# CLINICAL DECISION SUPPORT SYSTEM AS A RISK ASSESSMENT TOOL TO AID IN EARLIER DIAGNOSIS OF PANCREATIC CANCER

**By**

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## ABSTRACT

**Background:** Pancreatic cancer is the most aggressive and the most deadly type of cancer. More than 85% of diagnoses are made during the advanced stage. Currently, there is no systematic approach for early diagnosis of pancreatic cancer, hence, a proposal to develop a clinical decision support system in diagnosing pancreatic cancer earlier that later.

**Objectives:** To develop a clinical decision support system that can identify pancreatic cancer risk levels in individuals, and also provide recommendations and alerts tailored towards each individual's situation.

**Design:** A multi-method approach using quasi-experimental and quantitative study.

**Methods:** Knowledge and probabilistic basis were used to define the variables and parameters and their respective weighted scores. Five weight groups of 100, 60, 30, 15, and 5 were created with "100" as maximum risk and "5' as minimum risk. Fourteen common risk factors were used and within these risk factors, 87 parameters were defined and categorized into one of the five weight groups. Three risk levels; high risk, moderate risk, low risk and their scores were defined. At the end of the test, the system provides immediate feedback in the form of total risk factor score and other vital information.

**Results:** Twelve case scenarios were used to validate the system. Among the 12 cases, nine were diagnosed with pancreatic cancer, one was a healthy individual with no diagnosis of any sort and two were diagnosed with other health conditions. The results were as follows; two low risk patients, three moderate risk patients and seven high risk patients. In some cases, recommendations and alerts were generated for patients to seek immediate medical attention, screen for pancreatic cancer or get a scan of the pancreas.

**Conclusion:** The results show that it is possible to develop a system that can identify high risk individuals for pancreatic cancer. The impact the system will have on patient care and whether the system can reduce the number of misdiagnoses, delayed diagnoses, or lead to earlier diagnoses of pancreatic cancer is uncertain. Further studies will need to be conducted to expand the knowledge in using clinical decision support system for pancreatic cancer risk assessment.

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## List of Abbreviations

| | |
|---|---|
| RAT | Risk Assessment Tool |
| CDSS | Clinical Decision Support System |
| NIS | Nationwide Inpatient Sample |
| DNA | Deoxyribonucleic Acid |
| CA 19-9 | Carbohydrate Antigen 19-9 |
| CEA | Carcinoembryonic Antigen |
| CARS | Chimeric Antigen Receptors |
| IPMTs | Intraductal Papillary Mucinous Tumors |
| IPMNs | Intraductal Papillary Mucinous Neoplasms |
| VIPomas | Vasoactive Intestinal Peptide-releasing tumor |
| MEN I | Multiple Endocrine Neoplasia type 1 |
| NET | Neuroendocrine Tumors |
| *LEPR* | Leptin Receptors |
| HIF-1α | Hypoxia-Inducible Factor 1-alpha |
| PanIN | Pancreatic Intraepithelial Neoplasia |
| CK 7 | Cytokeratin 7 |
| CK 20 | Cytokeratin 20 |
| EUS | Endoscopic ultrasound |
| MRI | Magnetic resonance imaging |
| CT | Computed tomography |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| MRCP | Magnetic resonance cholangiopancreatography |

| | |
|---|---|
| EUS-FNA | Endoscopic ultrasound-guided fine-needle aspiration |
| AI | Artificial intelligence |
| ANN | Artificial neural networks |
| HIPAA | Health Insurance Portability and Accountability Act |
| PHI | Protected Health Information |
| EHR | Electronic Health Records |
| EMR | Electronic Medical Records |
| HCUP | Healthcare Cost and Utilization Project |
| NIS | Nationwide Inpatient Sample |
| ACS | American Cancer Society |
| SEER | Surveillance, Epidemiology, End Result |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| SPSS | Statistical Package for the Social Sciences |
| SAS | Statistical Analysis System |
| ASCII | American Standard Code for Information Interchange |
| CCS | Clinical Classifications Software |
| ICD-9-CM | International Classification of Diseases, 9th Revision, Clinical Modification |

CHAPTER I

# INTRODUCTION

## 1.1 Introduction to the Problem

Pancreatic cancer is the most aggressive and the most lethal form of cancer[1–5] with a rise in incidence in the past several decades[1,6,7]. Pancreatic cancer is known to be highly resistant to treatment. Early diagnosis is the best hope for reducing the mortality rate for pancreatic cancer but a systematic approach for early diagnosis is not yet known[8–13]. The tumors often go undetected and often get detected during imaging for a different illness. First and foremost, what is cancer? Cancer is a type of disease that starts as an abnormal cell division in the body. The body is made up of trillions of cells that grow and die with age to aid in the growth and development process from infancy to adulthood. The cell division process is usually more rapid at a younger age. In adulthood, these cells continue the cell division process mainly to replace the dying once. This is the normal pattern of development at the cellular level but in the case of cancer cells, they grow and divide out of control and can invade other tissues unlike normal cells. The cancer cells can divide rapidly and also do not die off or get worn out like normal cells. The abnormality of these cells known as cancer cells is a result of a mutation somewhere in the Deoxyribonucleic Acid (DNA) during cell division. All cells contain DNA and would undergo DNA replication during the second phase in the cell cycle of cell division or reproduction. The problem with cancer cells is that, the gene mutation causes the DNA to misinterpret the genetic instruction; thus an abnormal cell division occurs which in turn begins the life of a cancer cell that develops into a tumor and starts to affect the functions of the tissues or organs where it is located. If this continues without treatment

to kill the cancerous tumors, the cell division will continue until these abnormal cells travel outside its original location. This process is known as a metastasis which is the spread of the cancer cells to other parts of the body.

In the case of pancreatic cancer, more than 85% of diagnoses have metastasized, therefore unresectable[14–16]. It is the most devastating diagnosis for any patient; hence the urgent need for an early diagnosis of this disease. The median survival rate is less than six months and at least 95% of those diagnosed with pancreatic cancer will succumb to the disease within 5 years of diagnosis[17–19]. According to the American Cancer Society, in 2015 about 48,960 people will be diagnosed with pancreatic cancer and about 40,560 people will die of pancreatic cancer. Cancer is the second leading cause of death in the United States following heart disease. Pancreatic cancer is the fourth leading cause of cancer-related death in the United States[11,15,19,20] with lung cancer as #1. Nevertheless, pancreatic cancer has the worst prognosis in all of medicine[17]. It has a somber prognosis[9,12,13,21] which can be explained as a reflection of the poor knowledge about its biology and etiology[17]. In addition, lack of symptoms in the early stages of the disease[14,22] is a contributory factor in the demise of pancreatic cancer diagnosis for patients. Even if the disease is caught before metastasis, treatment options are not very effective in ensuring full recovery and survival. Treatments for pancreatic cancer are either surgery if it is still localized or therapy if it has metastasized. Although, surgery presents the best treatment option with the highest survival rate, only about 15% of those diagnosed with pancreatic cancer fall under this category[23] and of those who undergo surgery, the five year survival rate is only 20%[17]. Because of the poor response to treatment, undergoing chemotherapy or radiation or both is not enough to prevent

recurrence or future metastasis because eventually, most patients will succumb to the disease. The reason for the poor response to treatment is still poorly understood, however some researchers believe it could be attributed to the location of the pancreas and the properties of the tumors in the pancreas. The pancreas is a difficult-to-reach organ during treatment and the tumors are often surrounded by dense tissues which is one of the reasons why treatment methods such as, chemotherapy are not as effective as in other forms of cancer. Essentially, properties of the tumors are problematic for drug delivery[24].

Surgery, which presents a much better prognosis, is also problematic because absolute resection without causing injury to the pancreas and surrounding tissues is difficult. Surgery poses extreme risk and because the pancreas is a delicate organ with high sensitivity, it makes it very challenging for surgeons to attain success. Another issue is, most pancreatic cancer diagnoses are unresectable because it is often diagnosed at an advanced stage when surgery is no longer an option and would make no difference in the metastasis of the cancer. Additionally, some pathologists believe that the lesions are hard to identify even when the pancreas is sliced open in front of you[25].

In order to fully understand the difficulty in early detection and treatment of pancreatic cancer, one has to understand the anatomy and physiology of the pancreas. The pancreas is a glandular organ located within the digestive system just under the stomach. It is shaped like a fish of size 6 inches long and less than 2 inches wide[26]. The head of the pancreas is to the right of the body just under or behind the stomach and the tail is to the left of the body next to the spleen[26]. Figure 1.1 shows the position of the pancreas within the abdominal cavity.

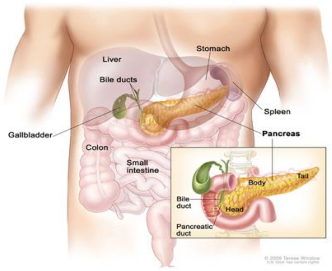



**Figure 1.1: The Human Pancreas**. Figure from National Cancer Institute. The human pancreas is a delicate organ located towards the right side of the body just behind the stomach. The location of the pancreas is thought to be a contributory factor in the tumor's resistance to treatment and the difficulty in carry out Whipple procedure (resection), the most effective treatment for pancreatic cancer.

The pancreas is both endocrine and exocrine, meaning, it secretes its products directly into the blood and through a duct respectively. The endocrine gland is responsible for secreting hormones such as insulin, somatostatin, glucagon and pancreatic polypeptide which circulates in the blood to carry out other biological functions. The exocrine gland is responsible for secreting digestive juice containing enzymes to assist with digestion and absorption of nutrients in the small intestine. These enzymes help to breakdown carbohydrates, protein, and lipids from food or other sources. That said, most pancreatic malignancies are thought to begin as lesions from duct cells in the pancreas. The pancreas is made up of several cells. The endocrine gland has five cells (islets of Langerhans), namely; alpha cell, beta cells, delta cells PP and epsilon, all of which perform different function in the secretion of the different types of hormones. The exocrine gland has two cells, namely; cento acinar cell and basophilic cells.

The most common types of pancreatic cancer are those of the exocrine gland with over 95% of pancreatic cancer diagnosis. It has a median survival of six months and a five-year survival of less than 5%, while the endocrine has an incidence of 3% to 5% of all pancreatic malignancies with an overall 5-year survival rate of about 42%.

Pancreatic adenocarcinoma is an exocrine tumor believed to develop from epithelial ducts cells[17]. This is the most aggressive and the most common type of all pancreatic malignancies. Most studies about pancreatic cancer are on pancreatic adenocarcinoma and when pancreatic cancer is mentioned, it often means pancreatic adenocarcinoma which is also reflected in this study.

As earlier stated, pancreatic cancer is the most lethal form of cancer although the number of new cases is low compared to other forms of cancer. Figure 1.2 below shows the 12 most common types of cancer and a comparison between their mortality rates. As shown in the graph, pancreatic cancer has the highest mortality of the 12 types of cancer but the lowest incidence.

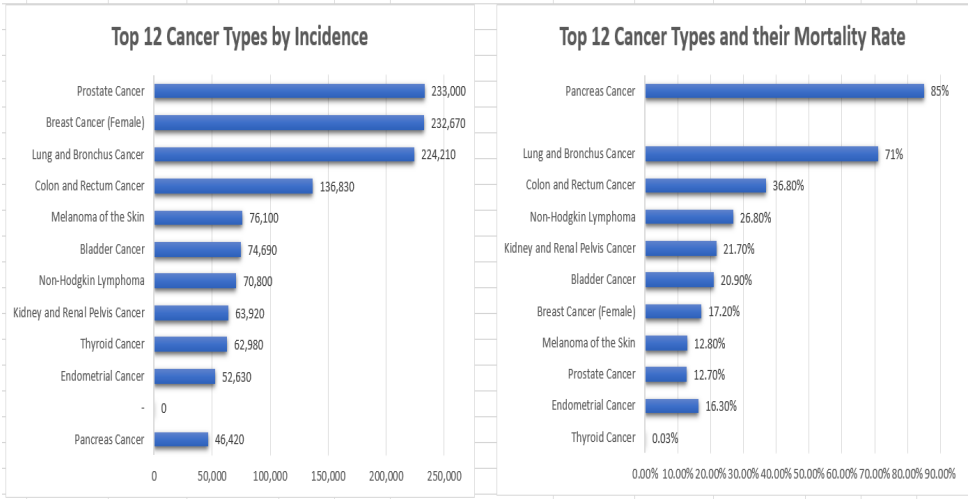



**Figure 1.2: Top 12 most common Types of Cancer and their Mortality Rate**

The cause of pancreatic cancer is not well known, however the risk factors associated with the different types of pancreatic cancer has been extensively studied and reported. Some of the risk factors specifically associated with pancreatic adenocarcinoma are genetic, smoking, age, gender and race. A number of factors have been suggested as high risk factors that can lead to the onset of pancreatic cancer. Smoking is the strongest

environmental risk factor. Familial pancreatic cancer and genetic syndromes have elevated risks that are not within an individuals' control. Studies indicate there is a 2.8-fold risk of someone developing pancreatic cancer if a first-degree familial pancreatic cancer exist in comparison with the general population at age 65[27] and this risk increases with each affected relative[28]. Age and gender are factors that have been proven over time in studying and analyzing the incidence of pancreatic cancer. Statistical analyses show the disease is more common with increasing age and more common in men than women. Men are 30% more likely to develop pancreatic cancer than women. Tobacco use in men is higher than in women and this may explain the gender disparity, although in recent times, the gap is becoming smaller. With regard to age, the median age for pancreatic cancer patients is 71 years[29]. The rates of new cases are higher in people of age between 75 and 84 years old as shown in figure 1.3.

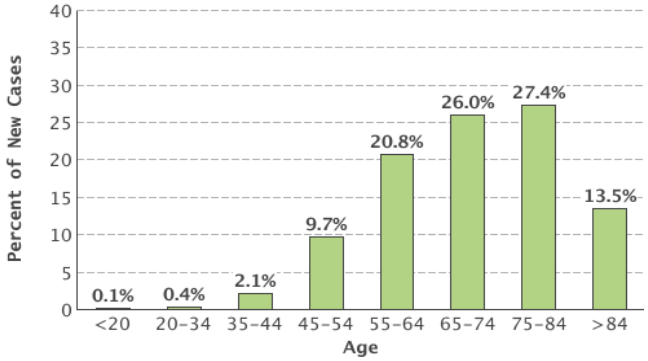



**Figure 1.3: New Cases of Pancreatic Cancer by Age**. Data from surveillance, epidemiology, and end results (SEER)

Another risk factor is indicated by mortality of pancreatic cancer in different race. The incidence among blacks is decreasing while increasing among whites and all other race. However, mortality among blacks remains higher than any other race. Researchers reported that pancreatic cancer deaths among white men in the United States decreased by 0.7% per year between 1970 and 1995 but increased by 0.4% per year from 1995

through 2009. In addition, a study published in the Journal of the National Cancer Institute showed that rates among white women increased slightly between 1970 and 1984 and remain stable until the late 1990s, then increased 0.5% per year through 2009. The reason for the difference in rates of developing pancreatic cancer in whites vs blacks is uncertain, however there has been speculations that higher rate of smoking, diabetes and obesity may be partly responsible[26]. Studies have shown the risk of getting pancreatic cancer is at least twice as high among smokers than non-smokers[26]. Scientists suspect the cancer-causing chemical in cigarette smoke can enter the pancreas and cause injury to the pancreas which can lead to pancreatic cancer[26]. Other than cigarette, cigars and pipe smoking are also risk factors for pancreatic cancer. Smokeless tobacco is also a risk factor and those who use them are more likely to get pancreatic cancer. The goodnews is that quitting smoking helps lower the risk. Those who have quit for a period of 10 years have the same probability as those who never smoked[26].

Among all the studies on methods to reduce the mortality of pancreatic cancer, the use of clinical decision support system (CDSS) is the least studied. Clinical decision support systems are computer systems that can be developed either with knowledge or artificial intelligence to produce results that could aid the user in their decision-making. Studies have reported the effectiveness of utilizing CDSS in health conditions such as asthma[30], chronic obstructive pulmonary disease[31], pain therapy[32], cardiovascular disease[33], breast cancer detection[34] and a host of other health conditions with the exception of pancreatic cancer. The notion of CDSS has been around for the past 30 years however, implementation and acceptance of using CDSS in health care settings are still at the bare minimum. Because pancreatic cancer diagnosis at the early stage is still a

fundamental question yet to be answered, we propose developing a CDSS to be used as a risk assessment tool to identify risk levels for pancreatic cancer and to aid in the diagnostic process for patients. The use of a CDSS by the general public will provide at least a heuristic approach in recognizing risk factors and symptoms associated with pancreatic cancer.

