue the practice of having every skin biopsy examined by a pathologist in order not to miss any malignancy. The problem of over-biopsying must be addressed at the source, not another step along in the process. Clinical diagnostic accuracy must improve in order to reduce the number of biopsies and not to miss any malignancy.

III. *Why Sensitivity and Specificity*

Throughout the dermatological literature, it has been argued that predictive values, especially predictive value positive, are the estimate on which to focus. The

argument of having an incomplete and unattainable C cell (false negatives) is used to support the argument. However, this is the case in every area of medicine. Unless every individual is tested, presenting with symptoms or not, the C cell will always be incomplete and unattainable. However, it is argued here that sensitivity and specificity serve as better measures of clinical accuracy.

Predictive values simply relate how good a clinician was in one study. This is a very good goal, but why does one want to know if she is accurate? So the physician can help future patients. Even though the C and D cells may be poor estimates, only the sensitivity and specificity can be used in diagnosing the next patient. Furthermore, as has been observed in many studies, if only sensitivity is reported and not specificity, then a complete picture of accuracy is unavailable. It is imperative for the clinician to know both their false negatives and false positives. If sensitivity and specificity both are not known, it is difficult for a clinician to have the confidence required to avoid over-biopsying. Some may counter with the idea that a patient will return for further treatment if the lesion worsens or changes. Or some clinicians may continue the practice of over-biopsying, with the mindset of "the word of the pathologist will be final." However, a clinician must use clinical diagnosis in order to decide which lesions to biopsy. Furthermore, if the clinician has low-income patients or uninsured patients, it is absolutely necessary to know her estimates of sensitivity and specificity because there is little money to pay for unnecessary biopsies.

IV. *Strengths*

A. *Sampling*

The sampling scheme for this study was created to avoid systematic error in alphabet-related European differences in ancestry. Thus, by using a random table of numbers, systematic error was prevented.

B. *Timing of Clinical and Pathological Diagnoses*

The study architecture was such that the clinical diagnosis was given prior to the lesion being sent off for pathology. Therefore, this prevented the clinician being influenced by the pathological analysis. Rather, the clinical diagnosis was recorded prior to receiving the pathology report, both in the clinical notes and on the biopsy form in the medical record.

C. *Sample Size*

The large number of lesions for which data were gathered in this study greatly enhanced the precision of the estimates, due to the larger number of lesions creating a higher level of precision.

D. *Categorization of Data*

The dermatological literature was thoroughly reviewed for different categorization of lesions to create four different tiers for analyzing our data. Certain patterns were seen in literature and were used to formulate the groupings discussed in the Methods Chapter and illustrated with Table 7. This allows the data gathered in this study

to be used by practitioners subscribing to different paradigms concerning skin malignancy.

E. *Estimates of Geographical Location*

By providing estimates of geographical location through the latitude and longitude noted above, clinicians may use the results from this study in their practice if the environmental effects are similar.

F. *Collection of variables*

The collection of data for patient, clinician, and dermatopathologist variables for each lesion allowed the ability to stratify across potential confounders and investigate if any of the variables were having an impact on clinical diagnosis or the Kappa statistic.

V. *Synthesis and Conclusion*

The estimates of sensitivity and specificity of malignant melanoma were 0.1739 (0.0495, 0.3878) and 0.9952 (0.9920, 0.9974) with a likelihood ratio positive (LR+) of 36.23 and a likelihood ratio negative (LR-) of 0.83. The estimates of sensitivity and specificity of squamous cell carcinoma were 0.0833 (0.0312, 0.1726) and 0.9976 (0.9950, 0.9990) with a likelihood ratio positive (LR+) of 34.71 and a likelihood ratio negative (LR-) of 0.11. The estimates of sensitivity and specificity of basal cell carcinoma were 0.2178 (0.1630, 0.3878) and 0.9910 (0.9867, 0.9938) with a likelihood ratio positive (LR+) of 24.20 and a likelihood ratio negative (LR-) of 0.79. The estimates of sensitivity and specificity of benign lesions were 0.4942 (0.4715, 0.5169) and 0.9305 (0.99135, 0.9450) with a likelihood ratio positive (LR+) of 7.11 and a likelihood ratio negative (LR-) of 0.54. The Kappa statistics for MM, SCC, BCC, and benign lesions were 0.1896

(0.0261, 0.3532), 0.1898 (0.0899, 0.2896), 0.3308 (0.2608, 0.3532), and 0.3585 (0.3319, 0.3850) respectively. The estimated Kappa statistics for MM, SCC, and BCC were higher than those expected (found in the secondary goal of the Hypothesis Chapter). These estimates were calculated from data gathered from a general dermatological practice at approximate latitude of 30.6° latitude and -96.4° longitude amongst 2, 973 biopsied lesions. None of the patient or clinician variables demonstrated a significant impact on the clinical diagnosis.

These results challenge clinicians to continue to work toward improving their clinical diagnostic skills concerning malignant melanoma, squamous cell carcinoma, and benign lesions; such improvements can increase both sensitivity and specificity. This enhancement of clinical diagnostic skills could lead to decreased morbidity, decreased healthcare costs, and the delivery of a higher standard of care.

APPENDICES

APPENDIX A

Patient Data:

Study ID: _____

Gender:	Male	Female	
Ethnicity:	Caucasian	Asian	Other
Tanning Bed History:	Yes	No	
Family History of Skin Cancer:	Yes – NMSC None	Yes – MM Not known	Yes – both NMSC & MM
Personal History of Skin Cancer:	Yes – NMSC None	Yes – MM Not known	Yes – both NMSC & MM
History or presence of Atypical nevi:	Yes	No	Unknown

Biopsy Data:

Biopsy Date	Letter	Clinical DX	Pathological DX	Location	Age	MD	Lab # and ID

APPENDIX B

Codebook

(A) Biopsy ID (BID):

Each biopsy will be assigned a number. The ones, tens, and hundreds place identifies the biopsy; the number preceding the last three identifies the patient.

(B) Patient ID (PID):

Each patient will be assigned a Study ID by the researcher.

(C) Biopsy Month (mon)

(D) Biopsy Day (day)

(E) Biopsy Year (year)

(F) Biopsy Report Identification (slice):

1 = A
2 = B
3 = C
4 = D
5 = E
6 = F
7 = G
8 = H
9 = I
10 = J

(G) Clinical Diagnosis (clinDX):

Diagnosis	**clinDX**	**clin4**
Acrochordon	acroDX	0
Angiofibroma	afDX	0
Actinic Keratosis	akDX	5
Angioma	angDX	0
Basal Cell Carcinoma	bccDX	1
Basal Cell Carcinoma vs. Benign Lichenoid Keratosis	bccVSblk	11
Basal Cell Carcinoma vs. Fibrous Papule	bccVSfp	11
Basal Cell Carcinoma vs. Lichen Simplex Chronicus	bccVSlsc	11

Basal Cell Carcinoma vs. Irritated Nevus	bccVSnevir	11
Basal Cell Carcinoma vs. Intradermal Nevus	bccVSnid	11
Basal Cell Carcinoma vs. Sebaceous Hyperplasia	bccVSsh	11
Benign Lichenoid Keratosis	blkDX	0
Cicatriz	cicDX	0
Comedone	cmdDX	0
Condyloma	condDX	0
Cutaneous Horn	cuhDX	0
Cyst	cystDX	0
Cyst vs. Cicatriz	cystVScic	9
Cyst vs. Keloid	cystVSkel	9
Dermatofibroma	dfDX	0
Dermatitis	dmDX	0
Dermatitis vs. Eczema	dmVSecz	9
Eczema	eczDX	0
E. multiforme.	emfDX	0
Fibrosis	fbrDX	0
Foreign Body	fbdDX	0
Fibrous Papule	fpDX	0
Granuloma Annulare	gaDX	0
Herpes	herpDX	0
Hidrocystoma	hidDX	0
Irritated Seborrheic Keratosis	iskDX	0
Keratoacanthoma	kerDX	8
Lentigo	lentDX	0
Lentigo vs. Lentigo Maligna	lentVSlm	13
Lentigo Maligna	lmDX	4
Lipoma vs. Soft Nodule	lipVSnod	9
Lichenoid Planus	lpDX	0
Lichen Simplex Chronicus vs. Psoriasis	lscVSpsor	9
Malignant Melanoma	mmDX	4
Malignant Melanoma vs. Superficial Basal Cell Carcinoma	mmVSbcc	15
Malignant Melanoma vs. Nevus	mmVSnev	13
Malignant Melanoma vs. Solar Lentigo	mmVSsl	13
Molluscum	molDX	0
Morphea	morphDX	0
Atypical Nevus	nevatypDX	6
Blue Nevus	nevbDX	0
Congenital Nevus	nevcDX	0
Halo Nevus	nevhDX	0
Nevus	nevDX	0
Dysplastic Nevus	nevdyspDX	7
Irritated Nevus	nevirDX	0
Spitz Nevus	nevsp	0
Nevus vs. Acrochordon	nevVSacro	9
Nevus vs. Lentigo	nevVSlent	9

Nevus vs. Seborrheic Keratosis	nevVSsk	9
Nevus vs. Verruca	nevVSverr	9
Neurofibroma	nfDX	0
Accessory Nipple	nipDX	0
Nodule	nodDX	0
Onychomycosis	onDX	0
Pemphigus Foliaceus vs. Scabies	pfVSscab	9
Pilomatricoma	pmtDX	0
Pyoderma Granulosum	pgDX	0
Prurigo	pnDX	0
Psoriasis	psorDX	0
Psoriasis vs. Eczema	psorVSecz	9
Rule Out Skin Cancer	roscDX	10
Red Patch	rpDX	0
Superficial Basal Cell Carcinoma	sbccDX	2
Squamous Cell Carcinoma	sccDX	3
Squamous Cell Carcinoma vs. Actinic Keratosis	sccVSak	14
Squamous Cell Carcinoma vs. Irritated Seborrheic Keratosis	sccVSisk	12
Shingles	shinDX	0
Seborrheic Keratosis	skDX	0
Seborrheic Keratosis vs. Condyloma	skVScond	9
Seborrheic Keratosis vs. Solar Lentigo	skVSsl	9
Tinea	tinDX	0
Tinea vs. Urticaria	tinVSurti	9
Verruca	verrDX	0
Verruca vs. Fibrous Papule	verrVSfp	9

(H) Clinical Diagnosis Classification (clin4):

0 = ben
1 = bcc
2 = sbcc
3 = scc
4 = mm
5 = ak
6 = atyp nev
7 = dysp nev
8 = ker
9 = benVSben
10 = r/o sc
11 = benVSbcc
12 = benVSscc
13 = benVSmm
14 = akVSscc
15 = mmVSbcc

16 = bccVSak
17 = akVSben
18 = kerVSben
19 = roscVSother
20 = nevatypVSben
21 = nevatypVSmalignant

(I) Pathological Diagnosis (path):

	path	**path4**
Acne Necrotica	acnec	0
Acrochordon	acro	0
Actinic Cheilitis	actch	0
Advanced Actinic Keratosis	advak	7
Angiofibroma	af	0
Actinic Keratosis	ak	6
Actinic Keratosis, consider Early Squamous Cell Carcinoma	akscc	8
Atypical Melanocytic Hyperplasia	amh	10
Angioma	ang	0
Basal Cell Carcinoma	bcc	1
Benign Lichenoid Keratosis	blk	0
Cicatriz	cic	0
Comedone	cmd	0
Chondrodermatitis Nodularis Helicis	cnh	0
Cutaneous Horn	cuh	0
Cyst	cyst	0
Contact Dermatitis	dermcon	0
Lichenoid Dermatitis	dermlch	0
Granuloma Dermatitis	dermg	0
Spongiatic Dermatitis	dermsp	0
Dermatofibroma	df	0
Dermatitis Herpetiformis	dh	0
Dyskeratoma	dysk	0
E. multiforme.	emf	0
Excoriation	excor	0
Fibroepithlioma	fbe	0
Foreign Body	fbd	0
Fibrosis	fbr	0
Atypical Fibroxanthoma	fbx	3
Follicular Hamartoma	fhr	0
Folliculitis	fol	0
Benign Focal Mucinosis	fm	0
Fibrous Papule	fp	0
Granuloma Annulare	ga	0
Granuloma Fasciitis	gf	0