### 1.2 Background and Statement of the Problem

Pancreatic cancer is known to be highly aggressive and responds poorly to treatment. The problems researchers are experiencing with pancreatic cancer are the little to no knowledge about the biology and etiology of pancreatic cancer[17], understanding the dynamic of the progression of lesions, and finding out the root cause of the lesions that eventually become malignant. Some risk factors associated with pancreatic cancer are well established but a method with high sensitivity and specificity for early diagnosis is yet to be determined. Lack of symptoms early in the disease also pose a major problem. Symptoms are often presented during the advanced stage of the disease and most of the symptoms can be easily mistaken for a non-life threatning illness. In some cases, patients were asymptomatic. Patients and clinicians can also downplay diagnosis when there are no serious symptoms like jaundice, and even with such a symptom, some clinicians can overlook or eliminate pancreatic cancer as a potential cause leading to a delay in diagnosis or a misdiagnosis. For example, symptoms such as; weight loss and poor appetite or abdominal pain and back pain are associated with pancreatic cancer but the initial belief may be of something minor. The patient may ignore signs for a while or seek medical attention later rather than immediately; perhaps, because the initial symptoms are

manageable and mostly associated with other minor health issues. Other reasons may be, a concern of being thought of as, overreacting or hypochondriac, especially if after seeking medical attention it turns out to be "nothing serious." Some of these behaviors may contribute to reasons researchers have difficulty in confirming how long it takes for pancreatic cancer to progress from the early stage to an advanced stage.

One of the biggest challenges facing early diagnosis is the difficulty in identifying highly sensitive and specific biomarkers for pancreatic malignancies. Using molecular markers thought to identify the presence of pancreatic cancer is not currently recommended because researchers are yet to identify specific biomarkers[22,35,36] and the reliability of the currently used biomarkers is yet to be proven. A number of suspected biomarkers have been thought to aid in the diagnosis of pancreatic cancer. In recent times, a teen prodigy developed a biosensor that could detect the presence of mesothelin, a soluble cancer biomarker believe to aid in determining if a patient has pancreatic cancer at the early stage[37,38]. He believes this sensor is 90% accurate in identifying the levels of mesothelin, making his technique better than the current technique used in identifying mesothelin in pancreatic cancer patients. His claims are yet to be proven but his discovery may lead to a proven and workable cancer diagnostic test[38]. Previous studies have shown mesothelin to be expressed in cancer cells and they have indicated it is a promising target for immunotherapy for pancreatic malignant tumors[39,40]. Even with this knowledge, when it comes to pancreatic cancer, a blood test cannot be routinely carried out to detect the presence of pancreatic cancer at the very early stages of the tumor and there are no known tests to predict the onset of the disease. Other than mesothelin, blood test for levels of carbohydrate antigen 19-9 (CA19-9) can be used to indicate the presence

of pancreatic malignancy. CA19-9 and carcinoembryonic antigen (CEA) can be used to diagnose exocrine pancreatic cancer[26,41]. However, the use of such biomarkers are not specific to pancreatic cancer and it is still questionable whether or not they can be used as an indicator for pancreatic cancer because not all diagnosis have shown the presence of these biomarkers. CA19-9 can however, be used to monitor the effect of treatment for pancreatic cancer[1].

Blood tests to identify cancer-specific molecules, including proteins, transcripts or genes and epigenetic markers can offer hope for early detection of pancreatic cancer at a non-invasive stage[42]. On the other hand, the non-existing routine screening of patients for pancreatic cancer, such as, the existing screenings for other types of cancer is problematic. Example, routine mammogram screenings for breast cancer, Pap smear screening for cervical cancer, and PSA blood test for prostate cancer are currently being utilized to prevent late stage diagnosis but there is no such screening for the most aggressive form of cancer, pancreatic cancer. Other factors that could lead to a solution for early detection of pancreatic cancer are; finding out those particular genes that are responsible for the anomalies, discovering a method of prohibiting gene mutation, and how to improve the delivery of treatment to the tumors in the pancreas for a better outcome than what is it now.

Recent studies have indicated cysts (fluid-filled compartments) in the pancreas may develop into cancer. Cysts in the pancreas are often found in 1 out of 10 people above the age of 70 and also common in younger people. These cysts can be detected by computed tomography (CT) scan or magnetic resonance imaging (MRI) but the challenge is current imaging technology cannot determine which cysts will become malignant. This

leaves the option of puncturing the cyst to collect samples for tumor marker analysis; however, these analyses are not reliable. In 2013, researchers from the University of Gothenburg recently discovered a new method of identifying which cysts are precursors to cancer[43]. This method was proven to predict accurately with 97% certainty cysts that are potentially malignant. Their technique was to detect mucus protein (mucins) in the cystic fluid and this technique was able to correctly diagnose 77 out of 79 that were examined. Another challenge is a prophylactic approach which may involve the removal of the cysts through surgery but because surgery poses high risks for the patient, this may not be a better option. Additionally, after surgery and analyses of the cyst, the results may indicate non-malignancy which may not be worth the risk of causing damage to the pancreas and other tissues. According to Vasen et al., cystic lesions of the main duct and side branches (duct ectasias) have evidence of rapid growth of tumors, which means, treatment has to commence quickly after a cyst is discovered[44] but other studies in computational modelling indicate a large window of opportunity at least a decade long; the problem is, most cases are diagnosed after this window of opportunity has passed[45]. Besides lesions and cyst turning malignant, it is believed that pancreatitis which is an inflammation of the pancreas and other forms of damage or injury to the pancreas can result in pancreatic cancer. Pancreatitis can often cause lesions which could become malignant but the reason for this transition, other than genetic mutation is unknown. Finding answers to the causes of the altered cell division process and the mutations that lead to the growth of tumors in the pancreas will deliver breakthrough outcomes.

Imaging surveillance of high-risk individuals for pancreatic cancer might increase the chance for early detection, however the best strategy for surveillance is yet to be

determined[44]. Currently, there are several imaging technology used in detecting tumors in the pancreas, namely; endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging and Computed tomography (CT). One of the problems with the current imaging technology is the limitation on the size of the tumor that can be detected. To address this issue, researchers developed a technique used in dogs that produced images with increased brightness and standard deviation derived from the gray-scale histogram to produce detectable pancreatic parenchyma to quantify them in terms of the type of cells present[28]. Whether this technology will work in humans is yet to be determined.

Another notable problem is the lack of clinical decision support systems (CDSS) for diagnosis and management of pancreatic cancer in patients. Although, clinicians are experts in their own right, the level of knowledge across the board varies which is where a CDSS comes in and may help in ensuring that misdiagnosis or delayed diagnosis does not happen to patients. Clinical decision support systems are computer systems that are built using an algorithm based on knowledge and evidence or artificial intelligence and expert-knowledge. In this study, the focus of the CDSS is to identify the risk levels of individuals and to point individuals and their providers in the direction of screening to eliminate pancreatic cancer before making a final diagnostic decision. The ultimate goal is to discover the disease sooner than later. Implementation of a CDSS could positively impact patient care and aid clinicians in making better decisions and accurate diagnosis earlier. The proposed CDSS is a risk assessment tool that comprise of several questions with a holistic approach to collect the necessary information to produce a total score that

can tell the user which category of risk they belong, whether a high risk, moderate risk or low risk.

The purpose of this research is to develop a CDSS that will aid individuals or health care providers in identifying high risk individuals and ultimately lead to a better clinical diagnostic outcome for pancreatic cancer patients.

### 1.3 Significance of the Study

Pancreatic cancer is the most lethal type of cancer with a dismal prognosis. Most pancreatic malignancies are ductal, meaning, it originates from ductal epithelial cells. Pancreatic adenocarcinoma is known to be the most aggressive and most problematic of all pancreatic cancer types and the challenges facing researchers in finding a method for early detection are enormous. Recent studies in other areas except the use of CDSS have revealed revolutionary findings related to pancreatic cancer. For example, Mayo clinic researchers recently discovered possible causes of cell transformation in chronic pancreatitis patients which could point to ways in identifying pancreatitis patients at risk of pancreatic cancer and to develop potential drug therapies that might reverse the process[46]. A new study at Perelman School of Medicine at the University of Pennsylvania revealed that *T cells* in pancreatic cancer patients can be reprogrammed to recognize and destroy pancreatic cancer cells by using an approach that genetically modifies the *T cells* to express protein complexes as chimeric antigen receptors (CARS)[47]. Another study demonstrated there are other factors besides the previously known factors about the poor response of pancreatic cancer to treatment. Previously, it was believed that the poor penetration of the drugs into the pancreatic tumors was the main cause of the difficulty in

treating pancreatic cancer, however this recent study showed there are survival factors inside the tumors that provide pro-life signals that over power the drug effects of chemotherapy. The new approach is to combine medicines and chemotherapy to block the survival signals of the tumor and potentially achieve better treatment results for patients[48].

Several recent reports and studies have been released and shown to have possibilities and potentials for treatment, management and diagnosis of pancreatic cancer but none have presented CDSS as a possible method. Because of the alaming mortality rate of pancreatic cancer and the current five-year survival of less than 6%, a method for early diagnosis is indispensable, hence the significance of this study. This study has proposed the development of a CDSS for identification of the risk levels of individuals for pancreatic cancer which can lead to earlier diagnosis. There is evidence of a few studies on CDSS for other health conditions but none has pointed in the direction of pancreatic cancer. In this study, the CDSS is designed to categorize individuals into one of three groups; high risk, moderate risk or low risk and also provides recommendations to individuals with symptoms associated with pancreatic cancer. CDSS have been reported as efficient in reducing medical errors, workflow and other benefits in patient care. Therefore, the development of such a system and the evidence of its effectiveness may provide a significant difference in the diagnostic outcome for patients with pancreatic cancer. The proposed CDSS will not be tested on actual patients or clinicians but will be tested using case reports to simulate actual users.

The significance of this study, therefore, is the insight into the possibility of the use of a CDSS for an earlier diagnosis of pancreatic cancer if used as a risk assessment

tool (RAT) to screen the general population. This is highly important because most diagnoses of pancreatic cancer are made at an advanced stage resulting in an extremely poor prognosis. Even with the presence of symptoms, diagnosis may be prolonged either because the symptoms mimic those of other health conditions or because comorbidities of pancreatic cancer are mistaken as the cause of the symptoms. The use of a CDSS will reduce medical errors of this nature and alert clinicians of the need to screen for pancreatic cancer. In this case, the decision will not be based on the expert knowledge only. The proposed CDSS is a standalone system that will collect the patient's demographic information, medical records, lifestyle factors, and family history. A holistic approach to an individual's medical data is needed in order for the system to generate reliable results. The CDSS will provide questions to the user and utilize built-in knowledge, clinical evidence and facts, and a set of logic rules to analyze the answers before generating the overall risk factor score and/or suggesting a course of action to the user.

### 1.4 Research Goals and Objectives

The goal of this study is to develop a clinical decision support system for pancreatic cancer such that individuals in the general population can utilize it as a heuristic tool in identifying their level of risk for pancreatic cancer, and also to aid both the general public and health care providers in their decision-making of health related issues if it pertains to pancreatic cancer. Another goal is to discover the possibilities in utilizing a CDSS and to capture the interest of other researchers in developing other prototypes that could potentially lead to a wide acceptance of a CDSS for pancreatic

cancer. The history of pancreatic cancer and studies that have been done to-date are yet to answer the most pertinent questions. Several years of research and millions spent have not provided us a solid understanding of the disease and how to prevent or stop the progression of an existing neoplasm of the pancreas. Additional goals and objectives include finding a systematic approach in using a CDSS as a first resort to obtain more knowledge about pancreatic cancer and symptoms associated with it. Since pancreatic cancer is known to be highly lethal and difficult to treat and detect early, it is only proper to focus on methods of reducing misdiagnoses and delayed diagnoses. The CDSS will provide vital information to both experts and non-experts in making better decisions at the point-of-care of patients and in real-time for individuals. The overall goal is to point the general public in a direction that may reduce advanced stage diagnosis of the disease, extend life expectancy after diagnosis and reduce mortality of pancreatic cancer.

### 1.5 Research Hypotheses

It is believed that this study will provide a valid tool that can be used by individuals in the general public and healthcare providers to identify pancreatic cancer risk levels. Below is a list of the research hypotheses posed.

a. It is possible to develop a clinical decision support system that can identify high risk individuals for pancreatic cancer.
b. It is possible to design a clinical decision support system that will provide important information about pancreatic cancer to both the general public and health care providers.

c. It is possible to develop a clinical decision support system that can lead to earlier diagnosis of pancreatic cancer, reduce the number of misdiagnoses and delayed diagnoses of pancreatic cancer in patients.

CHAPTER II

# LITERATURE REVIEW

## 2.1 Epidemiology of Pancreatic Cancer

Pancreatic cancer has an alarming mortality but a low number of new cases in comparison to other forms of cancer. It is the fourth leading cause of cancer-related death in the United States with a rise in mortality in the past two decades[1]. According to recent research conducted by the Pancreatic Cancer Action Network, pancreatic cancer will be the second leading cause of cancer-related death by the year 2030[49].

Research on pancreatic cancer has provided little to no knowledge about the biology of the disease. The etiology of pancreatic cancer is still poorly understood, however, studies have identified several risk factors that are likely to increase the chances of developing pancreatic cancer. Some of the risk factors are behavioral and could be addressed to reflect a decrease in the chances of developing pancreatic cancer. On the other hand, those that are not behavior-based, such as genetic syndromes, are still under investigation to determine exactly which genes are responsible for the mutation that lead to the growth of malignant tumors or lesions in the pancreas. Not all individuals with high risk factors will develop pancreatic cancer and having a low risk factor does not 100% ensure against the development of pancreatic cancer. This phenomenon is one of the reasons why scientists are working hard to find a cure and prophylactic measures against any form of cancer.

*2.1.1 Types of Pancreatic Cancer*

The most common type and most aggressive type of pancreatic cancer is pancreatic adenocarcinoma which is responsible for 95% of all pancreatic cancer[26]. Pancreatic adenocarcinoma is the fourth leading cause of death from cancer in the United[17]. Pancreatic adenocarcinomas have resistant phenotypes and are highly metastatic. Pancreatic cancer is either exocrine or endocrine. Exocrine pancreatic cancer are; acinar cell carcinoma, adenosquamous carcinoma, pancreatoblastoma, cystic tumors (mucinous cystic, serous cystic tumors, solid pseudo papillary tumors, intraductal papillary mucinous tumors (IPMTs) or intraductal papillary mucinous neoplasm (IPMNs)). Endocrine types of pancreatic cancer are categorized into two groups, functional and non-functional. Functional endocrine pancreatic cancer are hormone producing and mostly benign while non-functional endocrine pancreatic cancer do not produce hormones and 90% of them are malignant. Examples are, gastrinomas, glucagonomas, insulinomas, somatostatinomas, VIPomas (vasoactive intestinal peptide-releasing tumor or verner-morrison syndrome), and multiple endocrine neoplasia type 1 (MEN I).

Tumors of the exocrine gland account for more than 95% of all pancreatic cancer. Although research has shown that pancreatic cancer has the worst prognosis in all of medicine, there is an iota of hope because not all pancreatic malignancies have such dismal prognosis. The IPMTs or the IPMNs known as intraductal papillary mucinous tumors or intraductal papillary mucinous neoplasms are slow-growing and less invasive type of pancreatic cancer. This type of tumor was introduced to the United States almost four decades ago. Since then, views about treatment approach have been mixed because it

is still unknown how long the progression of these tumors is from the early stage to the advanced stage. Recent studies have shown that it is fairly common in the elderly at least age 80-89 years old[50]. The good news is, a growing number of patients are now being diagnosed before they develop symptoms[50].

Table 2.1 and 2.2 are a quick overview of the different types of pancreatic cancer and some of their features.

**Table 2.1: Malignant Tumors of the Endocrine Gland**
(Also known as; Pancreatic Neuroendocrine Tumors (NETs) or islet cell Tumors

| Type of Tumor | Origin | Histopathological Features | Mutations | Frequency of Occurrence |
|---|---|---|---|---|
| Insulinomas | Cells that make insulin | Hormone production | MEN1 | Most common of all NETs; 10% are malignant and 5% to 8% are associated with MEN-1 syndrome |
| Glucagonomas | Cells that make glucagon | Hormone production | MEN1 | Third in frequency; 1 in 20 million and about 75% are malignant |
| Gastrinomas | Cells that make gastrin | Hormone production | MEN1 | Second most common of all NETs; Up to 33% have liver metastases, 50% are malignant and about 15% to 35% are associated with the MEN-1 syndrome |
| Somatostatinomas | Cells that make somatostatin | Hormone production | MEN1 | The least common; particularly rare but most of these tumors are malignant and have metastases at diagnosis. |
| VIPomas (vasoactive intestinal peptide-releasing tumor or verner-morrison syndrome) | Cells that make vasoactive intestinal peptide (VIP) | Hormone production | MEN1 | 2nd least common; Diagnosis is 1 per 10,000,000 per year and approximately 60-80% are malignant and have metastasized at the time of diagnosis. About 5% are associated with (MEN) type 1 syndrome |
| PPomas | Cells that make pancreatic polypeptide | Hormone production | MEN1 | Also the third most common |
| Multiple endocrine neoplasia type 1 (MEN I) or Werner's syndrome | Type 1 gene mutation | Affects the endocrine glands; pituitary, parathyroid and the pancreas | MEN1 | A genetic disorder that affects 1 in 30,000 people |

**Table 2.2: Malignant Tumors of the Exocrine Gland**

| Type of tumor | Origin | Histopathological Features | Mutations | Frequency of occurrence |
|---|---|---|---|---|
| Pancreatic Adenocarcinoma | They begin in the pancreatic ducts known as pancreatic intraepithelial neoplasia(PanIN) | Ductal morphology with resistant phenotypes and telomere dysfunction | KRAS, CDKN2A, TP53, SMAD4, NCOA3 | Highly metastatic; the most aggressive and the most common tumor accounting for more than 95% of all pancreatic malignancies |
| Adenosquamous carcinoma | Ductal and sometimes, unknown | Pancreatic duct epithelia, with mucin production | Unknown | Rare but aggressive; 1 to 4% of exocrine malignancies |
| Squamous cell carcinoma | Unknown | Pancreatic duct epithelia, with mucin production | Unknown | Incidence of 0.005% in exocrine pancreatic cancer |
| Signet ring cell carcinomas | Epithelial and a form of adenocarcinoma | Produces mucin | Unknown | Extremely rare |
| Solid pseudopapillary | Unknown | Cystic and solid pseudopapillary cells | Unknown | A rare malignancy with 6% of all exocrine pancreatic tumours |
| Undifferentiated carcinomas | Ductal adenocarcinoma | Pancreatic duct epithelia, with mucin production | Unknown | |
| Undifferentiated carcinomas with giant cells | Ductal adenocarcinoma | Pancreatic duct epithelia, with mucin production | Unknown | |
| Ampulla of Vater or Ampullary cancers | Unknown | | | Extremely rare |
| Acinar cell carcinoma | Acinar cells | Zymogen granules | APC/β-catenin | |
| Pancreatoblastoma | Acinar cell | Epithelial;, hemorrhage, capsule formation and necrosis | Unknown | Congenital, 0.5% of all exocrine tumors |
| Cystic tumors (mucinous cystic, serous cystic tumors, solid pseudopapillary tumors, IPMTs or IPMNs) | Unknown | Ductal morphology; cystic growth | KRAS | Slow progression and rarely metastatic |
| Serous cystadenocarcinoma | Unknown | Ductal morphology; cystic growth. Mucin-producing epithelium | VHL | 1-2% of pancreatic neoplasms |

*2.1.2 Symptoms Associated with Pancreatic Cancer*

The different types of pancreatic cancer present varying symptoms, however, patients with the vast majority of pancreatic malignancies, in particular, pancreatic adenocarcinoma may experience some of the symptoms listed below. The challenge is identifying the symptoms early and seeking immediate medical attention. The problem is that symptoms could be mistaken for other types of health conditions such as, gastrointestinal reflux diseases, gallstone disease and others even after seeking medical attention. Another problem is that, because of the positioning of the pancreas, sitting right in front of the spine, symptoms such as pain could be mistaken as arthritis or muscle ache[51]. Some signs and symptoms associated with pancreatic cancer are namely;

i. Jaundice
ii. Abdominal pain
iii. Back pain
iv. Weight loss and poor appetite
v. Digestive problems
vi. Gall bladder enlargement
vii. Blood clot or fatty tissue abnormalities
viii. Sudden onset of Diabetes mellitus type II
ix. Black or tarry stool
x. Diarrhea
xi. Itchy skin, palms or soles of feet

Symptoms usually manifest at the advanced stage of pancreatic malignancy especially symptoms like unexplained weight loss of about 5 lbs. or more.

*2.1.3 Risk Factors of Pancreatic Cancer*

Several risk factors of pancreatic cancer have been identified over the years but not all researchers agree with the findings of all of the risk factors. Risk factors for pancreatic cancer as shown in table 2.3 are namely; age, gender, race, smoking, obesity, lack of physical activity, diabetes, chronic pancreatitis, cirrhosis of the liver, occupational exposure, family history, genetic syndromes, stomach problems, obesity, diet, coffee, and last but not least, alcohol. Not all studies have agreed with all of these risk factors because there have been discrepancies in research reports on some of these risk factors. In addition, some of these risk factors may have been proven in older studies but not in recent studies. For example, some older studies indicate drinking coffee is linked to pancreatic cancer while some recent studies have not proven this fact[26]. Diet is another risk factor that is debatable because of the different findings by researchers. Some researchers believe that pancreatic cancer can be linked to diets high in fat while some believe that high fruit and vegetable diet can reduce the risk for pancreatic cancer. On the other hand, some researchers believe there is no link between diet and pancreatic cancer[26]. Some studies have indicated that a Mediterranean diet can reduce the risk of pancreatic cancer[52] probably because of the limited intake of red meat, a food source some researchers have associated with pancreatic cancer[53,54]. Heavy alcohol intake is one risk factor that has been confirmed not just for the development of pancreatic cancer but for several other types of cancer[52]. Age, gender, race are apparent and can be determined from analysis of data showing the trend of incidence over time, moreover, reports about age and smoking as a risk factor have been consistent.

**Table 2.3: Risk Factors for Pancreatic Cancer and Relevant Findings**

| Factors | Increased Risk | Relevant Findings |
|---|---|---|
| Smoking | 2.7-fold | Smoking is the strongest risk factor |
| Patient's history of Lung Cancer | 1.3-fold in men and 2.5-fold in women | Patients with lung cancer have an elevated risk because both lung cancer and pancreatic cancer are associated with smoking |
| Family History | 2.8-fold and increases with each family member | Possibly due to autosomal dominantly inherited factor |
| Family History & Smoking | 6.02-fold for first-degree relatives | Risk is greater than those with family history and no smoking |
| Genetic Syndromes | 100-fold | Elevated risk |
| Age | Nearly 9 in 10 are at least 55 years old | Risk increases with age, the average age at the time of diagnosis is 71. |
| Gender | The gap between men and women is closing | Cases of pancreatic cancer are higher in men than women. Men are 30% more like to develop pancreatic cancer |
| Race/Ethnicity | Varies with race and ancestral origin | Risk of developing the diseases is higher in African American than Whites. Ashkenazi Jews and Eastern Europeans also have an increased risk |
| Obesity | Unsure | Increased risk with very obese individuals |
| Lack of Physical Exercise | Unsure | Lack of exercise is suggested to be linked to several other risk factors, which in turn, could likely increase the risk of developing pancreatic cancer |
| Diabetes | Unsure | This factor is still under investigation and not fully confirmed by all researchers, however, type 2 diabetes have been linked with pancreatic cancer |
| Chronic Pancreatitis | 40%-75% lifetime risk | This factor is believed to be due to an inherited gene leading to a long term inflammation of the pancreas |
| Cirrhosis of the Liver | Unsure | Due to liver damage leading to elevated risk |
| Occupational Exposure | Unsure | Findings have not conclusively proven this risk |
| Stomach Problem | Unsure | Problems such as, gastrectomy and cholecystectomy pose a higher risk |
| Diet | Unsure | Diet high in fat and red meat may increase risk, while diet high in fruits and vegetables may reduce risk |
| Coffee | Unsure | Findings are not consistent, still questionable |
| Alcohol | Unsure | Findings are not consistent, still questionable |

Diabetes mellitus is another risk factor that has been positively associated with pancreatic cancer[55] and family history of diabetes has also been shown to increase the risk of pancreatic cancer. The most palpable risk factors are smoking, family history and genetic syndromes because findings on the correlation between these factors and pancreatic cancer, including other types of cancer, have also been consistent. Cigarette smoking, cigars, and even electronic cigarette are believed to contain carcinogens that can enter the blood stream and travel to organs, such as the pancreas and result in the development of cancerous tumors. Family history which is an indication of a genetic inheritance or disorder is one risk factor that significantly increases the risk of developing pancreatic cancer[56] particularly if smoking is involved[57]. 10% of pancreatic cancer is due to inherited predisposition like individuals with more than 3 first-degree close relative with diagnosis of the disease. For example, former president, Jimmy Carter, in a statement to Lustgarten foundation, said, "it killed my father…it killed my brother and both of my sisters, pancreatic cancer killed them all[25]" Unlike President Jimmy Carter, all were smokers and smoking is known to be one of the highest risk factor associated with pancreatic cancer. Family history and genetics are increasingly more important and obvious in predicting a disease. Family history and genetic markers hold a vital role in the detection of pancreatic cancer. Researchers are studying the genes and genetic mutations in families in whom pancreatic cancer appears in one generation after another. Studies on families such as former president Jimmy Carter who has a 56-fold greater chance of developing pancreatic cancer[25] could lead researchers in the right direction in identifying the disease at an early stage.

*2.1.4 Types of Genes that could cause Pancreatic Cancer*

Several genes linked with other types of cancer and genetic syndromes are under investigation and believed to be responsible for pancreatic cancer. Pancreatic cancer has a genetic predisposition about it and 10% of pancreatic adenocarcinomas have a genetic origin[58]. The cause of the genetic mutations of these genes, the reason why they begin to send the wrong message is still unknown. Some researchers believe that environmental factors, such as smoking can contribute to genetic mutations but this has not been fully confirmed and more studies are being conducted to discover a reason. The ability to inhibit gene mutation may give rise to a cure for cancer and other diseases.

Some of the genes under investigation are *BRCA-II*[25,59–61] gene linked to breast and ovarian cancer, *p16, p53, DPC4, STK11/LKB1, PRSS1, SPINK1, CDKN2A, APC, PALB2-*, and *ATM*-genes. Some of these genes are suspected to contribute to familial pancreatic cancer[61], however some studies show that familial pancreatic cancer genes are unknown[59]. A number of mutations have been known to cause pancreatic cancer, namely; *KRAS, CDKN2A, TP53*, and *SMAD4/DPC4*[17,57,62]. These are germline mutations that are passed on from one generation to the other. Also, oncogenes for pancreatic cancer have been identified to include, *KRAS, Notch, Cox-2, activated NF-kB, Akt-2, Myb, Src, Bcl-6, S100P,* and *cyclin D1*[19]. *KRAS* mutation is found in almost 100% of all pancreatic adenocarcinomas. *KRAS* is an abnormal protein found in the cells of almost all patients diagnosed with pancreatic cancer and this is true even when there is no familial history. In 2006, *palladin,* a protein was identified as a pancreatic cancer mutant in some families[57]. *Palladin* was overexpressed in both sporadic and hereditary pancreatic cancer development but the reason for the overexpression is unknown. Additionally, *NAC-1,* a

recently discovered cancer-recurring gene was identified. Because of the difficulty in treating pancreatic cancer in patients, recurrence of pancreatic cancer is high and most patients would eventually die from the disease. This has prompted researchers on finding out the most effective therapies and ways to reduce recurrence, hence the discovery of *NAC-1*. Studies are currently being done to learn more about *NAC-1*[63] and to discover its molecular foundation. Studies are also focusing on the cell function and drug resistance component of pancreatic cancer because pancreatic adenocarcinoma is still the most resistant to chemotherapy than any other type of cancer. Genes such as *LEPR*, leptin receptors may be valuable therapeutic targets for pancreatic cancer cells because studies have found that over-expression of hypoxia inducible factor 1-alpha (HIF-1α) and hypoxia increases the expression of *Ob-R*, a receptor for leptin in pancreatic cancer cells[64]. These receptors are adipocyte-specific hormones that carry out a series of functions including regulation of body weight. Hence mutation of this gene is associated with obesity and pituitary malfunction. In addition, alterations in microRNA expression are believed to be contributory factor in the development and progression of cancer in general. Pancreatic cancer has several microRNAs namely; miR-21, miR-34, miR-155, and miR-200 that are believed to be overexpressed, thus, contributing to its neoplastic progression[65]. As a result, some researchers believe that microRNAs could be used as biomarkers to detect the presence of pancreatic cancer in human plasma.

### *2.1.5 Clinical Significance*

The clinical significance of the epidemiology of pancreatic cancer is the use of the knowledge about the risk factors associated with pancreatic cancer conducting further

research and in finding new novel techniques for detecting pancreatic cancer. For example, without the knowledge on risk factors of pancreatic cancer it would be impossible to develop a reliable CDSS like the one proposed in this study. Age group, type of race or ethnicity, diet, smoking, gender type, alcohol, chronic pancreatitis, diabetes, family history, genetic syndromes, and obesity are some of the factors believed to increase the risk of developing pancreatic cancer. Studies have shown that the disease is more common in individuals 55 years and older. Pancreatic cancer is also higher in African Americans, Ashkenazi Jews and those from Eastern Europe[51]. 10% - 15% of all pancreatic cancer is related to genetic inheritance[66–68]. Those with close family members with a genetic mutation have a 40%-70% risk of developing the disease compared to an individual with no obvious risk with a 0.01% chance of developing the disease[69]. The biggest risk factor is smoking with about 40% of all diagnoses associated to smoking[68]. Pancreatic cancer is also more common in males than females[26]. There may be a synergistic effect of smoking and family history towards developing pancreatic cancer[57] and it is important to know that patients with lung cancer have an elevated risk because both lung cancer and pancreatic cancer are associated with smoking. All these information, together with the visceral reaction of the patient, and the expertise of the clinicians could reduce the delay in diagnosis, which may mean the difference between those resectable cases and unresectable cases. As earlier stated, surgery has the highest chance of survival of pancreatic cancer; however, only diagnosis in the early stage (tumors localized to the pancreas) can be operated on.

## 2.2 Pathology of Pancreatic Cancer

This section is a review of literature on the role of genetic mutation in pancreatic cancer development, the pathogenesis of pancreatic cancer cells, the blood markers known to aid in the detection of pancreatic cancer in patients and significant findings as it relates to early diagnosis and management of the disease.

### *2.2.1 Biological Role of Genetic Mutation in Pancreatic Cancer Development*

Pancreatic cancer has a strong correlation to inherited gene mutations which is often displayed in familial pancreatic cancer. Without mutation of such genes and other factors yet to be identified, pancreatic cancer and other forms of cancer may never develop. The challenge is, understanding the biological role of the mutations, why they occur, how to prevent its malfunction, and how to immediately identify the mutation before it results in a malignant tumor or any other tumor for that matter. What is known is that, normal genes undergo mutations that result in oncogenes and these oncogenes are those genes that could cause cancer. In addition, mutations of tumor suppressor genes also play a role in cancer development because these genes become inactivated or deleted[17]. They result in inability to suppress and prevent the development and activation of oncogenes, thus rapid abnormal cell division. The four genes most commonly associated with the development of pancreatic cancer are; *KRAS2, CDKN2A, TP53* and *SMAD4*, of these, *KRAS* is the most studied. The transformation of normal cells to carcinomas follow a PanIN-3 pathway and *KRAS* mutations are an early event in the pathway, followed by inactivating mutations in *CDKN2A*, while *TP53* and *SMAD4* alterations occur somewhat later during the pathway[17]. The study of gene mutation and the affected cells that lead to the tumors in the pancreas have provided little insight into

early diagnosis of the disease. Several studies have shown that pancreatic adenocarcinoma originates from ductal epithelial cells in the pancreas. This is the most common source for the development of pancreatic cancer, but the reason for this is not yet understood.

An experimental study on the human duct epithelial cell (HDPE) model for *KRAS* transformation using mice injected with HPDE-KRAS cells to study the tumorigenicity of this pancreatic oncogene was aimed in identifying the biological role of *KRAS* oncogene in duct cell carcinogenesis[70]. They developed an in vitro model for *KRAS* transformation using near-normal HPV-16E6E7-immortalized human pancreatic ductal epithelial (HPDE-E6E7) cells to create a means of looking further into the molecular and cellular mechanisms of human pancreatic duct cells carcinogenesis. It is believed that 95% of pancreatic adenocarcinomas also known as ductal adenocarcinomas result from mutations on *KRAS* genes that occur early during pancreatic duct cell carcinogenesis. *KRAS* mutations are some of the most studied oncogenes of pancreatic cancer, although, functional role of *KRAS* mutations in the malignant formation from normal pancreatic duct epithelial cells remain unknown[21]. This experimental study concluded that *KRAS* oncogenes manifest weak oncogenic activity in HPV16-E6E7-immortalized HPDE cells and only 50% of the animals implanted developed tumors. They also concluded that the model is not suitable for studying the transforming activity of *KRAS* oncogene alone in HPDE cells. Other studies on tumor suppressor genes and the reason for the mutation of normal genes (pro-oncogenes) have also been carried out but none has been able to find a technique for early diagnosis of pancreatic cancer. Approximately 50-70% of pancreatic adenocarcinoma diagnoses are associated with inactivated p53, a tumor suppressor gene

that undergoes mutation and unable to carry out its normal function of DNA repair and the control of apoptosis[13]. Even with this knowledge, it is still unclear what role p53 plays in the survival of pancreatic cancer because the prognostic implications of overexpression of this gene is unknown. Consequently, studies have not been consistent in their findings about the correlation of p53 and survival[13]. Some studies have found complex biological roles in controlling the fate of the cell division process that lead to cancer by suggesting that survivin, a member of the family of apoptosis inhibitor have demonstrated prognostic values[71,72], however, other studies have produced conflicting results[35]. Other than the mutations and cell origin, pancreatic cancer tumors have distinct complex biological features from many other types of cancer[23], and this is a promising factor in finding answers to pathological questions about the disease, and some day lead to an effective method for early detection of the disease.