Hematoma	hem	0
Hemangioma	hmg	0
Herpeatic Inflammation	herp	0
Hidrocystoma	hid	0
Inflammation	infm	0
Intertrigo	intg	0
Irritated Seborrheic Keratosis	isk	0
Jessner's Lymphocytic Infiltration	jli	0
Junctional Nevus	jxn	0
Junctional Nevus with Dysplasia	jxndysp	12
Keloid	kel	0
Keratoacanthoma	ker	9
Angiokeratocanthoma	kerang	9
Leiomyoma	lei	0
Lentigo	lent	0
Actinic Lentigo	lentact	11
Leukemia Cutis	leu	5
Lipoma	lip	0
Lentigo Maligna	lm	4
Lichen Planus	lp	0
Lichenoid Simplex Chronicus	lsc	0
Lupus	lup	0
Nevus – Mild Dysplasia	mild	12
Malignant Melanoma	mm	4
Nevus – Moderate to Severe Dysplasia	modsev	12
Molluscum	mol	0
Morphea	morph	0
Nevus	nev	0
Blue Nevus	nevb	0
Congenital Nevus	nevc	0
Dysplastic Melanocytic Nevus	nevdm	12
Dysplastic Nevus	nevdysp	12
Halo Nevus	nevh	0
Irritated Nevus	nevir	0
Nevus Lentigo	nevlent	0
Spitz Nevus	nevsp	0
Neurofibroma	nf	0
Intradermal Nevus	nid	0
Accessory Nipple	nip	0
No Tumor Seen	notum	0
Onychomycosis	on	0
Pap. Urticaria	purt	0
Porokeratosis of Mibelli	pkt	0
Polyp	polyp	0
Eccrine Poroma	prm	0
Prurigo Nodularis	pn	0

Psoriasis	psor	0
Rosacea	ros	0
Site Reaction	rxn	0
Superficial Basal Cell Carcinoma	sbcc	2
Squamous Cell Carcinoma	scc	3
Solar Elastosis	se	0
Syringoma	sgm	0
Sebaceous Hyperplasia	sh	0
Seborrheic Keratosis	sk	0
Seborrheic Keratosis with Actinic Keratosis	skak	6
Solar Lentigo	sl	0
Scleroderma Spectrum Disorder	ssd	0
Tinea	tin	0
Telangictasia	tlg	0
Trichilemmoma	trc	0
Urticaria	Urti	0
Verruca	verr	0
Venous Lake	vl	0
Juvenile Xanthogranuloma	xan	0

(J) Pathological Diagnosis Classification (path4):

0 = benign
1 = bcc
2 = sbcc
3 = scc
4 = mm
5 = leu
6 = ak
7 = advak
8 = akscc
9 = ker
10 = amh
11 = lentact
12 = nevus showing dysplastic features
13 = solar elastosis

(K) Location (loct)

1 = Head, neck, and scalp
2 = Upper back and shoulders
3 = Mid to lower back
4 = Upper chest
5 = Mid to lower chest
6 = Trunk, abdomen and flank

7 = Upper arm
8 = Forearm and hand
9 = Thigh and buttock
10 = Calf, shin, and foot

(L) Age of patient:

_____ age in years and months at time of biopsy

Number of Months	Decimal
1	0.08
2	0.17
3	0.25
4	0.33
5	0.42
6	0.50
7	0.58
8	0.67
9	0.75
10	0.83
11	0.92

(M) Medical Doctor Designation:

1 = Physician ID #1
0 = Physician ID #2

(N) Lab Number:

1= Pathology Lab #1
0 = Pathology Lab #2

(O) Lab ID:

0 = Pathology Lab #1 – Pathologist ID #0
1 = Pathology Lab #1 – Pathologist ID #1
2 = Pathology Lab #1 – Pathologist ID #2
3 = Pathology Lab #1 – Pathologist ID #3
4 = Pathology Lab #2 – Pathologist ID #4
5 = Pathology Lab #2 – Pathologist ID #5
6 = Pathology Lab #2 – Pathologist ID #6
7 = Pathology Lab #2 – Pathologist ID #7
8 = Pathology Lab #2 – Pathologist ID #8
9 = Pathology Lab #2 – Pathologist ID #9
10 = Pathology Lab #2 – Pathologist ID #10
11 = Pathology Lab #2 – Pathologist ID #11

12 = Pathology Lab #2 – Pathologist ID #12
13 = Pathology Lab #2 – Pathologist ID #13
14 = Pathology Lab #2 – Pathologist ID #14
15 = Pathology Lab #2 – Pathologist ID #15
16 = Pathology Lab #2 – Pathologist ID #16
17 = Pathology Lab #2 – Pathologist ID #17
18 = Pathology Lab #2 – Pathologist ID #18

(P) Gender of patient:

1 = Female
0 = Male

(Q) History of or presence of atypical nevi:

1 = Yes
0 = No

(R) Tanning Bed History:

1 = Yes
2 = History of sun exposure
0 = None

(S) Family History of Skin Cancer:

0 = No
1 = Yes, non-melanoma skin cancer
2 = Yes, melanoma skin cancer
3 = Yes, both non-melanoma and melanoma skin cancers
4 = Unknown

(T) Patient (Individual) Skin Cancer History

0 = No
1 = Yes, non-melanoma skin cancer
2 = Yes, melanoma skin cancer
3 = Yes, both non-melanoma and melanoma skin cancers
4 = Unknown

APPENDIX C

Glossary

ABCD(E) criteria: major clinical diagnostic criteria for melanoma outlined by the acronym ABCD; A stands for lesional asymmetry, border irregularity, color variegation and diameter greater than 6 mm; few melanomas meet all of these criteria; sometimes, melanomas meet none of these criteria; E is sometimes added to the acronym and stands for evolving to encompass the changing nature of a questionable lesion[85,109,258]

Actinic: used to describe damage to the skin by light, particularly UV light[128]; more specific than the term "solar," which refers to the sun as the cause, while actinic refers to a variety of rays[258]

Actinic keratosis: also known as solar keratosis; precancerous changes on the sun-exposed skin found in middle-aged and older patients who do not tan readily[24]; often found as multiple lesions[258]; between 8-20% of actinic keratoses change into squamous cell carcinomas[258]; up to 60% of squamous cell carcinoma develop from actinic keratoses; however, some clinicians consider actinic keratoses to be squamous cell carcinoma in situ[24,258]; Habif calls the actinic keratosis an intraepidermal squamous cell carcinoma in his text[109]; cumulative exposure to sunlight seems to be important, as does intermittent intense exposure to UV light in childhood[258;] actinic keratosis is considered an occupational and environmental disorder[258;] differential diagnosis often includes squamous cell carcinoma, superficial basal cell carcinoma, and spongiotic dermatoses;

patients with actinic keratoses need periodic evaluation and repeated treatment to prevent aggressive cancers from developing[109]

Analytic criteria recognition: recognition of a lesion using a standardized criteria and set of definitions; in dermatology, using the ABCD criteria is an example of analytic criteria recognition[93]

Atrophic: a lesion that has the defining characteristic of a decreased amount of tissue, manifesting itself in surface changes, loss of collagen, or loss of cutaneous fat[2]

Atypia: "the condition of nuclei that are large, hyperchromatic, variable in size and shape, and associated often with prominent nucleoli"[2,24]; is correlated with an elevated risk of developing malignant melanoma[85]

Atypical nevus: synonymous with dysplastic nevus, Clark's nevus, and nevus with architectural disorder[258] that are common at a 5% to 20% prevalence rate[128, 258]; atypical nevi have an increased risk of developing into melanoma[258] and are considered precursors for melanoma, as well as a "marker" for increased likelihood of developing melanoma de novo[109]; an atypical nevus appears differently than the common mole, has irregular borders and irregular color[109,128,186]; considered to be along the spectrum from common nevus to superficial spreading malignant melanoma; most commonly found on the trunk[128]

Basal cell carcinoma (BCC): most common cutaneous tumors, comprising 70% of all skin malignancies[258]; most common cancer in the United States[128]; typically 80% are found on the head and neck, while 15% are found on the shoulder's, chest, and back[258]; recurrence statistics vary from about 40% of patients who have had a BCC will have another within 10 years[85] to 44% of those with a BCC will develop another within 3

years[128]; light skin color with prolonged exposure to sunlight are seen as the main predisposing factors to developing BCC[85]; sunburns, radiation therapy, family history of BCC, immunosupression, fair complexion, and tendency to sunburn are all important risk factors for BCC; BCCs typically arise from follicular matrix cells[258]; differential diagnosis includes squamous cell carcinoma, trichoepithelioma[128], hidrodoma, Merkel cell carcinoma, actinic keratosis, and seborrheic keratosis[24]

Biopsy: removal of a small piece of tissue[186]; in our study a piece of skin tissue; depending on the lesion, different methods of biopsy are used[128]

Bivariate analysis: the analysis of two variables; in our study, the bivariate analysis of the clinical diagnosis and the pathological diagnosis produce sensitivity, specificity, and likelihood ratios

Bowen's disease: squamous cell carcinoma in situ that often appears on the sun-exposed parts of the body and can closely resemble psoriasis, eczema, actinic keratosis, superficial basal cell carcinoma, seborrheic keratosis and malignant melanoma[109]; risk factors include HPV infection and prolonged exposure to solar radiation; Bowen's is an important precursor to invasive squamous cell carcinoma[258]

Breslow thickness: the thickness of a melanoma tumor used in order to classify a melanoma; can be measured by biopsy or ultrasound; most important predictor used in melanoma prognosis[258]

Carbon dioxide laser: laser used in cryotherapeutic techniques[258]

CASH: algorithm used for dermoscopic diagnosis, which stands for color, architecture, symmetry, and homogeneity[203]

Categorical data: data that falls within discrete categories and has a finite and countable number of values; non-continuous data

Cautery: treatment of abnormal skin tissue by burning, searing, or destroying tissue

Clark's level: anatomical level to which a melanoma tumor has penetrated; measure used to classify melanomas; consists of five different levels (confined to the epidermis, invasion of the papillary dermis, invasion to the papillary/reticular dermal interface, invasion into the reticular dermis, invasion in to the subcutaneous fat)[258]

Clinical diagnosis: the diagnosis of a disease by the clinician after taking the patient history and performing the physical exam; considered to be a clinical test; in our study, is compared against the pathological diagnosis (as is specified by the pathology report) with bivariate analysis to find the sensitivity, specificity, and likelihood ratio[202]

Clinical accuracy: the measurement of diagnostic accuracy; the sum of diseased patients that are correctly diagnosed and the disease-free patients that are correctly diagnosed divided by the total number of patients; (A+D)/(A+B+C+D)[202]

Cohort study: a study that follows a cohort (a group of subjects) over time that measures specific characteristics at the beginning of the study and periodically takes measurements of these characteristics over time to determine the possible outcomes[124]

Confidence intervals: interval estimate for a point estimate that gives an upper and lower bound that potentially encloses the true estimate

Continuous data: data that have an infinite number of values; non-categorical data

Cross-sectional study: study in which the researcher takes all the measurements of the sample at one time[124]