### *2.2.2 Pathogenesis of Pancreatic Cancer*

The Pathogenesis of pancreatic cancer is an area that has been widely studied with consistent findings. The knowledge about the origin, development and resultant effects of pancreatic cancer emerged from epidemiological and genetic studies. The biochemical and cellular events resulting from the genetic mutations of certain genes can lead to a gene expression that results in lesions and its progression in the pancreatic duct can resulting in pancreatic intraepithelial neoplasia (PanIN). PanIN are pancreatic cancer that begins in the pancreatic duct. PanIN are microscopic papillary or flat, non-invasive epithelial neoplasms that come from smaller pancreatic ducts. PanIN have columnar to cuboidal cells with different amounts of mucin. They are distinguishable from IPMTs

based on their size because they tend to be <5mm while IPMTs are > 1cm with occasional exceptions[18]. As earlier stated, it is believed that, pancreatic adenocarcinoma are PanIN while IPMTs are not. The mutation that leads to pancreatic cancer occurs in a progressive PanIN stage but its events are unknown. According to Chang et.al, majority of pancreatic cancer are believed to have developed from a series of hyperplastic and dysplastic ductal lesions also known as PanIN. Each type of pancreatic cancer has its own histological features and mutations. Genetic progression model of pancreatic adenocarcinoma show progressive stages of neoplastic growth with majority of the chromosome with telomere attrition (loss of function). According to Bardeesy et al, studies have shown that telomere dysfunction is an early step in the pathogenic process of pancreatic cancer, however, other studies have shown the length of telomeres have been shortened by tumors and also revealed that the activation of telomerase is a late event[17]. What is known is pancreatic cancer develops progressively through a multistage event that can be defined histopathologically by the origin of lesions in the duct as shown in figure 2.1 and 2.2.

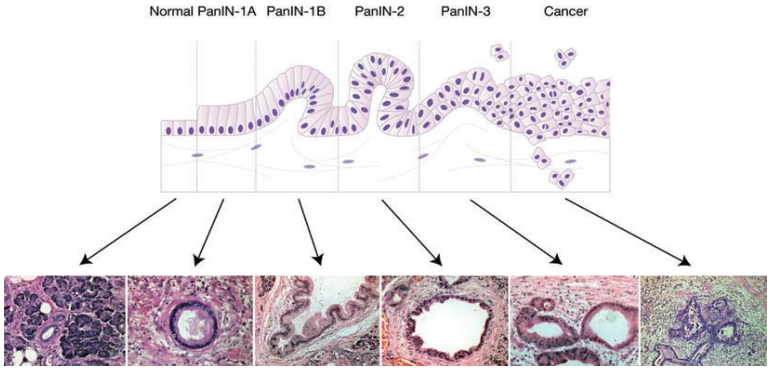



**Figure 2.1: Transformation of Normal Cells to Pancreatic Cancer Cells.** Image from Chang DK et.al. 2008**.** This figure shows the gradual transformation of normal cells in the pancreas to malignant cells. The process passes through a PanIN stage 1, 2 and 3 before becoming malignant.

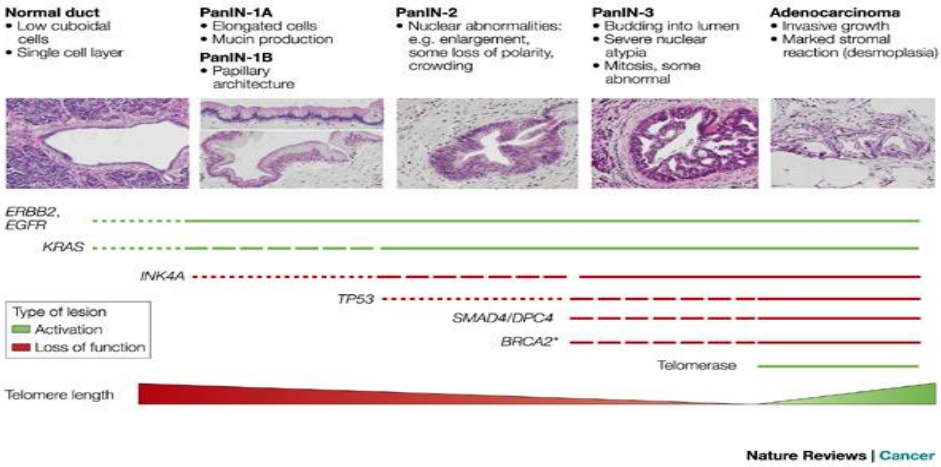



**Figure 2.2: The Progression of Normal Cell to Pancreatic Adenocarcinoma.** Image from Bardeesy NRA, DePinho R, 2002**.** Figure 2.2 shows the morphological changes of normal cells to PanIN and eventually to cancer cells. This image includes the stage at which certain genes undergo mutation to become active or to lose their normal functions.

Studies and review by researchers and scientists are focused on finding more about the pathogenesis of pancreatic cancer at the molecular level. Studies have found that multiple subsets of genes undergo genetic changes via activation and inactivation or during the development and progression of pancreatic cancer[19]. These genetic changes

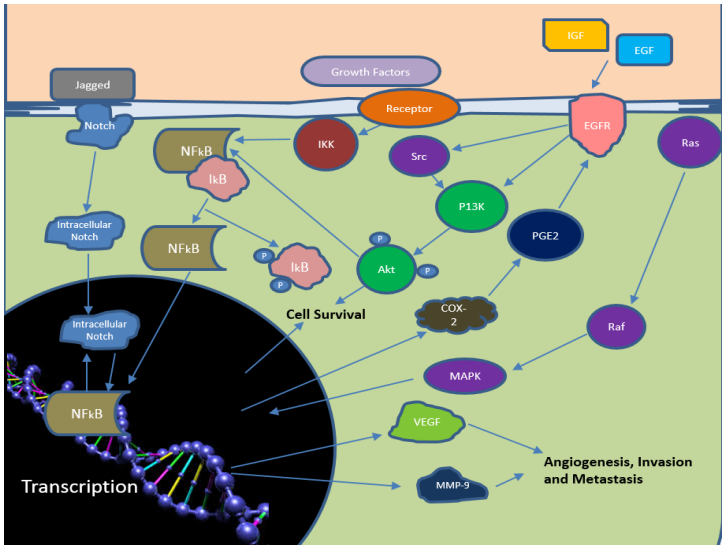



**Figure 2.3: Cell Signaling Pathways for Pancreatic Cancer**

develop as a result of the activation of oncogenes and the inactivation of tumor suppressor genes and this process is believed to be partly responsible for the initiation

and progression of pancreatic cancer[19]. Figure 2.3 below illustrates the cell signaling pathways involved in the pathogenesis of pancreatic cancer. These pathways show a connection between the oncogenes and tumor suppressor genes during the DNA transcription process. There are also other gene mutations believed to be responsible for the alteration of normal cells that become malignant in the pancreas. Some of these gene mutations are associated with other forms of cancer, including, breast cancer, lung cancer and colon cancer. With all the studies that have been carried out, findings have indicated the possibility of regulating the *KRAS* pathway for pancreatic adenocarcinoma[19]. *TGFβ* (spermatogenesis) and 15 other genes within the four signaling pathways, including Ion transport and immune phagocytosis have been identified and confirmed to have a strong correlation with pancreatic cancer survival[73], meaning, they can regulate many cellular activities including cell growth, differentiation and apoptosis.

### *2.2.3 Blood Markers for Pancreatic Cancer*

Specific blood markers for detecting pancreatic cancer have not been proven however there are indications for blood markers such as CA19-9 that may be beneficial in the detection of pancreatic cancer. CA19-9 is a carbohydrate antigen seen in blood samples of patients with pancreatic cancer and could also be seen in blood samples due to other types of cancer. However CA19-9 is not always seen in all patients with pancreatic cancer. Normal reading is between 0 and 36 but in some pancreatic cancer patients, levels could be up to 5000[51]. Other blood test could show elevated bilirubin, a bile pigment that is associated with the presence of jaundice and yellowing of the skin, a strong indication of pancreatic cancer. According to a report by the National Cancer Institute, there are no

tumor specific markers for pancreatic cancer. Even though CA19-9, a serum cancer antigen can be used, it has a low specificity and not 100% reliable. However, it can be used to monitor the effects of treatment[1]. Another serum cancer antigen is CEA (carcinoembryonic antigen) which can also be elevated in patients with pancreatic cancer.

In a study by Schwarz et al, a retrospective chart audit and review of histopathological materials were used to study pancreatic cancer tumors in patients with lung malignancies. Based on the results of the study, cytokeratin 7 (CK 7) and cytokeratin 20 (CK 20) immunohistochemistry expression can be used to aid in early diagnosis and treatment of pancreatic cancer[74] because the retrospective chart of all patients, of those with pancreatic cancer and IPMTs, 100% had a positive cytokeratin 20 (CK 20). CK 7 and CK 20 are proteins encoded by the KRT gene with an epithelial origin. Because most pancreatic cancer tumors originate from epithelial duct cells, it is believed that CK 7 and CK 20 can be used as blood markers to identify the presence of neoplasia[74,75]. In this study, those with positive CK 20 were females older than 65, so it is not known whether gender has anything to do with the positive CK 20 results and the number of participants or charts reviewed was quite small, which may be not be a true reflection of the population or of the relationship between pancreatic cancer and CK 20.

Mesothelin is another biomarker that has been around for several decades and has been shown to be expressed in other types of cancer. Mesothelin is a glycosylphosphatidylinositol-linked glycoprotein. Recently, mesothelin gained some attention in the media when a teen prodigy developed a sensor that could identify mesothelin levels in patients and used to determine the stage of pancreatic cancer diagnosis. His claims are yet to be proven by other researchers. Furthermore, other

studies have reported mesothelin as a promising target for immunotherapy for pancreatic malignancies[39,76]. Because mesothelin is not strongly expressed in normal pancreas, it makes sense to say the presence of mesothelin in a patient's sample is a good indication of pancreatic cancer cells especially in small biopsy or cytopathological samples, however some findings have concluded that mesothelin alone cannot be used for clinical diagnosis of pancreatic adenocarcinoma due to its low specificity[77]. Other types of proteins that have been studied as possible biomarkers for pancreatic cancer include, prostate stem cell antigen, fascin, 14-3-3 sigma, and S100P. Of these, research shows S100p has the strongest diagnostic characteristics when both sensitivity and specificity are considered[77]. In addition, claims have been made that the use of both S100P and mesothelin in cytological borderline cases can produce accurate diagnostic result[77].

*2.2.4 Relevant & Significant Findings*

In Feb 2007, a group of researchers at the university of Michigan Medical Center discovered a small number of cells in pancreatic cancer that are capable of fueling tumor growth and pancreatic cancer stem cells. With this discovery, researchers can now develop drugs that can target and kill those specific pancreatic cancer stem cells. In spite of this discovery, there are currently no existing drugs to increase the survival rate of patients with the disease. On the other hand, on March 3, 2014, a new report by the National Cancer Institute outlining scientific framework to address pancreatic cancer was released[78]. A new initiative to develop drugs that target *KRAS* has been established. *KRAS* is a mutant gene present in most patients with pancreatic cancer. According to the report, there will be a program announcement for biomarkers to aid in early detection of

pancreatic cancer. This is critical in advancing research and improving pancreatic cancer patients' outcome. A national strategic plan and accountability for making progress toward improving the survival rate for pancreatic cancer will be monitored by the pancreatic cancer action network, an organization that has long advocated for progress in pancreatic cancer diagnosis and treatment. This initiative and national strategic plan are aligned with the goals and objectives of this study, hence the significance and relevance in carrying out this study.

In a recent report by Mayo clinic, researchers decoded the origin of inflammation-driven pancreatic cancer. They revealed a process by which chronic inflammation (pancreatitis) transitions into pancreatic cancer. Their goal was to enable identification of pancreatitis of patients with risk of developing pancreatic cancer and to potentially develop a drug therapy that might reverse the process. Pancreatitis can lead to pancreatic cancer when the inflammation pushes acinar cells in the pancreas to transform into duct-like cells. Mutations can occur as these cells change and reprogram themselves, and this change could result in a transition into cancer cells. According to the Mayo clinic report, Dr. Storz stated that these cells reprogram themselves and the reason though unknown, could be because they do it to avoid producing enzymes in an organ that is already injured in order to prevent further damage. The good news is that the damage is reversible and can prevent the development of pancreatic cancer[46]. A number of molecules involved in the pathway that might be targeted to reverse this process from the new duct-like cells back to acinar cells were identified[46]. This discovery can help to eliminate the risk of an individual with pancreatitis from developing pancreatic cancer. Currently, researchers are testing mice models with human pancreatic cancer for the

ability of existing drugs in the market to reverse this cellular transformation in the pancreas.

The search for genetic markers as a means of preventing and treating pancreatic cancer is of high need. The pancreas is a hard-to-reach organ that is part of the digestive system. Forty years ago, medical students learned that, if the tumor is located at the head, it means,....four months to live and if it is located at the tail, it means…six months to live[25]. This fear of dying still lingers on today with little hope of a new form of tumor that was discovered by researchers in Japan. This discovery has brought an array of hope to individuals with new diagnosis of pancreatic cancer. Its prognosis is slow-growing, less invasive, more torpid form of pancreatic tumor. It is less aggressive and often referred to IPMT (intraductal papillary mucinous tumor) or IPMN (Intraductal papillary mucinous neoplasm). The other type of pancreatic cancer that is far more aggressive and life threatening is pancreatic adenocarcinoma which accounts for approximately 95% of all pancreatic cancer diagnoses.

Since the knowledge and discovery of IPMT, the views of researchers and clinicians in the United States, Japan and other countries have varied and mostly in disagreement about how to treat these tumors. Even though these tumors are thought to be slow-growing and less life threatening, the conflict about removing them surgically or left alone and carefully watched is still under debate. In the case of IPMTs, unfortunately there is lack of evidence as to how long IPMTs behave benign or remain less invasive before they become life threatening. Even with this knowledge, some surgeons recommend a prophylactic medical approach, namely, Whipple surgery be performed. Whipple surgery could be performed to remove IPMT but some cytologists in China,

Japan and elsewhere feel that it is unnecessary particularly on patients with IPMTs that might never become aggressive or become a problem with their health during their life time. The process involved in Whipple surgery is cutting into the bile and the pancreatic ducts, and then rejoining these two without any complications associated with leakage. However, this is difficult to achieve making the decision to perform the Whipple surgery a difficult one. Surgery presents huge risks and may not always be beneficial. If digestive enzymes (trypsin and chymotrypsin) leak into the abdominal cavity, it can lead to a series of problems by attacking the tissue that produces them. According to Perry and Servaas, a radiologist stated to them during an interview that "the pancreas is an angry organ and if all does not go well with the Whipple surgery, the pancreas can become inflamed and lead to other detrimental problems." Nevertheless, more research is needed on the history, biological behavior and progression of IPMTs[25]. So far, there is a great uncertainty and controversy about this form of pancreatic cancer.

Other areas of research and areas of concern suggested the search for genetic markers to help determine the exact type of pancreatic neoplasm an individual may have. This is one of the most active areas of research on pancreatic cancer. A diagnosis on the correct type of pancreatic cancer an individual has is essential in deciding the treatment plan and prognosis of the disease. The role of a cytologist in pancreatic cancer diagnosis plays a huge role in determining the type of cancer cells and staging of the disease. The cytologist is responsible for performing tests on a sample of pancreatic juice or tissue obtained from a mucinous tumor. A sample of mucin from a pancreatic cyst is obtained using an endoscopic ultrasound and a fine needle aspiration. Mucins are glycosylated proteins produced by epithelial tissues. They are part of the lining of certain internal

organs and skin, and they produce mucin, the main component of mucus. Overexpression of the mucin protein is often associated with many forms of cancer, especially the MUC 1 type[25,79]. These can lead to mucinous carcinomas which is a type of cancer that results from the epithelial cells. Pancreatic adenocarcinomas often cause increased mucin production[43]. MUC 1 and MUC 4 are two membrane mucins that have been extensively studied as regard to their pathological implications in pancreatic cancer disease process. In conducting a test for pancreatic cancer, a biopsy of the tissue might miss some areas where the cancer cells exist, thus, leading to a false negative result but a fine needle aspiration of a fluid mucinous cyst is a good sample that is more reliable in detecting cancer cells. The clinical significance in using mucin rather than tissue is the higher reliability factor[25].

Understand the biology of pancreatic cancer may lead to advances in the pathological classification and pancreatic cancer genetics. According to Bardeesy et al, "how can information and technological advances be integrated to create a roadmap for an improved understanding of pancreatic cancer biology and how might such systems lead to more effective treatments?" Since the biology and pathogenesis of pancreatic cancer are not exactly understood, the next best thing will be a systematic approach for early detection. On the other hand, there is a dire need for targeted therapeutic strategies and treatment for pancreatic cancer[19]. The current mortality rate and survival rate is a representation of the ineffective technique for early detection and ineffective treatment methods including those pancreatic neoplasia that are resectable.

## 2.3 Current Imaging Technologies for Pancreatic Cancer Diagnosis

There are several types of imaging used in detecting tumors but the most commonly used imaging for pancreatic cancer diagnosis are, endoscopic ultrasound (EUS), magnetic resonance imaging (MRI) and computed tomography (CT). EUS can be combined with endoscopic retrograde cholangiopancreatography (ERCP) to increase its diagnostic results[80] and MRI can also be combined with magnetic resonance cholangiopancreatography (MRCP)[44] for the same reason as ERCP. To perform a pre-surgical biopsy, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is mostly used to obtain samples from suspected abnormalities in the pancreas. EUS-FNA is the most effective and least invasive method used in aspirating samples for biopsy[81].

Because of the location of the pancreas, current imaging technologies have some difficulties in scanning the pancreas[24]. A study conducted to determine the effectiveness of imaging technologies for pancreatic cancer diagnosis showed, CT detected sub centimeter cyst in 11% of high risk individuals with pancreatic lesion, MRI detected 33% and EUS detected 36%[82]. Other studies have also shown that EUS and MRI are better in screening for pancreatic lesions than CT[82]. EUS is the most invasive but also the most sensitive imaging technology because of the high resolution of image[83] it produces. Unlike CT and MRI, EUS can detect small lesions, $< 1$cm in diameter[84]. Even though EUS is the most recommended and has played outstanding role in the diagnosis of pancreatic cancer over the past three decades, limitations exist. The expertise and skills of an endosonographer can make a significant difference in the diagnostic yield of EUS, although, even with an experienced endosonographer false negative rates of EUS guided FNA are extremely high in some clinical establishments[85]. Furthermore, under-diagnosis

or over-diagnosis of pancreatic cancer[84] continues to occur. Another problem with the use of EUS is the difficulty in differentiating between a malignant lesion and inflammation due to chronic pancreatitis. Chronic pancreatitis is believed to increase the chances of developing pancreatic cancer. The appearance of inflammatory changes due to chronic pancreatitis and an actual pancreatic lesion is similar[85] which may be the reason some endosonographers report false-negative or false-positive results. With this knowledge, a second opinion is highly recommended, however prolonging and delaying diagnosis is not recommended because pancreatic cancer can be very aggressive and problematic.

Some researchers suggest imaging surveillance for high risk individuals to increase the survival of pancreatic cancer but others disagree and believe the risks and challenges out way the benefits. The belief that imaging surveillance will reduce advanced stage diagnoses is yet to be proven. In addition, the best approach for pancreatic cancer screening is not yet known, although some studies have reported frequent screening of asymptomatic high-risk-individuals resulted in the detection of small pancreatic cysts, including high-grade malignancies, and non-invasive and curable lesions. Currently, there is still insufficient evidence to recommend imaging surveillance of high risk individuals unless in clinical settings where the possibility of screening and its effectiveness can be evaluated.

### 2.4 Clinical Decision Support Systems

The use of clinical decision support systems (CDSS) is yet to be a fully adopted system in many clinical settings even though it has been around for over 30 years. CDSS is a type of medical informatics, a system that could aid clinicians in their decision-

making process not to take over their knowledge and expertise, but to increase their probability of making the best decision at the point-of-care for their patients. The purpose of a CDSS is to utilize the most relevant data in a patient's entire medical record and to use that information to produce new information to aid in the decision-making process. CDSS can be divided into three parts, namely; alert system, inference and reasoning mechanisms, and communication mechanism[86]. There are two main types; the knowledge-based and the non-knowledge based. The knowledge-based system uses rules, evidence and inference engine to generate results while the non-knowledge based uses artificial intelligence (AI) also known as machine learning[86]. AI applies artificial neural networks (ANN) and genetic algorithms to generate results for the user. The functions of CDSS are administrative support, management of complex clinical data and details, cost control, and decision support. There are four factors why CDSS are relevant in the health system; 1) providing alerts/reminders automatically as part of the workflow, 2) providing the suggestion at a time and location where the decisions were being made, 3) providing actionable recommendations, 4) computerizing the entire process[87,88].

### *2.4.1 Advantages of Clinical Decision Support Systems*

Several advantages in the implementation of CDSS exist but the benefits are not widely recognized because it is yet to be a fully adopted system. Improved patient care and workflow in a health care setting are among some of the reported benefits. The intelligence of technology is ever-evolving and more advanced techniques for safety and improved patient care is being added into information systems such as the EHR, CDSS and other health informatics. The CDSS is one system that is still of limited usage

regardless of its many advantages. As a computer program, it has all the benefits in terms of, speed, ability to store a large data, its ability to generate reliable outcome based on the built-in rules and knowledge and it can be portable. Unlike humans, CDSS can hold a large memory of information without memory loss. It cannot confuse one patient for another, it cannot combine medical records of more than one patient to make a decision, it eliminates medical errors in the absence of human errors, it will not be exhausted or overwhelm to produce a wrong decision, it cannot base its decisions on feelings or instincts, or on the appearance of the patient, it has so many positive outlook and it is mainly to add to the clinician's expert decision. CDSS allows for easy communication amongst providers from any location within the organization if availability of the system is authorized in that location. Access of CDSS to providers can help with immediate knowledge of a patient's change in medical status. Information could be related to the referred specialist within the organization without delay which could be vital in the diagnostic and treatment outcome for a patient. CDSS running under the same system can also be used to communicate patient's information amongst providers in different clinical settings. CDSS can be used by authorized health care providers in a clinical setting and not limited to Physicians' access only. It can also provide alerts and reminders to impact patient care.

Many clinical trials and pilot studies related to the use of CDSS have shown positive impact in patient care and a reduction in the cost of health care[87]. One study showed that the acceptance of CDSS are influenced by four main factors; usefulness (incorporating consultation issue, professional development and patient presence), facilitating conditions (incorporating workflow, training and integration), ease of use and

trust in the knowledge base[89]. In another study testing the impact of CDSS, providers without CDSS assistance needed an average of 1 minute 39 seconds to decide on recommendations for management of abnormal findings[90]. Another study showed that CDSS has the potential to decrease malpractice payments because of its known benefits for quality and safety[91]. The overall reports about the use of CDSS are positive and recommended to improve the safety and quality of patient care through alerts, reminders[92] and decision output.

### *2.4.2 Disadvantages of Clinical Decision Support Systems*

One of the challenges in adopting CDSS in clinical settings is the cost of integrating the system into established systems and in acquiring the system. Organizations are always looking for cost-effective methods of operation and allocating finances for the acquisition of a CDSS may not be something they are willing to undertake. Although, malpractice lawsuits could be pricy, implementation of a CDSS to prevent legal litigations and improve patients' care may not be enough reason to acquire the system. Other disadvantages include the complexity of CDSS. The design is complex and requires integration of knowledge from four major areas of research, namely; medical informatics, organizational knowledge, clinical domain in understanding the decision problem and the theoretical underpinnings in extracting patient preferences[93]. The user-interface for CDSS might have some similarities with EHRs or other existing information systems but it may still be quite intimidating to some users. Clinicians may also feel the need to rely on their expertise and memory rather than using the CDSS. Other providers may not be familiar with the use of such health informatics and may feel

burdened to learn how to use the system. If CDSS are not used correctly, it may produce undesirable and inconsistent results which could also lead to medical errors and/or dysfunction of the daily operation of the organization. A study on the effectiveness of CDSS, authorized by the Agency for Healthcare Research and Quality (AHRQ), concluded that the improper use of CDSS can cause more harm than not utilizing it at all[87].

One study on the use of a CDSS for cervical cancer screening reported that the complexity of the CDSS was based on the multiple guidelines and free-test processing it uses, which increases the propensity of the system to failures. According to this study, the CDSS had accuracy of 87% with 12 types of errors. This may be due to deficiencies in the system's guideline rules[94]. Some studies report the lack of integration of CDSS with mobile devices and the minimal use of web-based interfaces[95], a trend in technology that has continued to evolve over the years. Another study reported that new generation CDSS integrated with EHRs do not affect mortality and may only have a moderate improvement in morbidity outcomes across clinical settings[96]. One of the most notable disadvantages is that most CDSS lack interoperability features[97] such as, communication and exchange of data between systems and compatibility with other systems.

Furthermore, the use of CDSS as with other health informatics can carry the risk of breaching security and protection of patients' data even with guidelines and standards set by regulating agencies such as the Health Insurance Portability and Accountability Act of 1996 (HIPAA, Title II). This act demands all HIPAA covered businesses prevent unauthorized access to "Protected Health Information" (PHI). It is impossible to guarantee 100% compliance by all authorized employees because not all employees will

remain trustworthy through their employment. On the other hand, computer hackers pose a dilemma in ensuring the security, confidentiality and protection of patients' information. Further disadvantage is that the system has no way of knowing when the wrong information is input into the system. The credibility of the results generated by the CDSS relies on the accuracy of the data entered into the system. Data entry error may occur that could lead to consequent errors with patients' care.

### *2.4.3 History and Types of Clinical Decision Support Systems*

The first introduction to medical informatics was in 1959, a proposed mathematical model for diagnosis by Ledley & Lusted in an article. Since then, many studies have led to the development of obsolete and current CDSS. CDSS have a long history in the field of oncology but none has been created specifically for the diagnosis of pancreatic cancer. A known CDSS for oncology use is ONCOCIN created in the mid-1980s. Studies on the use of CDSS for the diagnosis and management of pancreatic cancer has not been carried out yet, however studies on the use of CDSS for some health conditions have been carried out and have shown benefits in reducing medical errors and improving the overall care of patients. Even though studies have shown the use of CDSS is beneficial in reducing medical errors and the like, challenges in developing and integrating them into existing medical informatics, such as electronic health records (EHR) or electronic medical records (EMR), still remain. EHR is widely known and utilized in many clinical settings but CDSS particularly for clinical diagnosis of pancreatic cancer is not.

Table 2.4 and 2.5 both show types of CDSS that have been proposed and created.

**Table 2.4: Clinical Decision Support Systems**

| CDSS/Creator | Timeline | Type and Purpose |
|---|---|---|
| Ledley and Lusted | 1959 | A mathematical model for diagnosis |
| CASNET/Glaucoma | 1960 | Developed for the diagnosis and treatment of glaucoma |
| Homer Warner | 1961 | A mathematical model for diagnosing congenital heart disease |
| Morris Collen | 1964 | A system for automated multiphasic diagnosis |
| Howard Bleich | 1969 | A system to suggest therapy for acid-base disorders. It was the first decision support system to propose a management plan in addition to a diagnosis |
| PIP | 1970 | A system that gathered data and generated hypotheses about disease processes in patients with renal disease |
| F.T. de Dombal | 1972 | A probabilistic model to diagnose abdominal complaints |
| The Health Evaluation through Logical Programming (HELP) | 1972 | This system forms the basis of many research projects in clinical decision support |
| Micromedex | More than 40 years | A system for medication safety, health and disease management, patient education, and toxicology. It also offers iPhone and iPad apps for its drug reference guide and medication interaction checker |
| INTERNIST I (1974) | 1974 | The first decision support system to span all of internal medicine |
| MYCIN/Ted Shortliffe | 1976 | An expert system for antibiotic dosing |
| Clem McDonald | 1976 | Protocol-based computer reminders |

**Table 2.5: Clinical Decision Support Systems cont.**

| | | |
|---|---|---|
| ABEL (Acid-Base and ELectrolyte program) | 1980 | An expert system, employing causal reasoning, for the management of electrolyte and acid base derangements |
| QMR | 1980 | Designed as an electronic textbook, as an intermediate level spreadsheet for the combination and exploration of simple diagnostic concepts, and as an expert consultant program |
| PKC (problem-knowledge coupling)/Lawrence Weed | 1980s | A problem-oriented medical record and the subjective, objective, analytical, and planning (SOAP) approach to clinical progress notes |
| ONCOCIN | Mid 1980s | A rule-based medical expert system for oncology protocol management |
| Perry Miller | 1983 | Attending system for anesthesia management, the first medical critiquing system |
| DXPlain | 1987 | A web version still available today |
| Elsevier | More than 25 years | A system divided into four categories: analytics and reporting; drug reference and decision support; evidence-based guidelines, clinical content, and tools; and learning and performance management |
| Brigham Integrated Computing System (BICS)/Jonathan Teich | 1993 | Provides nearly all clinical, administrative, and financial computing services |
| Isabel | 1999 | A system that offers a Web-based checklist to help clinicians process symptoms and test results |
| DiagnosisOne | 2003 | Includes components for clinical decision support, order sets, analytics, and public health recording and surveillance |
| ProVation | 2006 | Offers evidence-based clinical content and software for care plans |
| IndiGO | 2007 | Interfaces with electronic health records (EHRs) |
| Auminence | 2010 | Uses autonomy technology to retrieve diagnoses given fndings and organizes the diagnoses by body system |

Some of the challenges with implementing CDSS is that, it has to be integrated into an organization's system and workflow but this is difficult to accomplish without investing a great deal of time and funds. The importance of the integration is that, data mining can be performed to investigate a patient's medical history together with the functions of the CDSS to produce a more reliable result. CDSS that are not integrated into existing EHRs are standalone and these have more disadvantages because they may lack interoperability and may not have all of a patient's medical data. Even though there are challenges in using CDSS, proper use of the system can make significant contributions to the prevention, diagnosis, treatment and management of illnesses in patients.

CHAPTER III

# RESEARCH METHODOLOGY

## 3.1 Overview

This research draws on dual-tiered methodological approach, namely, quantitative and quasi-experimental. The quantitative aspect comprise analyses of three years (2010, 2011 and 2012) of the Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) data and review of reported data by the American Cancer Society (ACS) and the Surveillance, Epidemiology, End Result (SEER) program of the National Cancer Institute (NCI) at the National Institutes of Health (NIH). The quasi-experimental approach includes the development of the CDSS with a simulated test to discover the possibilities of the system and to prove the research hypotheses. The architecture of the CDSS and the type of program used will be discussed. The reason for the multi-method research approach is to ensure the developed CDSS is knowledge-based, and will hold all the necessary scientific evidence and facts about pancreatic cancer. Using a knowledge-based system can increase the credibility and reliability of the results and alerts produced. The decisions suggested by the system should aid individuals in the general population and/or health care providers in their decision-making and hopefully lead to a sooner diagnosis rather than later, particularly if the diagnostic outcome happens to be pancreatic cancer.

## 3.2 Research Design

A review of literatures from 2001 to date was conducted on pancreatic cancer. Search terms included; risk assessment tools for pancreatic cancer, risk assessment

questionnaires, risk assessment test, risk factors for pancreatic cancer, case reports, pancreatic cancer, pancreatic neoplasm, cancer of the pancreas, causes of pancreatic cancer or neoplasms, treatment for pancreatic cancer, the biology of pancreatic cancer, biomarkers for pancreatic cancer, genetic mutations of pancreatic cancer, imaging technology for pancreatic cancer, computer aided detection for pancreatic cancer, the pancreas, signs and symptoms of pancreatic cancer, pancreatic cancer patients, diagnosis and prognosis of pancreatic cancer, the use of clinical decision support systems for pancreatic cancer, clinical decision support systems, early detection of pancreatic cancer, pancreatic cancer genome project, imaging surveillance in pancreatic cancer patients, current reports on pancreatic cancer and a combination of anyone of these. This search was conducted on multiple databases namely; Rutgers University Library, MEDLINE, PubMed, Google Scholar, Science Direct, Scopus, and Web of Science. After an extensive review of literatures, the need for early diagnosis of pancreatic cancer was apparent because over 80% of pancreatic cancer diagnoses occur at an advanced stage[51,98,99]. To resolve this issue, we decided to conduct more review on the use of CDSS for cancer and in particular, for pancreatic cancer. This is one area that has not been widely researched as regard to pancreatic cancer but the belief is that, it is a relevant aspect for improving clinical diagnostic and treatment for patients. The findings from the search showed a lack of articles in the use of CDSS for pancreatic cancer related issues. A search in MEDLINE for articles on “CDSS” and “pancreatic cancer” with a map term for subject headings and “English language” produced only one article but when the search term was “CDSS” and “cancer” using the same filter, 82 articles were populated.

A search of “CDSS” presented 4,808 articles. Furthermore, articles related to risk assessment test for pancreatic cancer are also few.