Cryotherapy: therapy used to treat melanocytic tumors or precursor lesions that uses carbon dioxide or liquid nitrogen to destroy cells by ice crystals formed during rapid cooling[258]

Dermatopathologist: a pathologist (see definition below) who specializes in dermatologic diseases and disorders

Dermatopathology: pathology (see definition below) of the skin

Dermoscopy (dermatoscopy): a technique used to see lesional patterns and structures not visible to the naked eye using instruments such as a dermatoscope, a microscope ocular eyepiece or an ocular micrometer[109]

Differential diagnosis: determination of the disease that a patient is suffering from that is narrowed down from two or more diseases with similar symptoms to which the patient is presenting

Differential recognition: recognition characterized by the observation of an entity that is different from the general pattern; in dermatology, a nevus that does not belong to the general pattern of nevi on that particular patient; ugly duckling sign is an example of differential recognition use[93]

Dysplasia: abnormal anatomical structure due to abnormal growth or development[247]; cells that appear abnormal microscopically but are not yet considered to be cancer[186]

Dysplastic nevus: refer to definition of atypical nevus above

Epidemiology: "a branch of medical science that deals with the incidence, distribution, and control of disease in a population"[247]; study of the "frequency and pattern of disease and health-related events" that attempts to explain the contributing factors[169]

Excision: surgical removal or resection of a lesion[247]

Excisional biopsy: type of biopsy in which the entire tumor is removed for microscopic examination[128, 186]

Familial Atypical Multiple Mole/Malignant Melanoma Syndrome (Dysplastic Nevus Syndrome): syndrome that is characterized by many blood-related family members having multiple atypical (dysplastic) nevi and at least two members to display both multiple atypical moles and inherited malignant melanoma[128]

Fitzpatrick skin type: type of skin type classification system based on the amount of melanin in the skin; Type I is very fair white skin (with red or blonde hair, blue eyes, and freckles) that always burns and never tans; Type II is fair white skin (with red or blonde hair and blue, green or hazel eyes) that burns easily and tans poorly; Type III is darker white skin that tans after initial burn; Type IV is light brown skin that burns minimally and tans well (often associated with the Mediterranean skin type); Type V is brown skin that rarely burns and tans darkly easily (often associated with Middle Eastern skin type); Type VI is dark brown or black skin that never burns and always tans darkly[180]

Full-Body Skin Examination: a full body cutaneous exam performed by a clinician who is qualified to diagnose skin lesion; also known as a Total Skin Exam[203]

Glasgow 7-Point Checklist: "early melanoma diagnosis paradigm that examines change in size, shape, or color; sensory change; diameter of 7 mm or wider; presence of inflammation, crusting or bleeding"[203]

Gold standard: the gold standard in any field of medicine is the test considered to be the best estimate of the true state of disease in a patient; it is considered to be the best test available for the disease in determining the presence or absence of the disease[202]; in

dermatology, the pathology report is considered the gold standard in determining the presence or absence of a disease

Grading of dysplasia: system by which the dermatopathologist or histopathologist determines the level of dysplasia, which can be either mild, moderate or severe; the grading determines the further treatment of the particular lesion and may influence the future biopsying of other lesions suspected to be dysplastic

Histopathologist: physician who studies tissues to examine for evidence of disease

Histopathology: "a branch of pathology concerned with the tissue changes characteristic of disease;" "the tissue changes that affect a part or accompany a disease"[247]

History: "an account of the patient's individual and family background and the patient's past and present health"[247]

Incidence rate: the number of new cases per unit of person time; **cumulative incidence:** the proportion developing a disease within a specified amount of time[169]

Incisional biopsy: a type of biopsy formed on only a portion of the clinical lesion (rather than the whole lesion, as in excisional biopsy), which can be a necessary procedure if biopsying the entire lesion would not be cosmetically acceptable or feasible[128]

Incomplete excision: failure to remove the entire tumor during surgical excision; is either evident by biopsying the excised tumor and finding neoplasia or dysplasia that extends past the margins or by recurrence of the tumor in the same exact location

Inter-observer agreement: agreement between two observers in diagnosis

Intra-observer agreement: agreement between the same observers on different occasions concerning diagnosis

Invasive melanoma: melanoma that has penetrated epithelial layers below the original location of the tumor

In situ: tumor has yet to metastasize or invade tissue beyond the original tumor location

Kappa statistic: statistic used to measure inter-observer or intra-observer agreement beyond agreement due to chance; kappa = actual agreement beyond chance / potential agreement beyond chance

Keratinocytic skin cancer: see non-melanoma skin cancer

Lentigo maligna: considered to be malignant melanoma in situ by some, while others classify lentigo maligna as the precursor to lentigo maligna melanoma[152,258]

Lentigo maligna melanoma (LMM): subtype of malignant melanoma that comprises between 10-40% of the cases of MM[258]; lentigo maligna is considered to be its precursor lesion[258]; LMM is a macule that is characterized by irregular pigmentation[258]; LMM is primarily found in areas of actinic damage[109]

Lesion: an abnormality in the skin due to disease or injury; the primary lesion is the first lesion to appear in the disease; the lesion may take the form of a macule, papule, plaque, nodule, pustule, vesicle, bullae, wheal, scale, crust, erosion, ulcer, fissure, scar, or cyst[109]

Lifetime risk: the probability of developing or dying from a disease in one's lifetime

Likelihood ratios: expresses the odds of disease to non-disease in persons with a given level of a diagnostic test result[216]

Likelihood ratio negative: LR- = (1-sensitivity)/specificity or LR- = P(T-|D+)/P(T-|D-)

Likelihood ratio positive: LR+ = sensitivity/(1-specifcity) or LR+ = P(T+|D+)/P(T+|D-)

Malignant melanoma (MM): sixth most common cancer in the United States[203]; typically arise in the epidermis and can be tumorigenic (invasive), in situ, or non-

tumerogenic[85]; precursor lesions include atypical nevi, congenital nevi, and acquired melanocytic nevi[109]; prognosis is dependent on how early the patient presents the lesion to a clinician, as the thinner the lesion, the better the prognosis is[258]

Malignancy: refers to a neoplasm that has the potential to kill either by the effects of local tissue destruction or metastasis[2]

Margins: term can either apply to the edges of a biopsy (for example, a dermatopathologist may give a diagnosis of moderately dysplastic nevus, margins clear) or the space between the perimeter of the lesion and the excision during surgical removal[85,109]

Melanocytic lesion: lesion that is characterized by the presence of melanocytes, which are melanin producing cells[247]

Menzies method: dermoscopic diagnostic algorithm[203]

Metastasis: "the spread of cells, by blood vessels or lymph vessels (or across serosal surfaces), form a primary neoplasm to distant sites"[2]; the main site of metastases from malignant melanoma is the skin[128]; metastasis in melanoma typically occurs within five years of developing the primary lesion[85]; in about 4-10% of patients with metastatic melanoma present no primary tumor[85]; metastasis in melanoma is considered to be an indicator of a poor prognosis with a long-term survival rate of only 5%[258]; metastasis rate in SCC is very low, from 0.5% to 3%[85]; metastasis rate for basal cell carcinoma is extremely rare, occurring in about 0.0028%-0.55% of basal cell carcinomas[128]

Metastasize: the action of the spreading of malignant cells from the original neoplasm[2]

Mohs' micrographic surgery: a tissue-sparing surgical technique that employs horizontal frozen sections to control surgical margins; Mohs' micrographic surgery

allows for a high cure rates for both BCC and SCC; by observing each horizontal section under the microscope, margins are easily seen, allowing the surgeon to excise all of the tumor but spare surrounding normal tissue[128]

Morbidity: a disease state or symptom[247]; in our study refers to the damage or disease caused by or associated with a medical procedure

Multivariate analysis: analysis that examines more than two variables; in our study, it is the clinical test versus the pathology report while adjusting for different patient characteristics

Naked eye examination: examination of the skin without the use of any visual aid tools

Nevus: "benign proliferations of melanocytes; melanoma are their malignant counterparts"[128]; "tumor composed of melanocytic nevus cells" which can be benign or malignant and take on many different forms[85]; "it is generally accepted that all nevi be submitted for histological examination for medicolegal reasons; some 2.3% of clinically diagnosed benign nevi were microscopically (histopathologically) diagnosed as malignant tumors"[258]; a benign melanocytic nevus is often referred to as a common mole[128]; the number of nevi increases with the amount of sun exposure[128]; almost half of all melanomas develop from pre-existing nevi[128]

Non-melanoma skin cancer (NMSC): for the purposes of our study, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC); NMSC comprise 90% or more of all skin malignancies and creates a significant public health issue despite low mortality rate[258]; mortality rate is higher in squamous cell carcinoma than basal cell carcinoma and sharply increases with age[258]; lifetime risk of developing a skin cancer (both NMSC and MM) is 1 in 5[258]; it is difficult to estimate the actual prevalence of skin cancer, as it is not

in cancer registries in the United States[258]; ultraviolet light exposure is the major etiological factor[258]

Overall pattern recognition: recognition of an image by recalling a similar image that served as a model or pattern for a particular object, built on by prior experiences with different images[93]

Pathologist: "a doctor that identifies diseases by studying cells and tissues under a microscope"[186]

Pathology report: the report given by the pathologist that provides a pathological diagnosis for the biopsied lesion after histological examination of slices from the lesion

Pathology: "the study of the essential nature of diseases and especially of the structural and functional changes produced by them"[247]

Pathophysiology: the physiology of abnormal states, specifically the functional changes that accompany a particular syndrome or disease[247]

Photodynamic therapy: therapy used to treat particular cutaneous malignancies by applying photosensitizing agent to the lesion and allowing it to accumulate; following this step, a light source is applied, which releases toxic oxygen and destroys the targeted cells[258]

Physical exam: the process by which a physician examines the patient's body in order to find signs or evidence of disease

Posttest probabilities: also known as posterior probability; the probability that a patient will or will not have the disease after considering the pretest probability (prevalence) and the likelihood ratios (determined by sensitivity and specificity); the end product of Bayes' Theorem[1]

Precursor: in dermatology, a lesion that precedes the development of another, presumably malignant, lesion

Predictive value negative: the proportion of non-diseased patients among those with a negative diagnosis; P(D-|T-)

Predictive value positive: the proportion of diseased patients among those with a positive diagnosis; P(D+|T+)

Pretest probability: otherwise known as the prevalence in clinical medicine; P(D)

Prevalence: the proportion of cases of a disease existing in a population[169]; prevalence = number of cases/population

Radiotherapy: otherwise known as radiation therapy, which is the use of ionizing radiation to treat disease[247]

Risk factor: a factor that is associated with increased probability of a disease[169]

Saucerization: excavation of tissue in order to promote healing of a wound[247]

Sensitivity: among those individuals who have a disease (as ascertained by the pathology report) the proportion who were correctly given the clinical diagnosis of having the disease; P (positive clinical diagnosis | positive pathological report) or P(T+|D+)[202]

SOAP note: note composed by physician during the patient's visit; Subjective, Objective, Assessment, and Plan are the components of the SOAP note; the subjective section contains the patient's symptoms; the objective section contains the patient's signs; the assessment section includes differential diagnosis; and the plan section includes treatment and suggestions given to the patient[134]

Specificity: among those persons who are disease free the proportion of who are given the clinical diagnosis of being disease free. That is, P (negative clinical diagnosis | negative pathological report) or P(T-|D-)[202]

Squamous cell carcinoma (SCC): second most common form of skin cancer[258]; typically arises in sun-exposed areas of the skin; immunosuppression, genetic predisposition, prolonged exposure to UV-B rays, smoking, and HPV infection are all risk factors for SCC[258]; clinicians, pathologists and researchers disagree as to whether actinic keratoses, Bowen's Disease, keratoacanthoma, verrucous carcinoma, and trichilemmal cysts are considered to be squamous cell carcinomas, which blurs the line of what is a precursor lesion, what is a low-grade lesion, and what is a SCC[258]; squamous cell carcinomas arise from squamous epithelial cells[258]

Superficial basal cell carcinoma: a superficial form of basal cell carcinoma that exhibits very little tendency to invade or ulcerate[128]

Superficial shave biopsy: biopsy performed with a razor blade or scalpel that removes the lesion by a horizontal incision at the desired depth[128]

Total skin exam: examination of the skin by a qualified clinician

"Ugly duckling sign": a criterion used to diagnose malignant melanoma; essentially, the criterion focuses on lesions that appear or have changed so that they appear different from other nevi on the patient[85,128,258]

Ultra violet (UV) radiation: portion of the solar spectrum that is below 400 nm; the UV spectrum is divided into three bands: UVA (320-400 nm), UVB (280-320 nm), and UVC (200-280 nm); UVB rays are the most significant in sunburn and actinic damage[128] and are considered the most carcinogenic[258]

Univariate analysis: analysis of one variable at a time; the focus of descriptive statistics (usually mean, median, variance, standard deviation, skewness, and Kurtosis and confidence intervals associated with these point estimates)

3 point rule: dermoscopic diagnostic algorithm[251]

REFERENCES

1. Abell, TD. The probability, statistics, decision cube: Major types of problems faced in probability, statistics and decision making. 2008. Unpublished.