Analyzed data from ACS and SEER were collected and reviewed to gain knowledge about the description of the pancreatic cancer population and phenomenon, relationships and differences in groups, and the trends and change over time. The risk factors, high risk individuals and the synergistic effect of contributory factors for pancreatic cancer were all taken into consideration in the feasibility stage of the CDSS. The HCUP NIS data was analyzed to observe patterns and trends of the hospital population and to identify any new pattern for pancreatic cancer diagnosis. The NIS data is developed by Healthcare Cost and Utilization Project (HCUP) and it is the largest available all-payer inpatient health care database in the United States. The raw data collected from the NIS were analyzed using Statistical Package for the Social Sciences (SPSS), Statistical Analysis System (SAS) and Microsoft office Excel (Excel). The analyzed data corresponds with reports of preliminary studies and the current statistical reports on pancreatic cancer. After a satisfactory review of literature was conducted in addition with a review of existing analyzed data and analysis of the data from NIS, the variables & parameters, and their weighted scores were defined. The variables include patient’s age, gender, race, family history of cancer and relationship to patient, patient’s history of cancer, smoking habit, genetic syndrome, symptoms if any, and questions about other risk factors related to pancreatic cancer. Other variables are the confidence variables which provide the weighting for each variable and also assigns an alert to any variable as deemed fit by the programmer. The confidence variables include; risk factor score, recommendation to screen for pancreatic cancer, instruction to seek immediate

medical attention, and to obtain a scan of the pancreas. These variables were used to create a logical "step by step" order in the logic block of program. The logic block is where the steps for the program are created in an IF/THEN statement. There is no writing involved in this step, just a "click" and "add" in the position as determined by the programmer but in a logical IF/THEN order. Although the programming of this system is a simple IF/THEN rule, it can become complex depending on how many nodes and commands are created. Two examples of statements in the CDSS are as follows:

i. IF:
You are a smoker currently
AND: Your product type is Cigarette

THEN:
Your risk factor score: Confidence = 100
FORWARD BLOCK=**Smoking Freq**
**Smoking Freq**
IF:
You smoke more than 5 times a day

THEN:
Your risk factor score: Confidence = 100
FORWARD BLOCK=**Smoking duration**
**Smoking duration**
IF:
You have been a smoker for more than 10 years

THEN:
Your risk factor score: Confidence = 100

ii. IF:
Do you currently have any of the following symptoms? Unintended or unexplained weight loss OR Sudden onset of diabetes OR Black or tarry stool

THEN:
Your risk factor score: Confidence = 100
Seek immediate medical attention and screening for pancreatic cancer is strongly recommended, on a scale of 1-10, Confidence = 10

This CDSS had a total of 250 nodes which is equivalent to 250 statements in the logic block. Twenty-one logic blocks were created to reduce confusion and omission. The command block was created after completion of the algorithm in the logic block. The command block represents the design output of the CDSS, the questions that will be displayed and the results/alerts that will be displayed to the user. In other words, the command block tells the system what to do and what is visible to the user. In this CDSS, we want the overall risk factor score and any corresponding alert displayed to the user at the end of the risk assessment questionnaire. We also want the risk level chart with the three identified risk level; high risk score, moderate risk score and low risk score be displayed in the result view of the user-interface.

This CDSS is knowledge-based and evidence-based. Because of the urgent need of a reliable method of diagnosis, implementation of CDSS can be a first step in the right direction. This CDSS is a standalone system however, a CDSS integrated into existing EHR will provide a more valid outcome because it will have access to the entire patient data, such as; patients' demographics and medical history, family history and lifestyle habits. The CDSS was developed using the evaluation package of Exsys Corvid. Exsys Corvid is an expert system for software development that provides non-programmers a new way of building interactive web applications. To run the system, an internet connection is needed and java is also needed because the system runs on java applet. The user-interface uses the runtime page and this is where the system generates the questions and the final result page at the end of the risk assessment test. In this study, the simulated user followed steps that would be followed by a real-world user and the questions were answered as if an actual patient was present. After the questions are answered, the system

computes the total score and displays the overall score to the user, in addition to alerts as needed and the risk level chart. Due to limitations, five different weighted groups were defined and each variable was categorized in an assigned group based on the requirements gathered, the knowledge and evidence about pancreatic cancer. The weight groups are 100, 60, 30, 15, and 5 with 100 as "maximum risk" and 5 as "minimum risk." Fourteen common risk factors were used as the variables for the CDSS and within these variables, 87 parameters were defined. Each of the parameters has a weighted score and assigned into one of the five weighted groups as stated above. After an extensive review of the underlying factors and their level of risk in connection to pancreatic cancer were completed, in addition to running the system multiple times, three categories of scores were identified. These categories are namely; 1) a score greater than 500 signifies high risk, 2) a score between 250 and 500 signifies moderate risk, and 3) a score below 250 signifies low risk. For example, if the user answers yes to all of the questions believed to elevate the risk of developing pancreatic cancer, the score generated will be greater than 500. To validate the system, nine clinical case reports and 3 patient stories were used to test the CDSS. The case scenarios and results will be presented in the result chapter.

### 3.3 Development process and Architecture of the CDSS

The development of the CDSS was decided upon after a thorough review of literature and data. Figure 3.1 illustrates the design of the study. There are two phases to this system; the initial phase before the CDSS was developed and the development phase of the CDSS. The CDSS design incorporated three strategies; 1) Knowledge-based, which was created based on the clinical evidence from literatures and statistical analyses

for pancreatic cancer 2) Logic rules, which was designed using condition-action rules that represented experiential cognitive programming, and 3) Inference engine, the backbone of the CDSS that incorporates artificial intelligence to enable the CDSS think like an expert to reproduce new knowledge from the programmed knowledge.

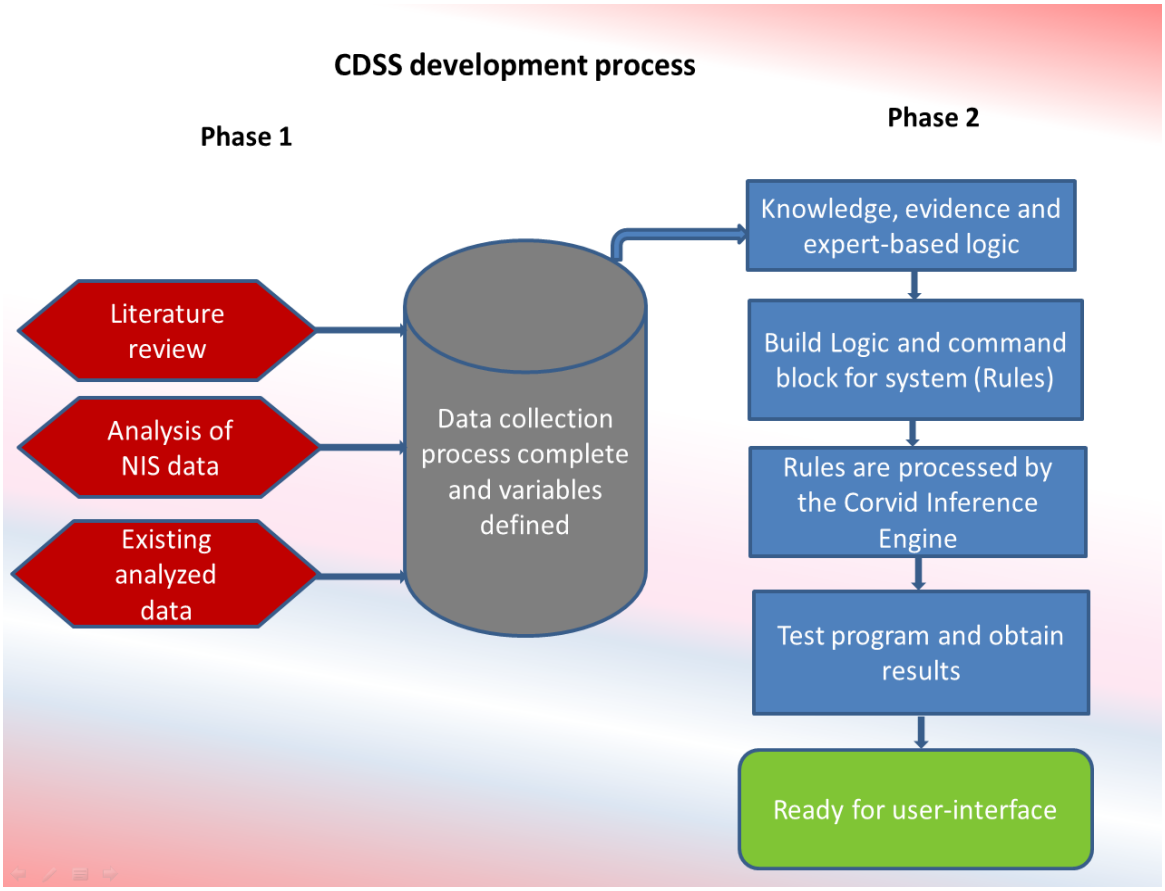



**Figure 3.1: Research Methodology**

The architecture of the developed CDSS follows a pattern as shown in figure 3.2 below. It is a knowledge-based, evidence-based system that if used in association with the knowledge and experience of a clinician, it should provide a better quality of care for patients with pancreatic cancer and high risk patients. It is a user friendly system that requires very little training. If the user is already familiar with the use of other computer programs, using this system will be even easier and not at all intimidating. The design has

simple questions that the user will have to answer. The information needed for the system may come from the individuals of the general population or health care providers. The system will analyze the given answers and provide an output at the end to the user. It is not mandatory for the user to follow the system's decision, however it is highly recommended that the user considers the CDSS' results and recommendations before deciding on a course of action. The ultimate goal is for the patient to have the best medical care, and an accurate and reliable medical diagnosis sooner than later.

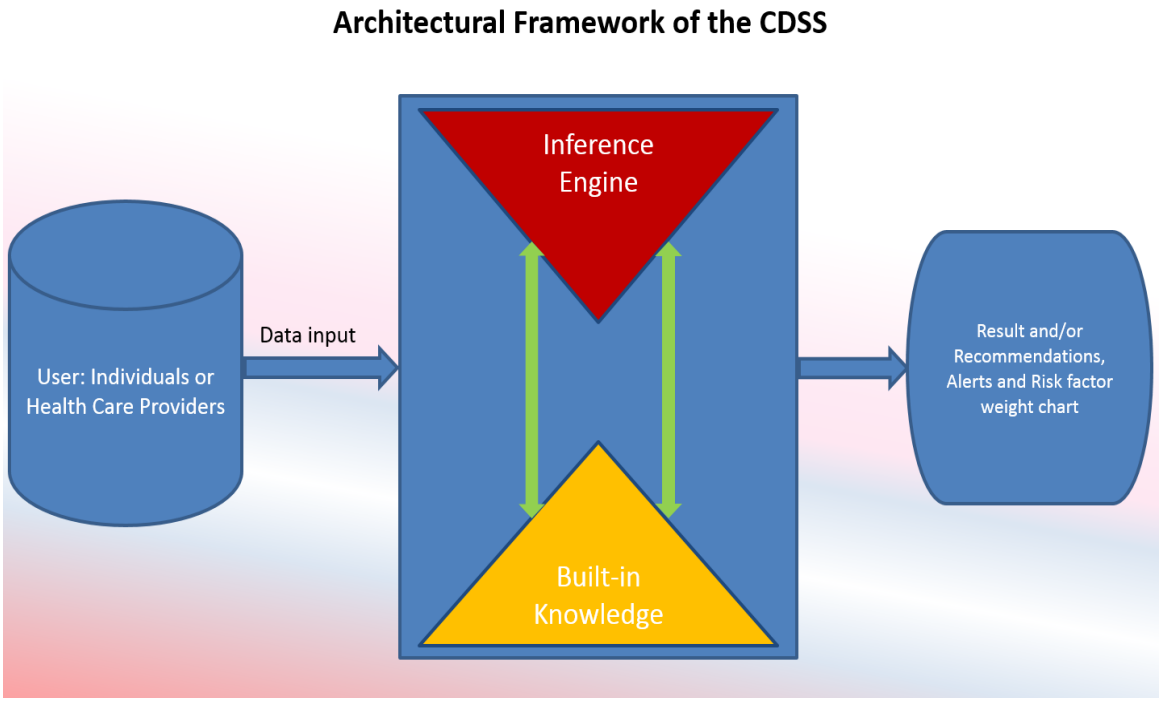



**Figure 3.2: Architecture of the CDSS**

*3.3.1 The CDSS Risk Assessment Questions*

The CDSS can be used as a risk assessment tool to identify the risk level for individuals such that earlier diagnosis of pancreatic cancer is possible. In this study, a maximum of 31 questions and a minimum of 15 questions are generated depending on

the subsequent answers provided by the user. Table 3.1 below shows the variables and parameters used including their weighted scores.

**Table 3.1: Pancreatic Cancer Risk Assessment Questions and Weights**

| Pancreatic Cancer Risk Assessment Questions with Weighted Scores Stratified into 5 groups | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Variables Used** | **Answer options** | **Parameters with a weight of 100** | **Parameters with a weight of 60** | **Parameters with a weight of 30** | **Parameters with a weight of 15** | **Parameters with a weight of 5** | **All symptoms have a weight of 100** |
| **Age** | | Age 55-84 | Age 45-54 or 85 and older | | Under age 45 | | Jaundice |
| **Gender** | | | | Males | Females | | Abdominal pain |
| **Race and Ethnicity** | | | | Blacks | All other Race | | Back pain |
| **Personal History of Cancer** | Yes | Pancreatic cancer, Lung cancer or more than one type | Breast, colon and all other type of cancer | | | | Weight loss and poor appetite |
| | No | | | | | No | Digestive problems |
| **Family History of Cancer** | Yes, type, number of family members and relationship to the individual | Father, Mother, sibling, Aunty and Uncle, Nephew and Niece, Grand parents and Great grand parents | Children and 1st cousins | 2nd cousins, other distant relatives and unsure | | | Gall bladder enlargement |
| | | Three or more family members | Two members | One member | | | Blood clot or fatty tissue abnormalities |
| | | Pancreatic, lung cancer, more than one type | Breast, colon and all other type of cancer | | | | Sudden onset of diabetes |
| | No | | | | | No | Stomach ulcers |
| **Genetic syndrome or known inherited gene** | Yes | Yes | | | | | Black or tarry stool |
| | No | | | | | No | Anemia |
| **Smoking Habit and History** | Currently | Cigarette, cigars and tobacco smokers | Electronic cigarette or Smokeless tobacco and all other smokers | | | | Diarrhea |
| | | Smoking more than 5 times a day and less than 5 times a day | Smoking once or twice a week | Smoking once or twice a month | | | Malnutrition |
| | | Smoker for more than 10 years | Smoker for less than 10 years | Smoker for less than 1 year | | | Red rash with swelling and blisters |
| | Previously | | Quit smoking less than one year ago | Quit smoking less than ten years ago | Quit smoking more than ten years ago | | Itchy skin, palms and sole of feet |
| | Never | | | | | Never | Flushing (skin turning red with a warm feeling) |
| **Diabetes Mellitus** | | | More than 30 years or 10 to 29 years | 1 to 9 years | Less than one year | | Two or more of the above but weight score will be 200 |
| **Obesity** | Age at onset and how much overweight? | | More than 300lbs overweight or 100 to 299lbs overweight | 50 to 99lbs overweight | Less than 50lbs overweight | | |
| | | | Before age 19 or between age 20 and 29 | Between age 30 and 54 | Between age 55 and 64 | 65 and older | |
| **Chronic Pancreatitis** | | More than 30 years or 10 to 29 years | 1 to 9 years or less than one year | | | | |
| **Cirrhosis of the Liver** | | | More than 30 years or 10 to 29 years | 1 to 9 years | Less than one year | | |
| **Occupational Exposure** | | | More than 30 years or 10 to 29 years | 1 to 9 years | Less than one year | | |
| **Stomach Problems** | | | More than 30 years or 10 to 29 years | 1 to 9 years | Less than one year | | |
| **Alcohol** | Yes | | More than 30 years or 10 to 29 years | 1 to 9 years | Less than one year | | |
| | | | More than 5 times a day or Less than 5 times a day | Once or twice a week | Once or twice a month | Once or twice a year | |
| | Never | | | | | Never | |

The scoring chart was stratified into five groups such that each variable is assigned a group depending on its risk level and association with pancreatic cancer. The

weight groups are 100, 60, 30, 15, and 5 with 100 as “maximum risk” and 5 as “minimum risk.”

The decision to use five groups is due to limitations on the number of nodes allowed in the version of exsys Corvid software acquired. The maximum number of allowed nodes was used in creating the CDSS otherwise a more comprehensive CDSS to expand weighted scores would have been developed. Nonetheless, we believe the CDSS incorporated the most consistently reported risk factors related to pancreatic cancer, hence we expect the generated results to be reliable.

Probabilistic basis for risk factors of pancreatic cancer were used to assign each variable a weighted score. Though difficult to fully justify, cutting mathematical corners could still yield a useful system[87]. In comparing the choice of our stratified weights used with previous implemented CDSS like QMR and DXplain that used a weighted score of 1-5 for frequency of disease and 0-5 for evoking strength per disease-finding relationship[87], our confidence factor make intuitive sense which is one aspect in deciding the scores for each variable. Further manipulation of the weight scores to increase the credibility of the results is always possible. One of the challenges facing developers of CDSS is the difficulty in designing a system with all the inclusion criteria that must be assigned to each event even when all the rules of logic and probability are utilized[87]. As with humans, even with experienced clinicians, their practice contain many examples of probability using vocabularies that include; unlikely, certainly, or almost certainly in all discussions with patients[100]. For computerized systems like CDSS, they must use some form of numerical format to represent the likelihood of an event in order for the system to transform statements into conclusions[100]. Furthermore, a reference to studies that have

reported pancreatic cancer risk prediction model was made. The National Cancer Institute reported three categories of models, namely; absolute risk prediction[101], gene carrier status risk prediction model[102,103], and risk prediction models of people at high risk[104,105] and three previous studies were categorized under each model. After review of the three published studies, it was obvious that our CDSS is better considered an absolute risk prediction model.