2. Ackerman AB, Ying G, Lazova R, Kadu S. Differential diagnosis in dermatopathology II. New York: Ardor Scribendi, Ltd.; 2001. 202 p.

3. Ackerman A. What nevus is dysplastic, a syndrome and the commonest precursor of malignant-melanoma - a riddle and an answer. Histopathology. 1988. SEP;13(3):241-56.

4. Ackerman A, Mones J. Solar (actinic) keratosis is squamous cell carcinoma. Br J Dermatol. 2006. JUL;155(1):9-22.

5. Ahmed I, Piepkorn M, Rabkin M, Meye L, Feldkamp M, Goldgar D, Skolnick M, Zone J. Histopathologic characteristics of dysplastic nevi - limited association of conventional histologic criteria with melanoma risk group. J Am Acad Dermatol. 1990. MAY;22(5):727-33.

6. Altman D, Bland J. Diagnostic tests 2: predictive values. 4. Br Med J. 1994. JUL 9;309(6947):102.

7. Altman D, Bland J. Statistics notes – diagnostic tests 1: sensitivity and specificity. 3. Br Med J. 1994. JUN 11;308(6943):1552.

8. Cancer Facts and Figures 2012 Atlanta: American Cancer Society; c2012. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf.

9. Cancer Facts and Figures 2011 Atlanta: American Cancer Society; c2011. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-029771.pdf.

10. Cancer Facts and Figures 2010 Atlanta: American Cancer Society; c2010. Available from: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-026238.pdf.

11. Amerio P, Manzoli L, Auriemma M, Carbone A, Proietto G, Angelucci D, Tulli A. Epidemiology and clinical and pathologic characteristics of cutaneous malignant melanoma in Abruzzo (Italy). Int J Dermatol. 2009. JUL;48(7):718-22.

12. Andrulonis R, Secrest AM, McGuire ST, Geskin LJ, Ferris LK. The influence of age and sex on reasons for seeking and expected benefits of skin cancer screening. Arch Dermatol. 2010. OCT;146(10):1097-102.

13. Annessi G, Cattaruzza M, Abeni D, Baliva G, Laurenza M, Macchini V, Melchi F, Ruatti P, Puddu P, Faraggiana T. Correlation between clinical atypia and histologic dysplasia in acquired melanocytic nevi. J Am Acad Dermatol. 2001. JUL;45(1):77-85.

14. Annessi G, Bono R, Sampogna F, Faraggiana T, Abeni D. Sensitivity, specificity, and diagnostic accuracy of three dermoscopic algorithmic methods in the diagnosis of doubtful melanocytic lesions. J Am Acad Dermatol. 2007. MAY;56(5):759-67.

15. Argenziano G, Puig S, Zalaudek I, Sera F, Corona R, Alsina M, Barbato F, Carrera C, Ferrara G, Guilabert A, et al. Dermoscopy improves accuracy of primary care physicians to triage lesions suggestive of skin cancer. J of Clin Oncol. 2006. APR 20;24(12):1877-82.

16. Arumi-Uria M, McNutt S, Finnerty B. Grading of atypia in nevi: Correlation with melanoma risk. Modern Pathol. 2003. AUG;16(8):764-71.

17. Baade PD, Youl PH, English DR, Elwood JM, Aitken JF. Clinical pathways to diagnose melanoma: A population-based study. Melanoma Res. 2007. AUG;17(4):243-9.

18. Baade PD, Youl PH, Janda M, Whiteman DC, Del Mar CB, Aitken JF. Factors associated with the number of lesions excised for each skin cancer A study of primary care physicians in Queensland, Australia. Arch Dermatol. 2008. NOV;144(11):1468-76.

19. Bafounta M, Beauchet A, Aegerter P, Saiag P. Is dermoscopy (epiluminescence microscopy) useful for the diagnosis of melanoma? Results of a meta-analysis using techniques adapted to the evaluation of diagnostic tests. Arch Dermatol. 2001. OCT;137(10):1343-50.

20. Bakhai M, Hopster D, Wakeel R. A retrospective study comparing the accuracy of prehistology diagnosis and surgical excision of malignant melanomas by general practitioners and hospital specialists. Clin Exp Dermatol. 2010. JAN;35(1):63-7.

21. Balch C, Buzaid A, Soong S, Atkins M, Cascinelli N, Coit D, Fleming I, Gershenwald J, Houghton A, Kirkwood J, et al. Final version of the American joint committee on cancer staging system for cutaneous melanoma. J of Clin Oncol. 2001. AUG 15;19(16):3635-48.

22. Balch C, Soong S, Gershenwald J, Thompson J, Reintgen D, Cascinelli N, Urist M, McMasters K, Ross M, Kirkwood J, et al. Prognostic factors analysis of 17,600

melanoma patients: Validation of the American joint committee on cancer melanoma staging system. J of Clin Oncol. 2001. AUG 15;19(16):3622-34.

23. Barksdale S, Oberlender S, Barnhill R. "Rush" skin biopsy specimens in a tertiary medical center: Diagnostic yield and clinical utility. J Am Acad Dermatol. 1998. APR;38(4):548-54.

24. Barnhill RL, Crowson AN, Magro CM, Piepkorn MW. Dermatopathology. McGraw-Hill Medical; 2010. 1104 p.

25. Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. Cancer. 1996. AUG 1;78(3):427-32.

26. Barnhill RL, Hurwitz S, Duray PH, Arons MS. The dysplastic nevus - recognition and management. Plast Reconstr Surg. 1988. FEB;81(2):280-9.

27. Barnhill RL, Roush GC. Correlation of clinical and histopathologic features in clinically atypical melanocytic nevi. Cancer. 1991. JUN 15;67(12):3157-64.

28. Barnhill RL, Roush GC, Ernstoff MS, Kirkwood JM. Interclinician agreement on the recognition of selected gross morphological features of pigmented lesions - studies of melanocytic nevi. J Am Acad Dermatol. 1992. FEB;26(2):185-90.

29. Barnhill R. Malignant melanoma, dysplastic melanocytic nevi, and spitz tumors - histologic classification and characteristics. Clin Plast Surg. 2000. JUL;27(3):331-60.

30. Barzilai D, Freiman A, Dellavalle R, Weinstock M, Mostow E. Dermatoepidemiology. J Am Acad Dermatol. 2005. APR;52(4):559-73.

31. Bataille V, Bishop J, Sasieni P, Swerdlow A, Pinney E, Griffiths K, Cuzickz J. Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: A case-control study. Br J Cancer. 1996. JUN;73(12):1605-11.

32. Bauer J, Garbe C. Acquired melanocytic nevi as risk factor for melanoma development. A comprehensive review of epidemiological data. Pigment Cell Research. 2003. JUN;16(3):297-306.

33. Benelli C, Roscetti E, Dal Pozzo V, Gasparini G, Cavicchini S. The dermoscopic versus the clinical diagnosis of melanoma. Eur J Dermatol. 1999. SEP;9(6):470-6.

34. Berman B. Basal cell carcinoma and actinic keratoses: Patients' perceptions of their disease and current treatments. Int J Dermatol. 2001. SEP;40(9):573-6.

35. Black W, Hunt W. Histologic correlations with the clinical-diagnosis of dysplastic nevus. Am J Surg Pathol. 1990. JAN;14(1):44-52.

36. Bolognia J, Berwick M, Fine J. Complete follow-up and evaluation of a skin-cancer screening in Connecticut rid E-9608-2010. J Am Acad Dermatol. 1990. DEC;23(6):1098-106.

37. Bono A, Bartoli C, Cascinelli N, Lualdi M, Maurichi A, Moglia D, Tragni G, Tomatis S, Marchesini R. Melanoma detection - A prospective study comparing diagnosis with the naked eye, dermatoscopy and telespectrophotometry. Dermatology. 2002;205(4):362-6.

38. Bono A, Tolomio E, Trincone S, Bartoli C, Tomatis S, Carbone A, Santinami M. Micro-melanoma detection: A clinical study on 206 consecutive cases of pigmented skin lesions with a diameter <= 3 mm. Br J Dermatol. 2006. SEP;155(3):570-3.

39. Bordeaux JS, Lu KQ, Cooper KD. Melanoma: Prevention and early detection. Semin Oncol. 2007. DEC;34(6):460-6.

40. Brochez L, Verhaeghe E, Bleyen L, Naeyaert JM. Diagnostic ability of general practitioners and dermatologists in discriminating pigmented skin lesions. J Am Acad Dermatol. 2001. JUN;44(6):979-86.

41. Caini S, Gandini S, Sera F, Raimondi S, Fargnoli MC, Boniol M, Armstrong BK. Meta-analysis of risk factors for cutaneous melanoma according to anatomical site and clinico-pathological variant. Eur J Cancer. 2009. NOV;45(17):3054-63.

42. Carli P, de Giorgi V, Betti R, Vergani R, Catricala C, Mariani G, Simonacci M, Bettacchi A, Bottoni U, Lo Scocco G, et al. Relationship between cause of referral and diagnostic outcome in pigmented lesion clinics: A multicentre survey of the italian multidisciplinary group on melanoma (GIPMe). Melanoma Res. 2003. APR;13(2):207-11.

43. Carli P, de Giorgi V, Chiarugi A, Nardini P, Weinstock M, Crocetti E, Stante M, Giannotti B. Addition of dermoscopy to conventional naked-eye examination in melanoma screening: A randomized study. J Am Acad Dermatol. 2004. MAY;50(5):683-9.

44. Carli P, De Giorgi V, Palli D, Maurichi A, Mulas P, Orlandi C, Imberti G, Stanganelli I, Soma P, Dioguardi D, et al. Dermatologist detection and skin self-examination are associated with thinner melanomas - results from a survey of the Italian multidisciplinary group on melanoma. Arch Dermatol. 2003. MAY;139(5):607-12.

45. Carli P, Mannone F, de Giorgi V, Nardini P, Chiarugi A, Giannotti B. The problem of false-positive diagnosis in melanoma screening: The impact of dermoscopy. Melanoma Res. 2003. APR;13(2):179-82.

46. Carli P, Nardini P, Crocetti E, De Giorgi V, Giannotti B. Frequency and characteristics of melanomas missed at a pigmented lesion clinic: A registry-based study. Melanoma Res. 2004. OCT;14(5):403-7.

47. Carlson JA, Dickersin GR, Sober AJ, Barnhill RL. Desmoplastic neurotropic melanoma - a clinicopathological analysis of 28 cases. Cancer. 1995. JAN 15;75(2):478-94.

48. Carsin AE, Sharp L, Comber H. Geographical, urban/rural and socioeconomic variations in nonmelanoma skin cancer incidence: A population-based study in Ireland. Br J Dermatol. 2011. APR 11;164(4):822-9.

49. Cassileth B, Clark W, Lusk E, Frederick B, Thompson C, Walsh W. How well do physicians recognize melanoma and other problem lesions. J Am Acad Dermatol. 1986. APR;14(4):555-60.

50. Cerroni L, Argenyi Z, Cerio R, Facchetti F, Kittler H, Kutzner H, Requena L, Sangueza OP, Smoller B, Wechsler J, et al. Influence of evaluation of clinical pictures on the histopathologic diagnosis of inflammatory skin disorders. J Am Acad Dermatol. 2010. OCT;63(4):647-52.

51. Chang Y, Stanley R, Moss R, Van Stoecker W. A systematic heuristic approach for feature selection for melanoma discrimination using clinical images. Skin Res Technol. 2005. AUG;11(3):165-78.

52. Chang Y, Barrett JH, Bishop DT, Armstrong BK, Bataille V, Bergman W, Berwick M, Bracci PM, Elwood JM, Ernstoff MS, et al. Sun exposure and melanoma risk at different latitudes: A pooled analysis of 5700 cases and 7216 controls Int J Epidemiol. 2009. JUN;38(3):814-30.

53. Charles CA, Yee VSK, Dusza SW, Marghoob AA, Oliveria SA, Kopf A, Rigel D, Halpern AC. Variation in the diagnosis, treatment and management of melanoma in situ - A survey of US dermatologists. Arch Dermatol. 2005. JUN;141(6):723-9.

54. Chen S, Bravata D, Weil E, Olkin I. A comparison of dermatologists' and primary care physicians' accuracy in diagnosing melanoma - A systematic review. Arch Dermatol. 2001. DEC;137(12):1627-34.

55. Chen S, Pennie M, Kolm P, Warshaw E, Weisberg E, Brown K, Ming M, Weintraub W. Diagnosing and managing cutaneous pigmented lesions: Primary care physicians versus dermatologists. J Gen Intern Med. 2006. JUL;21(7):678-82.

56. Claridge E, Cotton S, Hall P, Moncrieff M. From colour to tissue histology: Physics-based interpretation of images of pigmented skin lesions. Med Image Anal. 2003. DEC;7(4):489-502.

57. Claridge E, Cotton S, Hall P, Moncrieff M. From colour to tissue histology: Physics based interpretation of images of pigmented skin lesions. Lect Notes Comput Sc. 2002;2488:730-8.

58. Collins GL, Nickoonahand N, Morgan MB. Changing demographics and pathology of nonmelanoma skin cancer in the last 30 years. Semin Cutan Med Surg. 2004. MAR;23(1):80-3.

59. Commens CA. Skin cancer: Changing paradigms of practice and medical education. Med J Aust. 2007. AUG 20;187(4):207-8.

60. Cooper S, Wojnarowska F. The accuracy of clinical diagnosis of suspected premalignant and malignant skin lesions in renal transplant recipients. Clin Exp Dermatol. 2002. SEP;27(6):436-8.

61. Cristofolini M, Zumiani G, Bauer P, Cristofolini P, Boi S, Micciolo R. Dermatoscopy - usefulness in the differential-diagnosis of cutaneous pigmentary lesions. Melanoma Res. 1994. DEC;4(6):391-4.

62. Cummings S, Tripp M, Herrmann N. Approaches to the prevention and control of skin cancer. Cancer Metastasis Rev.1997. SEP-DEC;16(3-4):309-27.

63. Curley R, Cook M, Fallowfield M, Marsden R. Accuracy in clinically evaluating pigmented lesions. Br Med J. 1989. JUL 1;299(6690):16-8.

64. Cust AE, Schmid H, Maskiell JA, Jetann J, Ferguson M, Holland EA, Agha-Hamilton C, Jenkins MA, Kelly J, Kefford RF, et al. Population-based, case-control-family design to investigate genetic and environmental influences on melanoma risk Australian melanoma family study. Am J Epidemiol. 2009. DEC 15;170(12):1541-54.

65. Dal Pozzo V, Benelli C, Roscetti E. The seven features for melanoma: A new dermoscopic algorithm for the diagnosis of malignant melanoma. Eur J Dermatol. 1999. JUN;9(4):303-8.

66. Dale AI. A history of inverse probability: From Thomas Bayes to Karl Pearson. 2nd ed. New York: Springer-Verlog; 1999. 724 p.

67. Davis D, Donahue J, Bost J, Horn T. The diagnostic concordance of actinic keratosis and squamous cell carcinoma. J Cutan Pathol. 2005. SEP;32(8):546-51.

68. De La Torre-Lugo EM, Figueroa LD, Sanchez JL, Morales-Burgos A, Conde D. Skin cancer in Puerto Rico: A multiannual incidence comparative study. P R Health Sci J. 2010. SEP;29(3):312-6.

69. Debloom,James R.,,II, Zitelli JA, Brodland DG. The invasive growth potential of residual melanoma and melanoma in situ. Dermatol Surg. 2010. AUG;36(8):1251-7.

70. Decoste S, Stern R. Diagnosis and treatment of nevomelanocytic lesions of the skin - a community-based study. Arch Dermatol. 1993. JAN;129(1):57-62.

71. Deeks J, Altman D. Statistics notes - diagnostic tests 4: Likelihood ratios. Br Med J. 2004. JUL 17;329(7458):168-9.

72. Del Mar C, Green A, Cooney T, Cutbush K, Lawrie S, Adkins G. Melanocytic lesions excised from the skin - what percentage are malignant. Aust J Public Health. 1994. JUN;18(2):221-3.

73. Del Mar CB, Balanda KP. Examination of skin naevi in australian general practice: Dissonance between care and need? Aust N Z J Public Health. 1998;22(3):397-9.

74. Skin Cancer Rates by State. Atlanta: Centers for Disease Control. Available from: Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute. Available from: http://www.cdc.gov/cancer/skin/statistics/state.htm.

75. DeRooij M, Rampen F, Schouten L, Neumann H. Total skin examination during screening for malignant melanoma does not increase the detection rate. Br J Dermatol. 1996. JUL;135(1):42-5.

76. DeWit P, Vanthofgrootenboer B, Ruiter D, Bondi R, Brocker E, Cesarini J, Hastrup N, Houjensen K, MacKie R, Scheffer E, et al. Validity of the histopathological criteria used for diagnosing dysplastic nevi - an inter-observer study by the pathology subgroup of the EORTC malignant-melanoma cooperative group. Eur J Cancer. 1993;29A(6):831-9.

77. Diepgen TL, Mahler V. The epidemiology of skin cancer. Br J Dermatol. 2002. APR;146:1-6.

78. Divito SJ, Ferris LK. Advances and short comings in the early diagnosis of melanoma. Melanoma Res. 2010. DEC;20(6):450-8.

79. Drugge RJ, Nguyen C, Gliga L, Drugge ED. Clinical pathway for melanoma detection using comprehensive cutaneous analysis with melanoscan. Dermatol Online J. 2010. Aug 15;16(8):1.

80. Duncan LM, Berwick M, Bruijn JA, Byers HR, Mihm MC, Barnhill RL. Histopathologic recognition and grading of dysplastic melanocytic nevi - an inter-observer agreement study. J Invest Dermatol. 1993. MAR;100(3):S318-21.

81. Durbec F, Vitry F, Granel-Brocard F, Lipsker D, Aubin F, Hedelin G, Dalac S, Truchetet F, Michel C, Batard M, et al. The role of circumstances of diagnosis and access to dermatological care in early diagnosis of cutaneous melanoma A population-based study in France. Arch Dermatol. 2010. MAR 10;146(3):240-6.

82. Eads T, Hood A, Chuang T, Faust H, Farmer E. The diagnostic yield of histologic examination of seborrheic keratoses. Arch Dermatol. 1997. NOV;133(11):1417-20.

83. Eisenberg J. Doctors' decisions and the cost of medical care: The reasons for doctors' practice patterns and ways to change them. Ann Arbor, Michigan: Health Administration Press Perspectives; 1986. 190 p.

84. Ek EW, Giorlando F, Su SY, Dieu T. Clinical diagnosis of skin tumours: How good are we? ANZ J Surg. 2005. Jun;75(6):415-20.

85. Elder DE, Elenitsas R, Johnson B, Murphy G, Xu G. Lever's histopathology of the skin. Tenth ed. Lippencott Williams and Wilkins; 2008. 1408 p.

86. Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. Expert Rev Anticancer Ther. 2010. NOV;10(11):1811-23.

87. Ermertcan AT, Ozturk F, Gencoglan G, Eskiizmir G, Temiz P, Horasan GD. Sensitivity, predictive values, pretest--posttest probabilities, and likelihood ratios of presurgery clinical diagnosis of nonmelanoma skin cancers. Cutan Ocul Toxicol. 2011. MAR;30(1):50-4.

88. Farmer E. The fundamental issue of diagnosis. Arch Dermatol. 2002. MAY;138(5):684-5.

89. Farmer E. Why a skin biopsy? Arch Dermatol. 2000. JUN;136(6):779-80.

90. Federman D, Hogan D, Taylor J, Caralis P, Kirsner R. A comparison of diagnosis, evaluation, and treatment of patients with dermatological disorders. J Am Acad Dermatol. 1995. MAY;32(5):726-9.

91. Fisher N, Schaffer J, Berwick M, Bolognia J. Breslow depth of cutaneous melanoma: Impact of factors related to surveillance of the skin, including prior skin biopsies and family history of melanoma RID E-9608-2010. J Am Acad Dermatol. 2005. SEP;53(3):393-406.

92. Fleming MG. Pigmented lesion pathology: What you should expect from your pathologist, and what your pathologist should expect from you. Clin Plast Surg. 2010. JAN;37(1):1-20.

93. Gachon J, Beaulieu P, Sei MF, Gouvernet J, Claudel JP, Lemaitre M, Richard MA, Grob JJ. First prospective study of the recognition process of melanoma in dermatological practice. Arch Dermatol. 2005. APR;141(4):434-8.

94. Gaechter T, Muehleisen B, Schaerer L, Dummer R, Burg G, Hofbauer GFL. Weight of decision-making impairs clinical assessment of melanocytic lesions RID B-2671-2010. J Cutan Med Surg. 2007. JAN-FEB;11(1):9-18.

95. Gard D. Nonpigmented premalignant lesions of the skin. Clin Plast Surg. 1987. APR;14(2):413-23.

96. Geller A. Screening for melanoma. Dermatol Clin. 2002. OCT;20(4):629-640.

97. Geller AC, Swetter SM, Brooks K, Demierre M, Yaroch AL. Screening, early detection, and trends for melanoma: Current status (2000-2006) and future directions. J Am Acad Dermatol. 2007. OCT;57(4):555-72.

98. Gerbert B, Bronstone A, Maurer T, Hofmann R, Berger T. Decision support software to help primary care physicians triage skin cancer - A pilot study. Arch Dermatol. 2000. FEB;136(2):187-92.

99. Girgis A, Campbell E, Redman S, Sansonfisher R. Screening for melanoma - a community survey of prevalence and predictors rid G-8660-2011. Med J Aust. 1991. MAR 4;154(5):338-43.