A flow diagram as shown in figure 3.3 below shows the design and order of

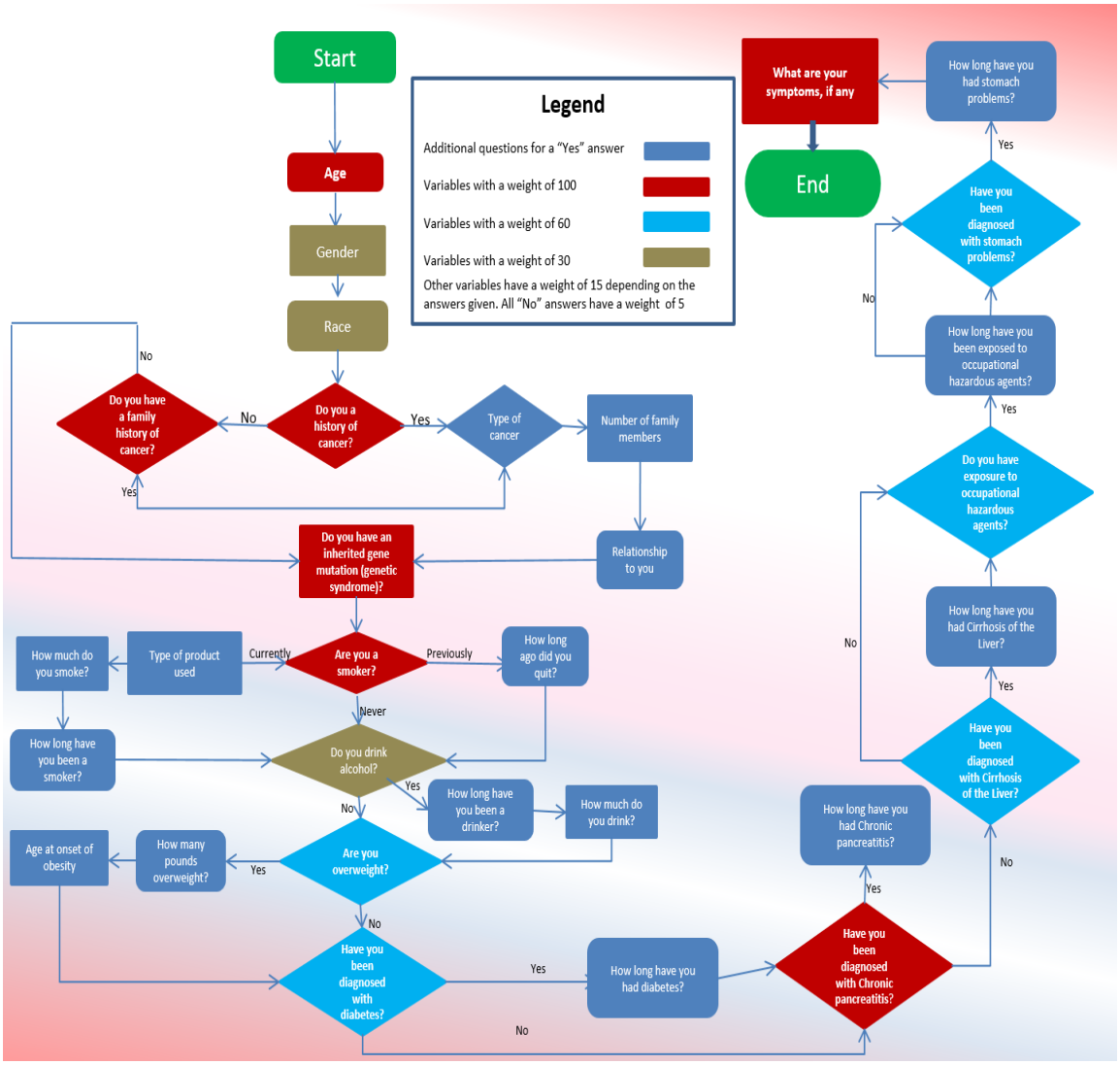



**Figure 3.3: Flow Diagram depicting the Order of Questions in the User-Interface**

questions presented by the CDSS to the user. This flow diagram is not entirely inclusive of the exact wording for all questions but it is inclusive of all potential information needed from the user from the beginning to the end. In order to identify the weighted score, a reference to table 3.1 is needed because the flow diagram did not include the weighting for each variable.

### 3.4 Research Hypotheses

It is believed that this study will provide a valid tool that can be used by individuals in the general public and healthcare providers to identify pancreatic cancer risk levels. Below is a list of the research hypotheses posed.

a. It is possible to develop a clinical decision support system that can identify high risk individuals for pancreatic cancer.
b. It is possible to design a clinical decision support system that will provide important information about pancreatic cancer to both the general public and health care providers.
c. It is possible to develop a clinical decision support system that can lead to earlier diagnosis of pancreatic cancer, reduce the number of misdiagnoses and delayed diagnoses of pancreatic cancer in patients.

### 3.5 Choice of Method

The choice of method was determined based on the need for studies on the use of CDSS as a possible means of identifying high risk individuals and for providing insight into pancreatic cancer for the general population in order that diagnosis is made sooner

than later. Since very little is known about the biology and etiology of pancreatic cancer, it is essential to conduct more research and other research design to mitigate the problem of advanced stage diagnosis of pancreatic cancer patients. This study follows a multi-method research design which is more effective than using one method or the other. The intention of choosing quantitative research method for this study is to use statistical analyses to identify the prevalence and patterns of pancreatic cancer as it relates to a broader population and to derive reasonable conclusions. The quantitative aspect of this research provided relevant information necessary in developing a knowledge-based system. The quasi-experimental aspect of this research provided the possibility of developing a CDSS and the possibility of using a well-developed CDSS to identify risk levels for pancreatic cancer.

### 3.6 Data Analyses

The data obtained from the NIS were the most recent three years, 2010, 2011 and 2012. These data were received in the form of a compressed American Standard Code for Information Interchange (ASCII) data. These data were uploaded into SPSS and converted into an active SPSS data file using the corresponding syntax. The active data set was then saved as an Excel file and a SAS file in order to be used as needed in those systems. The variables analyzed were selected based on the information of already analyzed data as reported by ACS and SEER, and the review of literature. The variables are namely; year, age, gender, race, alcohol abuse, drug abuse, chronic pancreatitis, acute pancreatitis, diabetes type I and II, and cirrhosis of the liver for pancreatic cancer patients. Pancreatic cancer was identified using the Clinical Classifications Software

(CCS) for the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). After identification of pancreatic cancer disease code, namely; 1570, 1571, 1572, 1573, 1574, 1578 and 1579, the data was reduced to include only relevant information pertaining to the interested variables and to minimize the processing time of the software output. Complex sampling of frequency distribution, descriptive statistics and measures of association were analyses performed. The output and graphs will be shown in the result chapter.

### 3.7 Limitations

Several limitations exist in conducting this study. Firstly, the software used in developing the CDSS presented multiple limitations that hindered our ability to create a more complex CDSS. In order to build a CDSS or any system that requires programming, software is needed; in this case, Exsys Corvid was used. In order to develop a well-designed CDSS with many features and capabilities, funding is necessary to acquire the appropriate software that would deliver a top notch CDSS. This study had no funds to acquire such software; hence the evaluation package of Exsys Corvid for academics was used. The evaluation package comes with limited privileges and inadequate technical support services. In this package, only a limited number of nodes (steps), precisely 250 nodes are allowed in the logic block. The limited number of nodes is the reason we decided five weight groups rather than more, which would have given us more room to design a CDSS with better precision. At the first attempt in building the CDSS, the limitation on the number of nodes was not notable until more than 1,000 nodes were created, thus resulting in the deletion of the entire logic block and rebuilding of the block

because, 1) the software has no “copy and paste” in the logic block section and 2) deleting more than 750 nodes individually was more time-consuming than deleting the entire logic block.

Secondly, there was more or less a “trial and error” type of challenge during the installation of the software. Initially, there were some software incompatibility issues with installing a working program on the computer. The Exsys Corvid system has specifications and requirements that were not compatible with certain versions of java. The developed CDSS runs on java so it was difficult to identify which version of java worked particularly because certain versions of java are incompatible with certain operating systems. We utilized both Windows 7 and Windows 8.1 until we were able to get both to work, however somewhere down the line, Windows 7 went through an automatic update and prevented the software from working properly. Windows 8.1 worked properly after a series of installation, uninstallation and re-installation of both java and Exsys Corvid and continued to do so during the course of this study.

Thirdly, finding clinical case reports that included all the information needed to run the CDSS was a challenge. We went through over 30 case reports and pancreatic cancer patients’ stories but none included all the information needed to answer the entire risk assessment questions in the CDSS.

Fourthly, there are no preliminary studies on developed CDSS for pancreatic cancer to use as a reference for the weighted scores used and the risk level chart used in this study. The accuracy and precision for the three groups, namely; high risk, moderate risk and low risk and their score chart cannot be fully validated because further studies

are needed to identify the cut off score for each risk level group and the precise weight for each variable.

CHAPTER IV

# RESULTS

## 4.1 Overview

This chapter will provide the findings and interpretation of the results. The results presented are graphical representations of the findings, images of data, and screen shots of the proposed CDSS. The data were derived from complex sampling of univariate statistics carried out to show the frequency distribution of race and gender of inpatients with pancreatic cancer for calendar year 2010, 2011 and 2012 of the NIS dataset, descriptive statistics for age of inpatients with pancreatic cancer and measures of association between pancreatic cancer and some health conditions. The CDSS was tested to simulate real-life users using clinical cases reports and patients' stories. The CDSS screen shots are representation of the development phase and the testing phase.

## 4.2 Data Analyses

The data below are existing analyzed data reported by the American cancer society and the surveillance, epidemiology, and end result program. Figure 4.1 shows the incidence rate of pancreatic cancer by age & sex and by age & race for calendar year 2005-2009. According to the data, the incidence rate per 100,000 persons is higher in males than females and higher in older individuals. The second data shows a higher incidence amongst African Americans than Whites. This data was adjusted to the 2000 United States standard population.

*4.2.1 A Review of Existing Data*

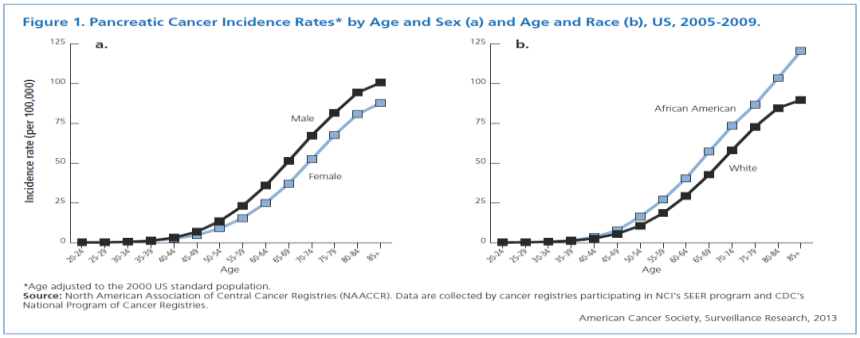



**Figure 4.1: Pancreatic Cancer Incidence Rate.** Data from American Cancer Society[106]

The data in figure 4.1 shows the rate of incidence for pancreatic cancer is higher in males than females and this may be a correlation with the smoking habits of males and females. It has been known that smoking is more common in males than females. The data to the right shows that incidence of pancreatic cancer is higher in African Americans than Whites. This may be related to the type of diet and the rate of obesity in the different groups. Obesity is higher in African Americans than Whites. The two graphs also indicate the rate of incidence of pancreatic cancer increases with age.

Figure 4.2 below is another data showing the incidence and mortality of pancreatic cancer by race and ethnicity for calendar year 2005-2009. The rate per 100,000 people in the United States shows that African Americans have the highest incidence and mortality than any other race or ethnic group. In comparing the data from the American Cancer Society with those from SEER, a consistent report was observed. Figure 4.3 below is a data from SEER showing the percent of new cases of pancreatic cancer by age. Literature supports this data that shows the chances of developing pancreatic cancer significantly increases after age 55.

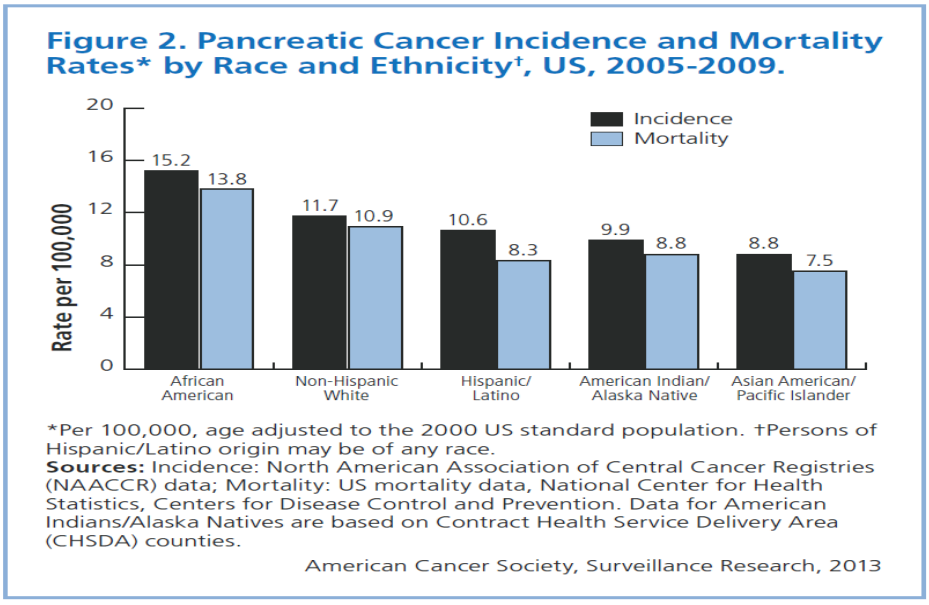



**Figure 4.2: Pancreatic Cancer Incidence and Mortality.** Data from American Cancer Society[106]

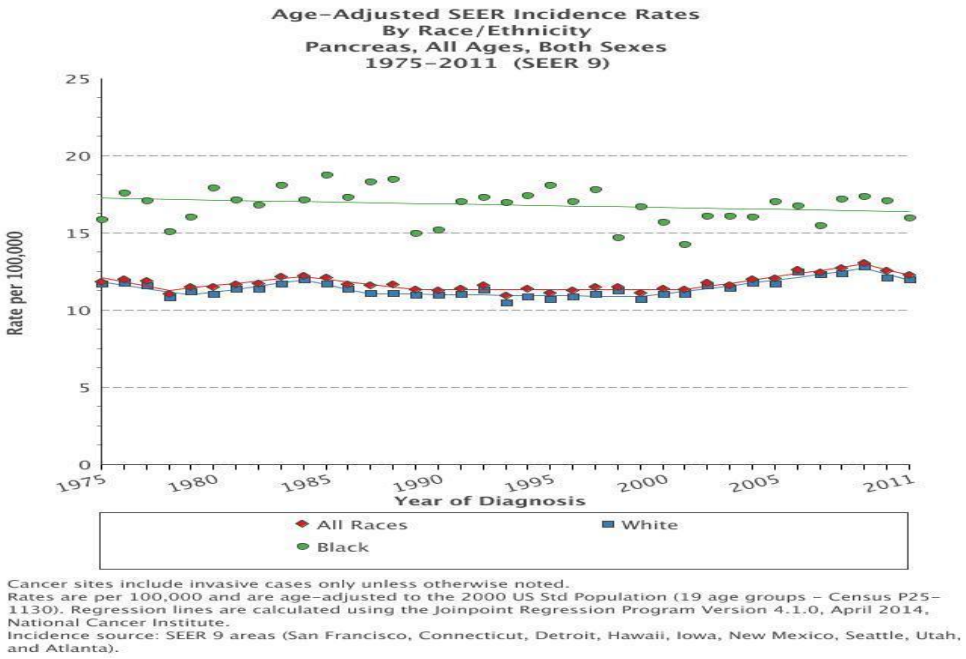



**Figure 4.3: New Cases of Pancreatic Cancer by Race/Ethnicity.** Data from SEER, NCI at NIH

Figure 4.3 shows the incidence of pancreatic cancer by race and ethnicity. The scattered plot of green clusters represents the incidence of pancreatic cancer in the black race from calendar year 1975 to 2011. This data shows that incidence is higher in blacks

than all other race group; however there is a steady decline in incidence while the incidence amongst whites and all other race/ethnic group is rising.

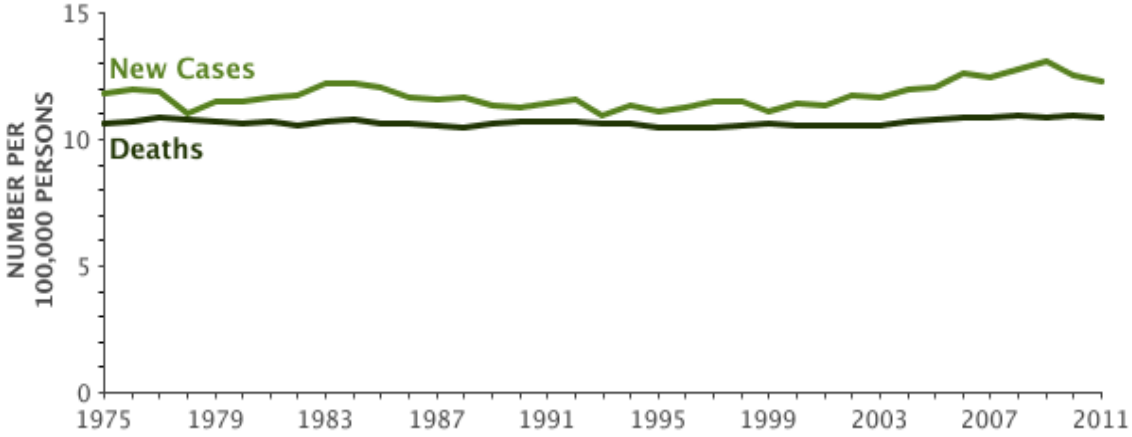



**Figure 4.4: New Cases and Deaths for Pancreatic Cancer over the Years.** Data from SEER, NCI at NIH

This data supports the findings reported in literatures about the rise of new cases of pancreatic cancer in the past two decades. The number of new cases and mortality of pancreatic cancer has gradually risen and continues to rise with no new knowledge to support this increase. Although, environmental factors and the longer lifespan as compared to previous years may be a theoretical explanation for this increase.