100. Glass A, Hoover R. The emerging epidemic of melanoma and squamous-cell skin-cancer. Jama – J Am Med Assoc. 1989. OCT 20;262(15):2097-100.

101. Goldberg MS, Doucette JT, Lim HW, Spencer J, Carucci JA, Rigel DS. Risk factors for presumptive melanoma in skin cancer screening: American academy of dermatology national Melanoma/Skin cancer screening program experience 2001-2005. J Am Acad Dermatol. 2007. JUL;57(1):60-6.

102. Goodson AG, Grossman D. Strategies for early melanoma detection: Approaches to the patient with nevi. J Am Acad Dermatol. 2009. MAY;60(5):719-35.

103. Grant-Kels J, Bason E, Grin C. The misdiagnosis of malignant melanoma. J Am Acad Dermatol. 1999. APR;40(4):539-48.

104. Green A, Leslie D, Weedon D. Diagnosis of skin-cancer in the general-population - clinical accuracy in the Nambour survey. Med J Aust. 1988. MAY 2;148(9):447-50.

105. Grin CM, Kopf AW, Welkovich B, Bart RS, Levenstein MJ. Accuracy in the clinical-diagnosis of malignant-melanoma. Arch Dermatol. 1990. JUN;126(6):763-6.

106. Grob J, Gouvernet J, Aymar D, Mostaque A, Romano M, Noe M, DiConstanzo M, Bonerandi J. Count of benign melanocytic nevi as a major indicator of risk for nonfamilial nodular and superficial spreading melanoma. Cancer. 1990. JUL 15;66(2):387-95.

107. Guitart J, Lowe L, Piepkorn M, Prieto VG, Rabkin MS, Ronan SG, Shea CR, Tron VA, White W, Barnhill RL. Histological characteristics of metastasizing thin melanomas - A case-control study of 43 cases. Arch Dermatol. 2002. MAY;138(5):603-8.

108. Gumport S, Harris M, Roses D, Kopf A. The diagnosis and management of common skin cancers. CA-Cancer J Clin. 1981;31(2):79-90.

109. Habif TP. Clinical dermatology. 5th ed. Mosby Elsevier; 2010. 1040 p.

110. Habif TP, Campbell JL, Quitadamo MJ, Zug KA. Skin disease: Diagnosis and treatment. St. Louis: Mosby; 2001. 557 p.

111. Hallock G. Punitive damages ... just so you know. Plast Reconstr Surg. 1996. DEC;98(7):1322.

112. Hallock G, Lutz D. Prospective study of the accuracy of the surgeon's diagnosis in 2000 excised skin tumors. Plast Reconstr Surg. 1998. APR;101(5):1255-61.

113. Halpern A, Guerry D, Elder D, Clark W, Synnestvedt M, Norman S, Ayerle R. Dysplastic nevi as risk markers of sporadic (nonfamilial) melanoma - a case-control study. Arch Dermatol. 1991. JUL;127(7):995-9.

114. Halpern AC, Lieb JA. Early melanoma diagnosis: A success story that leaves room for improvement. Curr Opin Oncol. 2007. MAR;19(2):109-15.

115. Hansen C, Wilkinson D, Hansen M, Argenziano G. How good are skin cancer clinics at melanoma detection? Number needed to treat variability across a national clinic group in australia. J Am Acad Dermatol. 2009. OCT;61(4):599-604.

116. Har-Shai Y, Hai N, Taran A, Mayblum S, Barak A, Tzur E, Schafer I, David R, David E, Linn S. Sensitivity and positive predictive values of presurgical clinical diagnosis of excised benign and malignant skin tumors: A prospective study of 835 lesions in 778 patients. Plast Reconstr Surg. 2001. DEC;108(7):1982-9.

117. Hauck R, Manders E. Familial syndromes with skin tumor-markers. Ann Plast Surg. 1994. JUL;33(1):102-11.

118. Hauschild A, Egberts F, Garbe C, Bauer J, Grabbe S, Hamm H, Kerl H, Reusch M, Rompel R, Schlaeger M, et al. Melanocytic nevi. Journal Der Deutschen Dermatologischen Gesellschaft. 2011. SEP;9(9):723-34.

119. Heal CF, Raasch BA, Buettner PG, Weedon D. Accuracy of clinical diagnosis of skin lesions. Br J Dermatol.2008. Sep;159(3):661-8.

120. Heal CF, Weedon D, Raasch BA, Hill BT, Buettner PG. Agreement between histological diagnosis of skin lesions by histopathologists and a dermato-histopathologist. Int J Dermatol. 2009. DEC;48(12):1366-9.

121. Hemmings D, Johnson S, Tominaga G, Wong J. Cutaneous melanoma in a multiethnic population - is this a different disease? Arch Surg-Chicago. 2004. SEP;139(9):968-72.

122. Holly E, Kelly J, Shpall S, Chiu S. Number of melanocytic nevi as a major risk factor for malignant-melanoma. J Am Acad Dermatol. 1987. SEP;17(3):459-68.

123. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK. SEER Cancer Statistics Review: c1975-2008, National Cancer Institute. Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2008/.

124. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing clincial research. 3rd ed. Philadelphia: Lippincott Williams and Wilkins; 2007. 384 p.

125. Izikson L, Sober AJ, Mihm MC, Zembowicz A. Prevalence of melanoma clinically resembling seborrheic keratosis - analysis of 9204 cases. Arch Dermatol. 2002. DEC;138(12):1562-6.

126. Izikson L, Seyler M, Zeitouni NC. Prevalence of underdiagnosed aggressive non-melanoma skin cancers treated with Mohs micrographic surgery: Analysis of 513 cases. Dermatol Surg. 2010. NOV;36(11):1769-72.

127. Jagdeo J, Weinstock MA, Piepkorn M, Bingham SF, Dept VATTC Trial Grp. Reliability of the histopathologic diagnosis of keratinocyte carcinomas. J Am Acad Dermatol. 2007. AUG;57(2):279-84.

128. James WD, Berger TG, Elston DM. Andrews' diseases of the skin: Clinical dermatology. 11th ed. Saunders Elsevier; 2011. 968 p.

129. Jemec G. The diagnostic accuracy of danish GPs in the diagnosis of pigmented skin lesions. Fam Pract. 1999. DEC;16(6):619-20.

130. Jonna BP, Delfino RJ, Newman WG, Tope WD. Positive predictive value for presumptive diagnoses of skin cancer and compliance with follow-up among patients attending a community screening program. Prev Med. 1998. JUL-AUG;27(4):611-6.

131. Kang SW, Barnhill RL, Mihm MC, Fitzpatrick TB, Sober AJ. Melanoma risk in individuals with clinically atypical nevi. Arch Dermatol. 1994. AUG;130(8):999-1001.

132. Kantor J, Kantor DE. Routine dermatologist-performed full-body skin examination and early melanoma detection. Arch Dermatol. 2009. AUG;145(8):873-6.

133. Katz BJ, Oliviero M, Rabinovitz H. Dermoscopy and its impact on skin cancer diagnostics. J Drugs Dermatol. 2010. FEB;9(2):129-30.

134. Kettenbach G. Writing soap notes. 2nd ed. Philadelphia: F.A. Davis Company; 1990. 183 p.

135. Kiiski V, de Vries E, Flohil SC, Bijl MJ, Hofman A, Stricker BHC, Nijsten T. Risk factors for single and multiple basal cell carcinomas. Arch Dermatol. 2010. AUG;146(8):848-55.

136. Kim JH, Kim J, Jung Y, Yi Y, Ahn HH. Terror management theory in dermatology: Skin biopsy influences patient compliance. Acta Derm Venereol. 2010;90(3):246-50.

137. Kirkpatrick J, Taggart I, Rigby H, Townsend P. A pigmented lesion clinic - analysis of the first years 1055 patients. Br J Plast Surg. 1995. JUN;48(4):247-51.

138. Klein L, Barr R. Histologic atypia in clinically benign nevi - a prospective-study. J Am Acad Dermatol. 1990. FEB;22(2):275-82.

139. Kmetz EC, Sanders H, Fisher G, Lang PG, Maize JC, Sr. The role of observation in the management of atypical nevi. South Med J. 2009. JAN;102(1):45-8.

140. Koh H, Caruso A, Gage I, Geller A, Prout M, White H, OConnor K, Balash E, Blumental G, Rex I. Evaluation of melanoma skin-cancer screening in Massachusetts - preliminary-results. Cancer. 1990. JAN 15;65(2):375-9.

141. Koh H, Lew R, Prout M. Screening for melanoma skin-cancer - theoretic and practical considerations. J Am Acad Dermatol. 1989. FEB;20(2):159-72.

142. Kolm I, Hofbauer G, Braun RP. Early diagnosis of skin cancer. Ther Umsch. 2010. Sep;67(9):439-46.

143. Kopf A, Rigel D, Friedman R. The rising incidence and mortality-rate of malignant-melanoma. J Dermatol Surg Oncol. 1982;8(9):760-1.

144. Kopf A, Salopek T, Slade J, Marghoob A, Bart R. Techniques of cutaneous examination for the detection of skin-cancer. Cancer. 1995. JAN 15;75(2):684-90.

145. Koplin L, Zarem H. Recurrent basal-cell carcinoma - a review concerning the incidence, behavior, and management of recurrent basal-cell carcinoma, with emphasis on the incompletely excised lesion. Plast Reconstr Surg. 1980;65(5):656-64.

146. Krieger L. The new medical marketplace .2. cost and outcome studies. Plast Reconstr Surg. 1996. NOV;98(6):1102-7.

147. Krieger N, Hiatt R, Sagebiel R, Clark W, Mihm M. Inter-observer variability among pathologists evaluation of malignant-melanoma - effects upon an analytic study. J Clin Epidemiol. 1994. AUG;47(8):897-902.

148. Krige J, Isaacs S, Hudson D, King H, Strover R, Johnson C. Delay in the diagnosis of cutaneous malignant-melanoma - a prospective-study in 250 patients. Cancer. 1991. NOV 1;68(9):2064-8.

149. Kroemer S, Fruhauf J, Campbell T, Massone C, Schwantzer G, Peter Soyer H, Hofmann-Wellenhof R. Mobile teledermatology for skin tumour screening: Diagnostic accuracy of clinical and dermoscopic image teleevaluation using cellular phones. Br J Dermatol. 2011. Jan 11;164:973-999.

150. Kruschke JK. Doing Bayesian data analysis: A tutorial with R and bugs. Boston: Elsevier; 2011. 672 p.

151. Langley RGB, Walsh N, Sutherland AE, Propperova I, Delaney L, Morris SF, Gallant C. The diagnostic accuracy of in vivo confocal scanning laser microscopy compared to dermoscopy of benign and malignant melanocytic lesions: A prospective study. Dermatology. 2007;215(4):365-72.

152. LeBoit PE, Burg G, Weedon D, Sarasin A. Pathology and genetics of skin tumors. Lyon, France: International Agency for Research on Cancer; 2006. 355 p.

153. Lee PK. Common skin cancers. Minn Med. 2004. MAR;87(3):44-7.

154. Lindelof B, Hedblad M, Sigurgeirsson B. Melanocytic naevus or malignant melanoma? A large-scale epidemiological study of diagnostic accuracy. Acta Derm Venereol. 1998. JUL;78(4):284-8.

155. Lodha S, Saggar S, Celebi JT, Silvers DN. Discordance in the histopathologic diagnosis of difficult melanocytic neoplasms in the clinical setting. J Cutan Pathol. 2008. APR;35(4):349-52.

156. Losina E, Walensky RP, Geller A, Beddingfield,Frederick C.,,III, Wolf LL, Gilchrest BA, Freedberg KA. Visual screening for malignant melanoma - A cost-effectiveness analysis. Arch Dermatol. 2007. JAN;143(1):21-8.

157. MacKie RM, Bray C, Vestey J, Doherty V, Evans A, Thomson D, Nicolson M, Scottish Melanoma Grp. Melanoma incidence and mortality in Scotland 1979-2003. Br J Cancer. 2007. JUN 4;96(11):1772-7.

158. MacKie R. Clinical recognition of early invasive malignant-melanoma. Br Med J. 1990. NOV 3;301(6759):1005-6.

159. Madan V, Lear JT, Szeimies R. Non-melanoma skin cancer. Lancet. 2010. FEB 20;375(9715):673-85.

160. Mallett S, Deeks JJ, Halligan S, Hopewell S, Cornelius V, Altman DG. Systematic reviews of diagnostic tests in cancer: Review of methods and reporting RID C-5875-2009. Br Med J. 2006. AUG 26;333(7565):413-416A.

161. Marcos-Gragera R, Vilar-Coromina N, Galceran J, Borras J, Cleries R, Ribes J, Gispert R, Izquierdo A, Borras JM. Rising trends in incidence of cutaneous malignant melanoma and their future projections in catalonia, spain: Increasing impact or future epidemic? J Eur Acad Dermatol Venereol. 2010. SEP;24(9):1083-8.

162. Marghoob AA, Koenig K, Bittencourt FV, Kopf AW, Bart RS. Breslow thickness and clark level in melanoma: Support for including level in pathology reports and in american joint committee on cancer staging. Cancer. 2000. FEB 1;88(3):589-95.

163. Marghoob A, Slade J, Salopek T, Kopf A, Bart R, Rigel D. Basal-cell and squamous-cell carcinomas are important risk-factors for cutaneous malignant-melanoma - screening implications. Cancer. 1995. JAN 15;75(2):707-14.

164. Marghoob AA, Terushkin V, Dusza SW, Busam K, Scope A. Dermatologists, general practitioners, and the best method to biopsy suspect melanocytic neoplasms. Arch Dermatol. 2010. MAR 10;146(3):325-8.

165. Marks R. Who benefits from calling a solar keratosis a squamous cell carcinoma? Br J Dermatol. 2006. JUL;155(1):23-6.

166. Skin Biopsy. Mayo Foundation for Medical Education and Research. Available from: http://www.mayoclinic.com/health/skin-biopsy.

167. Non Melanoma Skin Cancer. Mayo Foundation for Medical Education and Research. Available from: http://www.mayoclinic.org/nonmelanoma-skin-cancer/types.html.

168. McMeniman E, De'Ambrosis K, De'Ambrosis B. Risk factors in a cohort of patients with multiple primary melanoma. Australas J Dermatol. 2010. NOV;51(4):254-7.

169. Merrill R. Enivoronmental epidemiology: Principles and methods. Boston: Jones and Bartlett Publishers; 2008. 483 p.

170. Merrill RM. Risk-adjusted melanoma skin cancer incidence rates in whites (united states). Melanoma Res. 2011. DEC;21(6):535-40.

171. Miller D, Weinstock M. Nonmelanoma skin-cancer in the united-states - incidence. J Am Acad Dermatol. 1994. MAY;30(5):774-8.

172. Miller M. How accurate are dermatologists in the diagnosis of melanoma - degree of accuracy and implications. Arch Dermatol. 1992. APR;128(4):559-60.

173. Moffatt C, Green A, Whiteman D. Diagnostic accuracy in skin cancer clinics: The australian experience. Int J Dermatol. 2006. JUN;45(6):656-60.

174. Mogensen M, Jemec GBE. Diagnosis of nonmelanoma skin cancer/keratinocyte carcinoma: A review of diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies. Dermatol Surg. 2007. OCT;33(10):1158-74.

175. Mogensen M, Joergensen TM, Nurnberg BM, Morsy HA, Thomson JB, Thrane L, Jemec GBE. Assessment of optical coherence tomography imaging in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: Observer-blinded evaluation by dermatologists and pathologists. Dermatol Surg. 2009. JUN;35(6):965-72.

176. Moore MW, Gasparini R. FISH as an effective diagnostic tool for the management of challenging melanocytic lesions. Diagn Pathol. 2011. AUG 11;6:76.

177. Morton CA, MacKie RM. Clinical accuracy of the diagnosis of cutaneous malignant melanoma. Br J Dermatol. 1998. FEB;138(2):283-7.

178. Moy R. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol. 2000. JAN;42(1):S8-S10.

179. Nachbar F, Stolz W, Merkle T, Cognetta A, Vogt T, Landthaler M, Bilek P, Braunfalco O, Plewig G. The abcd rule of dermatoscopy - high prospective value in the diagnosis of doubtful melanocytic skin-lesions. J Am Acad Dermatol. 1994. APR;30(4):551-9.

180. Skin Phototype: New Zealand Dermatological Society, Inc. Available from: http://dermnetnz.org/reactions/phototype.html.

181. O'Hagan A, Luce B, R. A primer on Bayesian statistics in health economics and outcomes research. MEDTAP International, Inc.; 2003.

182. Osborne JE, Chave TA, Hutchinson PE. Comparison of diagnostic accuracy for cutaneous malignant melanoma between general dermatology, plastic surgery and pigmented lesion clinics. Br J Dermatol. 2003. FEB;148(2):252-8.

183. Osborne J. Skin cancer screening and surveillance. Br J Dermatol. 2002. MAY;146(5):745-54.

184. Osborne J, Bourke J, Graham-Brown R, Hutchinson P. False negative clinical diagnoses of malignant melanoma. Br J Dermatol. 1999. MAY;140(5):902-8.

185. Paradela S, Pita-Fernandez S, Pena C, Fernandez-Jorge B, Garcia-Silva J, Mazaira M, Fonseca E. Complications of ambulatory major dermatological surgery in patients older than 85 years. J Eur Acad Dermatol and Venereol. 2010. OCT;24(10):1207-13.

186. Park JN, Parker PM. Skin cancer: A medical dictionary, bibliography, and annotated research guide to the internet references. San Diego: Icon Group International, Inc.; 2003.

187. Parslew RAG, Rhodes LE. Accuracy of diagnosis of benign skin lesions in hospital practice: A comparison of clinical and histological findings. Journal of the European Academy of Dermatology and Venereology 1997 SEP;9(2):137-41.

188. Pearl RA, Townley W, Stott D, Grobbelaar AO. Diagnosis of skin lesions by trainee surgeons: Experience improves accuracy. Ann R Coll Surg Engl. 2009. SEP;91(6):494-9.

189. Pearl R, McAllister H, Pruzansky J. An economic analysis of health care reform and its implications for plastic surgery. Plast Reconstr Surg. 1997. JAN;99(1):1-9.

190. Pflugfelder A, Weide B, Eigentler TK, Forschner A, Leiter U, Held L, Meier F, Garbe C. Incisional biopsy and melanoma prognosis: Facts and controversies. Clin Dermatol. 2010. MAY-JUN;28(3):316-8.

191. Piepkorn MW, Barnhill RL, Cannonalbright LA, Elder DE, Goldgar DE, Lewis CM, Maize JC, Meyer LJ, Rabkin MS, Sagebiel RW, et al. A multiobserver, population-based analysis of histologic dysplasia in melanocytic nevi. J Am Acad Dermatol. 1994. MAY;30(5):707-14.

192. Pinkus H, Mehregan A. Premalignant skin-lesions. Clin Plast Surg. 1980;7(3):289-300.

193. Pockney P, Primrose J, George S, Jayatilleke N, Leppard B, Smith H, Little P, Kneebone R, Lowy A. Recognition of skin malignancy by general practitioners: Observational study using data from a population-based randomised controlled trial. Br J Cancer. 2009. JAN 13;100(1):24-7.

194. Pua VSC, Huilgol S, Hill D. Evaluation of the treatment of non-melanoma skin cancers by surgical excision. Australas J Dermatol. 2009. AUG;50(3):171-5.

195. Pugliano-Mauro M, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. Dermatol Surg. 2010. OCT;36(10):1544-53.

196. Raasch BA, Buettner PG, Garbe C. Basal cell carcinoma: Histological classification and body-site distribution. Br J Dermatol. 2006. AUG;155(2):401-7.

197. Raasch B, Buettner P. Multiple nonmelanoma skin cancer in an exposed australian population. Int J Dermatol. 2002. OCT;41(10):652-8.

198. Rampen F, Casparievanvelsen I, Vanhuystee B, Kiemeney L, Schouten L. False-negative findings in skin-cancer and melanoma screening rid D-3357-2009. J Am Acad Dermatol. 1995. JUL;33(1):59-63.

199. Resnik D. To test or not to test - a clinical dilemma. Theor Med. 1995. JUN;16(2):141-52.

200. Richard M, Grob J, Avril M, Delaunay M, Gouvernet J, Wolkenstein P, Souteyrand P, Dreno B, Bonerandi J, Dalac S, et al. Delays in diagnosis and melanoma prognosis (I): The role of patients. Int J Cancer. 2000. MAY 20;89(3):271-9.

201. Richmond-Sinclair NM, Pandeya N, Ware RS, Neale RE, Williams GM, van der Pols JC, Green AC. Incidence of basal cell carcinoma multiplicity and detailed anatomic distribution: Longitudinal study of an Australian population. J Invest Dermatol. 2009. FEB;129(2):323-8.

202. Riegelman R, Hirsch R. Studying a study and testing a test. 2nd ed. Boston: Little, Brown and Company. 368 p.

203. Rigel DS, Russak J, Friedman R. The evolution of melanoma diagnosis: 25 years beyond the ABCDs. CA Cancer J Clin. 2010. SEP-OCT;60(5):301-16.

204. Rigel D, Friedman R. The rationale of the ABCDs of early melanoma. J Am Acad Dermatol. 1993. DEC;29(6):1060-1.

205. Rivers J, Shaw H. Skin-cancer - diagnostic ability compared with diagnostic-accuracy. Med J Aust. 1989. OCT 2;151(7):421-2.

206. Robinson J, McGaghie W. Skin cancer detection in a clinical practice examination with standardized patients. J Am Acad Dermatol. 1996. APR;34(4):709-11.

207. Rodriguez Caravaca G, Mosquera Gonzalez M, Villar Del Campo MC, Lopez Estebaranz JL, Pinedo Moraleda F, De La Torre Escuredo B. Validity of clinical diagnosis in dermatology. Eur J Derm. 2011. MAR-APR;21(2):223-8.

208. Rogers HW, Weinstock MA, Harris AR, Hinckley MR, Feldman SR, Fleischer AB, Coldiron BM. Incidence estimate of nonmelanoma skin cancer in the united states, 2006. Arch Dermatol. 2010. MAR 10;146(3):283-7.

209. Skin Biopsy. Healthwise Inc. Available from: http://www.emedicinehealth.com/skin_biopsy-health/article_em.htm.

210. Rosendahl C, Hansen C, Cameron A, Bourne P, Wilson T, Cook B, Baker M, Keir MJ, Dicker T, Reid M, et al. Measuring performance in skin cancer practice: The SCARD initiative. Int J Dermatol. 2011. JAN;50(1):44-51.

211. Roth M, Grantkels J, Ackerman A, Elder D, Friedman R, Heilman E, Maize J, Sagebiel R. The histopathology of dysplastic nevi - continued controversy. Am J Dermatopathol. 1991. FEB;13(1):38-51.

212. Roush GC, Barnhill RL, Ernstoff MS, Kirkwood JM. Interclinician agreement on the recognition of clinical pigmentary characteristics of patients with cutaneous malignant-melanoma - studies of melanocytic nevi .6. Br J Cancer. 1991. AUG;64(2):373-6.

213. Roush GC, Dubin N, Barnhill RL. Prediction of histologic melanocytic dysplasia from clinical observation. J Am Acad Dermatol. 1993. OCT;29(4):555-62.

214. Roush G, Nordlund J, Forget B, Gruber S, Kirkwood J. Independence of dysplastic nevi from total nevi in determining risk for nonfamilial melanoma. Prev Med. 1988. MAY;17(3):273-9.

215. Rubegni P, Cevenini G, Burroni M, Bono R, Sbano P, Biagioli M, Risulo M, Nami N, Perotti R, Miracco C, et al. Objective follow-up of atypical melanocytic skin lesions: A retrospective study. Arch Dermatol Res. 2010. SEP;302(7):551-60.

216. Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: A basic science for clinical medicine. Second ed. Boston: Little, Brown and Company; 1991. 442 p.

217. Schaefer D, Wolf J. Common dermatological disorders. Clin Plast Surg. 1987. APR;14(2):209-22.

218. Schmid-Wendtner M, Baumert J, Stange J, Volkenandt M. Delay in the diagnosis of cutaneous melanoma: An analysis of 233 patients. Melanoma Res. 2002. AUG;12(4):389-94.

219. Schwartz J, Wang T, Hamilton T, Lowe L, Sondak V, Johnson T. Thin primary cutaneous melanomas - associated detection patterns, lesion characteristics, and patient characteristics. Cancer. 2002. OCT 1;95(7):1562-8.

220. Sellheyer K, Bergfeld WF. A retrospective biopsy study of the clinical diagnostic accuracy of common skin diseases by different specialties compared with dermatology. J Am Acad Dermatol. 2005. MAY;52(5):823-30.

221. Sherry KR, Reid LA, Wilmshurst AD. A five year review of basal cell carcinoma excisions. J Plast Reconstr Aes. 2010. SEP;63(9):1485-9.

222. Shoaib T, Stewart DA, MacKie RM, Gray HW, Soutar DS. The unexpected sites of melanoma regional recurrences. J Plast Reconstr Aes. 2006;59(9):955-60.

223. Shors AR, Kim S, White E, Argenyi Z, Barnhill RL, Duray P, Erickson L, Guitart J, Horenstein MG, Lowe L, et al. Dysplastic naevi with moderate to severe histological dysplasia: A risk factor for melanoma. Br J Dermatol. 2006. NOV;155(5):988-93.

224. Silfen R, Amir A, Regev D, Hauben D. Role of physicians and patients in the diagnostic delay of cutaneous malignant melanoma. Ann Plast Surg. 2002. OCT;49(4):439-42.

225. Singh H, Sethi S, Raber M, Petersen LA. Errors in cancer diagnosis: Current understanding and future directions. J Clin Oncol. 2007. NOV 1;25(31):5009-18.

226. Sneyd MJ, Cox B. Clinical and histologic factors associated with melanoma thickness in New Zealand Europeans, Maori, and Pacific peoples. Cancer. 2011. JUN 1;117(11):2489-98.

227. Soares TF, Laman SD, Yiannias JA, Connolly SM, Lim KK, Wu Q, Swanson DL. Factors leading to the biopsy of 1547 pigmented lesions at Mayo Clinic, Scottsdale, Arizona, in 2005. Int J Dermatol. 2009. OCT;48(10):1053-6.

228. Soyer H, Kenet R, Wolf I, Kenet B, Cerroni L. Clinicopathological correlation of pigmented skin lesions using dermoscopy. Eur J Dermatol. 2000. JAN-FEB;10(1):22-8.

229. Stal S. Keratoacanthoma. Clin Plast Surg. 1987. APR;14(2):425.

230. Stanganelli I, Serafini M, Bucchi L. A cancer-registry-assisted evaluation of the accuracy of digital epiluminescence microscopy associated with clinical examination of pigmented skin lesions. Dermatology. 2000;200(1):11-6.

231. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: The 2002 national survey and trends since 1985. Med J Aust. 2006. JAN 2;184(1):6-10.

232. Stolz W, Riemann A, Cognetta A, Pillet L, Abmayr W, Holzel D, Bilek P, Nachbar F, Landthaler M, Braunfalco O. Abcd rule of dermatoscopy - a new practical method for early recognition of malignant-melanoma. Eur J Dermatol. 1994. OCT;4(7):521-7.

233. Strayer SM, Reynolds P. Diagnosing skin malignancy: Assessment of predictive clinical criteria and risk factors. J Fam Pract. 2003. MAR;52(3):210-8.

234. Swerlick R, Chen S. The melanoma epidemic: More apparent than real? Mayo Clin Proc. 1997. JUN;72(6):559-64.

235. Swetter S. Dermatological perspectives of malignant melanoma. Surg Clin North Am. 2003. FEB;83(1):77-95.

236. Terushkin V, Braga JC, Dusza SW, Scope A, Busam K, Marghoob AA, Gill M, Halpern AC. Agreement on the clinical diagnosis and management of cutaneous squamous neoplasms. Dermatol Surg. 2010. OCT;36(10):1514-20.

237. Terushkin V, Warycha M, Levy M, Kopf AW, Cohen DE, Polsky D. Analysis of the benign to malignant ratio of lesions biopsied by a general dermatologist before and after the adoption of dermoscopy. Arch Dermatol. 2010. MAR 10;146(3):343-4.

238. Titusernstoff L, Barnhill RL, Duray PH, Ernstoff MS, Kirkwood JM. Dysplastic nevi in relation to superficial spreading melanoma. Cancer Epidemiol Biomarkers Prev. 1993. MAR-APR;2(2):99-101.

239. Trakatelli M, Ulrich C, del Marmol V, Euvard S, Stockfleth E, Abeni D. Epidemiology of nonmelanoma skin cancer (NMSC) in europe: Accurate and comparable data are needed for effective public health monitoring and interventions. Br J Dermatol. 2007. MAY;156:1-7.

240. Tran H, Chen K, Shumack S. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol. 2003. NOV;149:50-2.

241. Tran KT, Wright NA, Cockerell CJ. Biopsy of the pigmented lesion-when and how. J Am Acad Dermatol. 2008. NOV;59(5):852-71.

242. Tripp JM, Kopf AW, Marghoob AA, Bart RS. Management of dysplastic nevi: A survey of fellows of the American academy of dermatology. J Am Acad Dermatol. 2002. MAY;46(5):674-82.

243. Trotter M, Bruecks A. Interpretation of skin biopsies by general pathologists - diagnostic discrepancy rate measured by blinded review. Arch Pathol Lab Med. 2003. NOV;127(11):1489-92.

244. Tsao H, Rogers G, Sober A. An estimate of the annual direct cost of treating cutaneous melanoma. J Am Acad Dermatol. 1998. MAY;38(5):669-80.

245. Tucker M, Halpern A, Holly E, Hartge P, Elder D, Sagebiel R, Guerry D, Clark W. Clinically recognized dysplastic nevi - A central risk factor for cutaneous melanoma. Jama-J Amer Med Assoc. 1997. MAY 14;277(18):1439-44.

246. Tucker M, Hartge P, Halpern A, Elder D, Gerry D, Clark W, Holly E, Sagebiel R. Differentiating dysplastic nevi from melanoma - reply. Jama-J Amer Med Assoc. 1997. AUG 20;278(7):548-9.

247. Medline Plus Medical Dictionary. Bethesda, MD.: U.S. National Library of Medicine. Available from: http://www.nlm.nih.gov/medlineplus/mplusdictionary.html.

248. Skin Cancer Facts For Your State. United States Environmental Protection Agency. Available from: http://www.epa.gov/sunwise/statefacts.html.

249. Van der Rhee JI, Bergman W, Kukutsch NA. The impact of dermoscopy on the management of pigmented lesions in everyday clinical practice of general dermatologists: A prospective study. Br J Dermatol. 2010. MAR;162(3):563-7.

250. Van Dijk MCRF, Aben KKH, van Hees F, Klaasen A, Blokx WAM, Kiemeney LALM, Ruiter DJ. Expert review remains important in the histopathological diagnosis of cutaneous melanocytic lesions. Histopathology. 2008. JAN;52(2):139-46.

251. Vestergaard ME, Macaskill P, Holt PE, Menzies SW. Dermoscopy compared with naked eye examination for the diagnosis of primary melanoma: A meta-analysis of studies performed in a clinical setting. Br J Dermatol. 2008. SEP;159(3):669-76.

252. Viera AJ, Garrett JM. Understanding inter-observer agreement: The kappa statistic. Fam Med. 2005. MAY;37(5):360-3.

253. Wachsman W, Morhenn V, Palmer T, Walls L, Hata T, Zalla J, Scheinberg R, Sofen H, Mraz S, Gross K, et al. Noninvasive genomic detection of melanoma. Br J Dermatol. 2011. APR 11;164(4):797-806.

254. Wagner R, Pellegrini J, DelZell E. Decreased risk of subsequent primary non-cutaneous malignancies among patients with primary cutaneous malignant-melanoma. J Dermatol Surg Oncol. 1985;11(11):1097-102.

255. Wagner R, Wagner D, Tomich J, Wagner K, Grande D. Diagnoses of skin-disease - dermatologists vs nondermatologists. J Dermatol Surg Oncol. 1985;11(5):476-9.

256. Walter FM, Morris HC, Humphrys E, Hall PN, Kinmonth AL, Prevost AT, Wilson ECF, Burrows N, Norris P, Johnson M, et al. Study protocol protocol for the MoleMate (TM) UK trial: A randomised controlled trial of the MoleMate system in the management of pigmented skin lesions in primary care. Bmc Family Practice. 2010. MAY 11;11.

257. Wang CY, Maibach HI. Why minimally invasive skin sampling techniques? A bright scientific future. Cutan Ocul Toxicol. 2011. MAR;30(1):1-6.

258. Weedon D, Strutton G, Rubin A. Weedon's skin pathology. 3rd ed. Churchill Livingstone Elsevier; 2010. 1060 p.

259. Weinstock M. Early detection of melanoma. Jama-J Amer Med Assoc. 2000. AUG 16;284(7):886-9.

260. Whited JD, Hall RP. Diagnostic accuracy and precision in assessing dermatologic disease - problem or promise? Arch Dermatol. 1997. NOV;133(11):1409-15.

261. Whited J, Grichnik J. Does this patient have a mole or a melanoma? Jama-J Amer Med Assoc. 1998. MAR 4;279(9):696-701.

262. Whited J, Grichnik J. Clinical diagnosis of moles vs melanoma - reply. Jama-J Amer Med Assoc. 1998. SEP 9;280(10):881-2.

263. Whited J, Hall R, Simel D, Horner R. Primary care clinicians' performance for detecting actinic keratoses and skin cancer. Arch Intern Med. 1997. MAY 12;157(9):985-90.

264. Winkler RL. Bayesion inference and decision. 2nd ed. Gainesville, Florida: Probabilistic Publishing; 2003. 464 p.

265. Wolf IH, Smolle J, Soyer HP, Kerl H. Sensitivity in the clinical diagnosis of malignant melanoma. Melanoma Res. 1998. OCT;8(5):425-9.

266. Wolf P, Quehenberger F, Mullegger R, Stranz B, Kerl H. Phenotypic markers, sunlight-related factors and sunscreen use in patients with cutaneous melanoma: An Austrian case-control study. Melanoma Res. 1998. AUG;8(4):370-8.

267. Youl PH, Janda M, Aitken JF, Del Mar CB, Whiteman DC, Baade PD. Body-site distribution of skin cancer, pre-malignant and common benign pigmented lesions excised in general practice. Br J Dermatol. 2011. JUL;165(1):35-43.