*4.2.2 Analyses of HCUP NIS Data*

The data below are data from the Nationwide Inpatient Sample (NIS) for 2010, 2011 and 2012. As expected the average age of pancreatic cancer patients is approximately 68 in the three years that were analyzed. This analysis is a reflection of the United States nationwide population with discharge weighting.

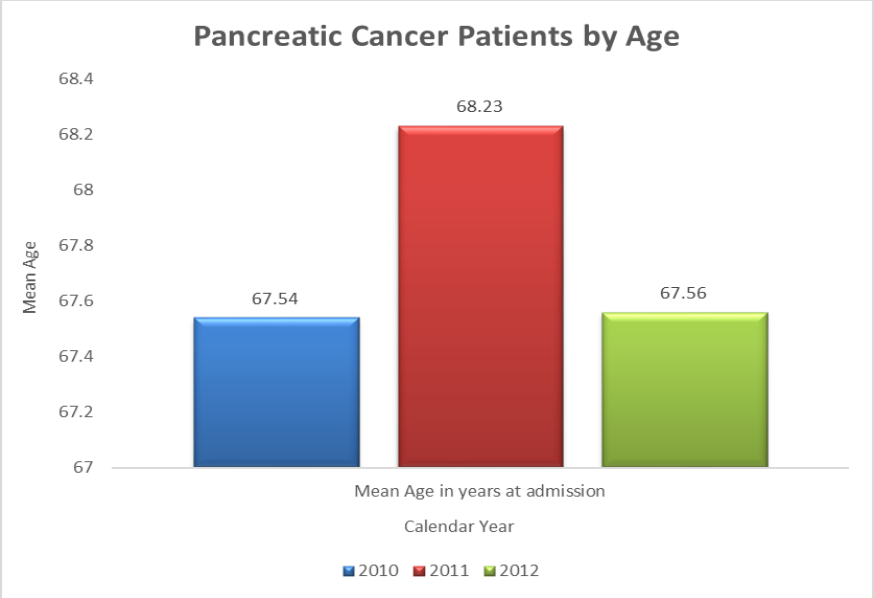



**Figure 4.5: Mean Age of Pancreatic Cancer Inpatient Sample.** This data corresponds with existing data that indicates pancreatic cancer increases with age and more common in those 55 years of age and older.

Figure 4.6 shows the breakdown of pancreatic cancer patients by race. When the ratio of the population per race was taken into consideration, the data revealed pancreatic cancer is more common in blacks than whites. The percentage of pancreatic cancer patients under the race category, "black" is higher than the national population percentage of blacks in the United States but the contrary is true for Whites. The data means that more white patients were seen but taken the ratio of the different race in the United States population; the data shows blacks have a higher inpatient rate for pancreatic cancer because the percentage of inpatients in the black race is higher than the percentage of blacks in the national population. The percentage of whites in this data is lower than the percentage of whites in the nationwide population. Examples of suspected reasons blacks are more prone to pancreatic cancer than all other race are genetic, lifestyle, and other environmental factors.

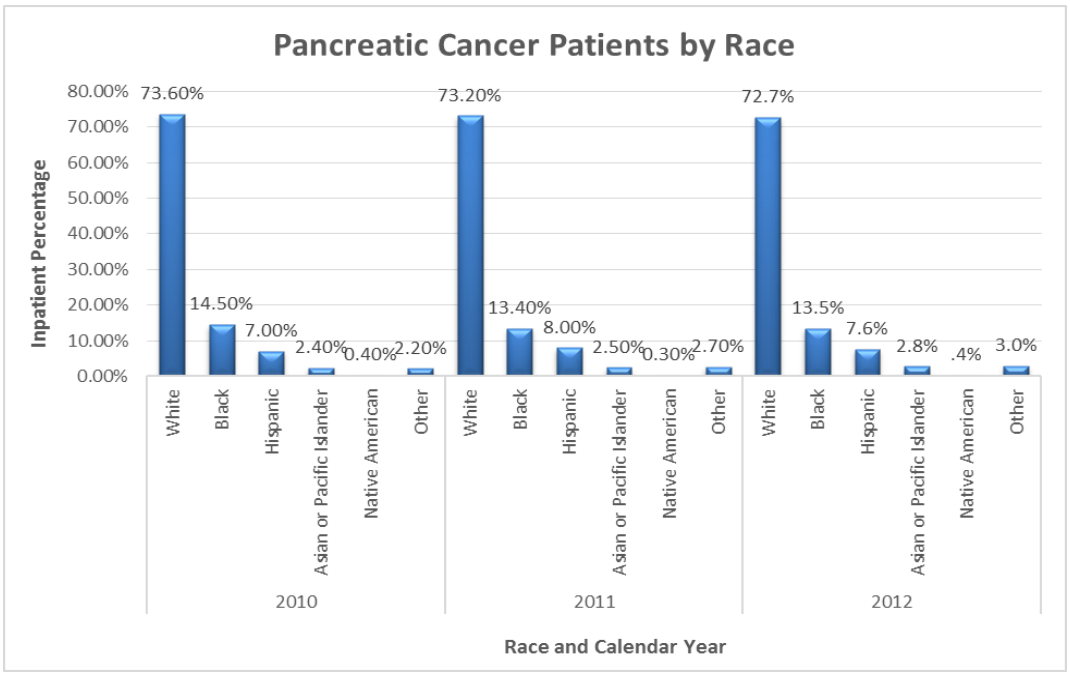



**Figure 4.6: Pancreatic Cancer Inpatient Sample by Race**

Figure 4.7 is an inpatient diagnosis for pancreatic cancer by gender. The data shows that the percentage of males admitted with pancreatic cancer is higher than females in 2010 and 2012 but for 2011, the contrary was the case. The reason for this disparity can be further explained in figure 4.8 when the confidence interval is taken into consideration.

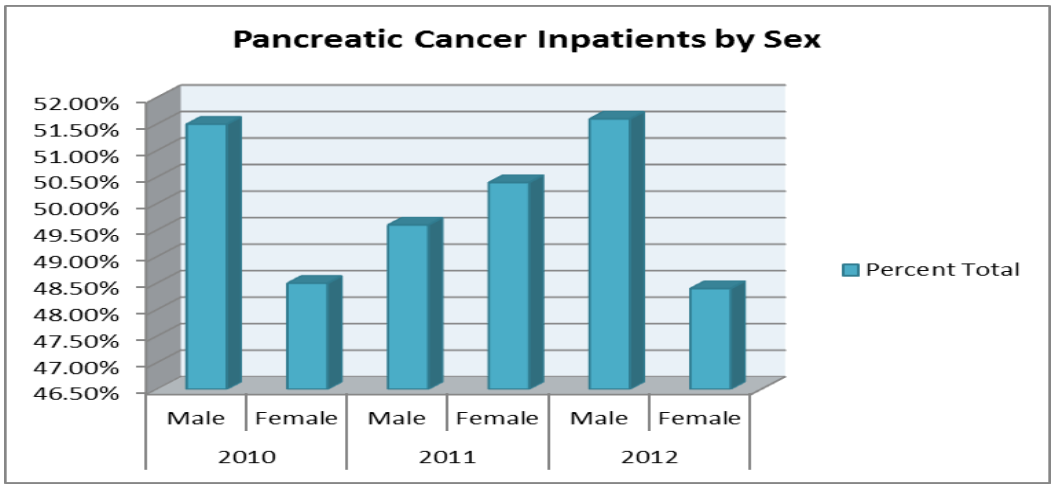



**Figure 4.7: Pancreatic Cancer Inpatient Sample by Sex**

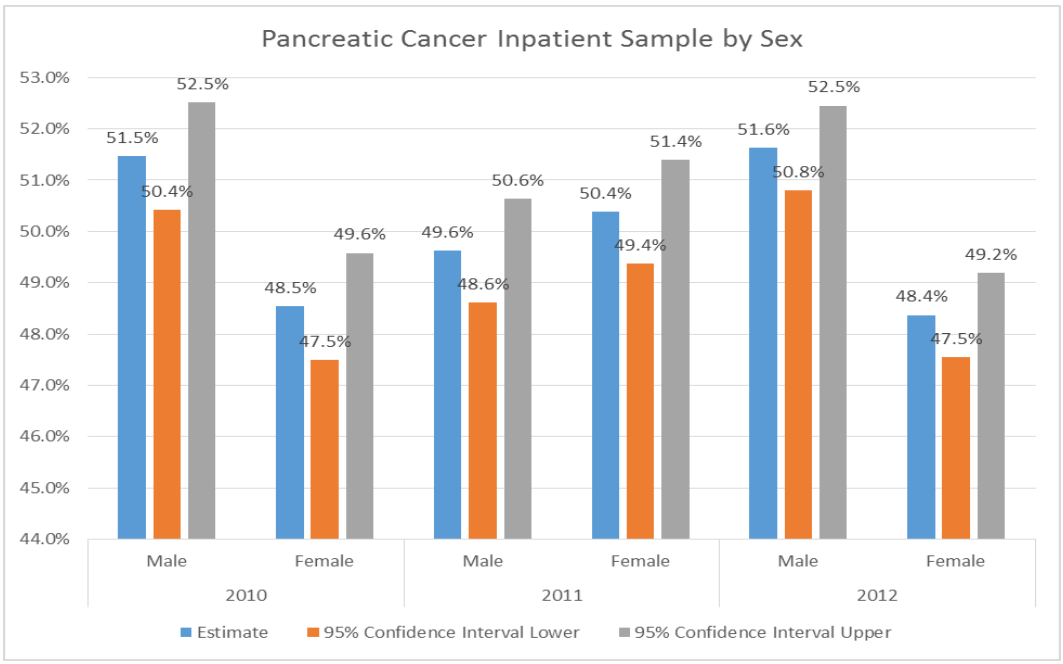



**Figure 4.8: Pancreatic Cancer Inpatient Sample by Sex with confidence Interval.** This data is the same as figure 4.7 without the confidence interval. To understand the difference in the percentage of male versus females in the three calendar years, the confidence interval provides a better explanation. 2010 and 2012 shows that males have a higher rate of admission and diagnosis for pancreatic cancer than females and in 2011, the confidence interval indicates that it is uncertain if females have a higher rate than males because both estimates lie within the lower and upper limits of the other; which means, they are likely more equal. In other words, there is no significant difference between the number of males and females.

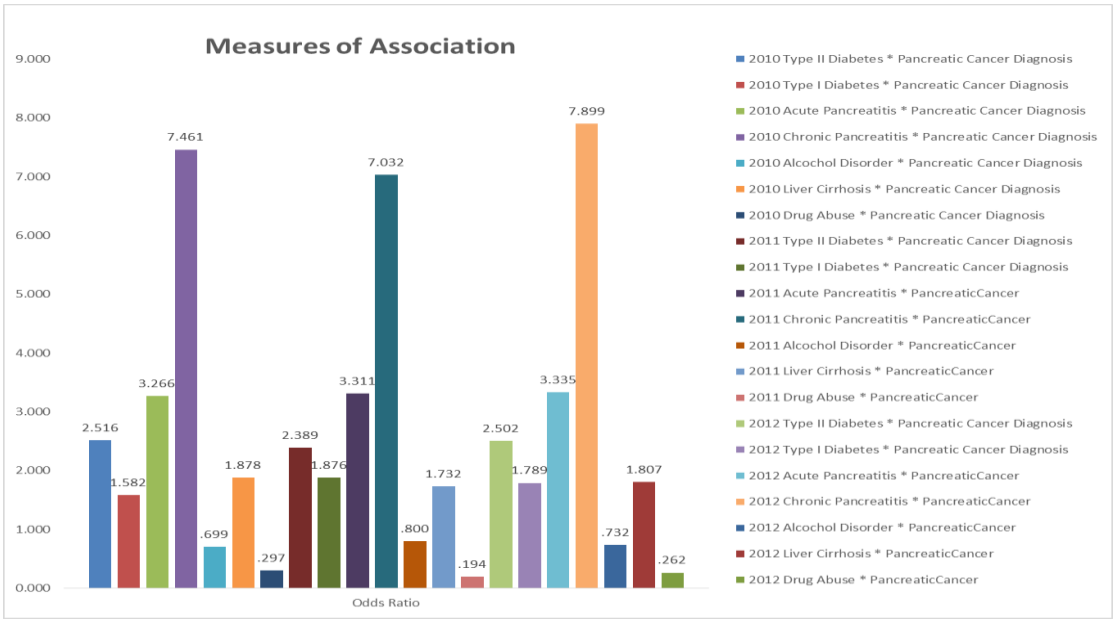



**Figure 4.9: Measures of Association of Pancreatic Cancer Diagnosis and health other conditions.** Odds Ratio > 1 means, exposure associated with higher odds of outcome, Odds Ratio = 1 means, exposure does not affect odds outcome, Odds Ratio < 1 means, exposure associated with lower odds of outcome

Figure 4.9 shows a graph of the odds ratio of several health conditions to pancreatic cancer diagnosis. This data represents the inpatient hospital population and out of the health conditions looked at, chronic pancreatitis has the highest measure of association with pancreatic cancer diagnosis.

## 4.3 CDSS Screen Shots for Pancreatic cancer Risk Assessment

The screen shots shown below are a few of the steps taken to develop the CDSS and some of the end-user interface results. These screen shots will provide insight into how the CDSS was developed, the variables used as stated in the previous chapter and an example of how the results are displayed. Figure 4.10 shows the defined variables that were used in creating the algorithm for the CDSS.

### *4.3.1 The Defined Variables*

This is the first step in the development process following the successful

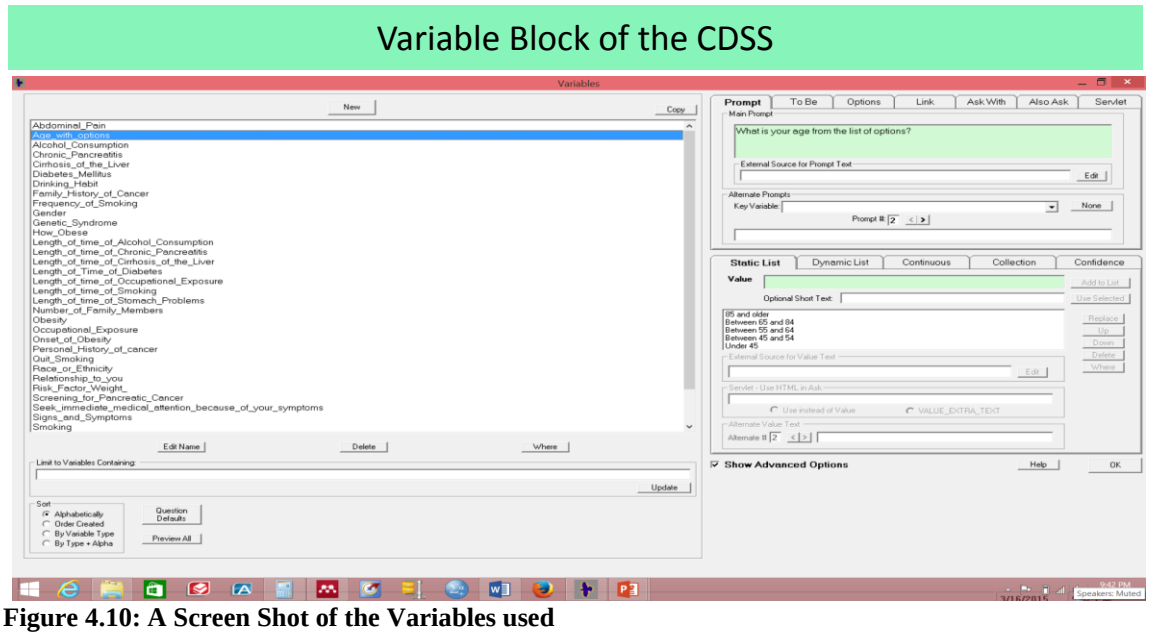



**Figure 4.10: A Screen Shot of the Variables used**

installation of Exsys Corvid software program. The variables consist of relevant information about the patient and the supportive knowledge about pancreatic cancer risk factors, signs and symptoms and methods of diagnosis.

### *4.3.2 The Logic Block*

This is the second step in the development process but the first step in designing the commands for the CDSS. This step utilizes the variables created in the first step. This

Logic Blocks of the CDSS

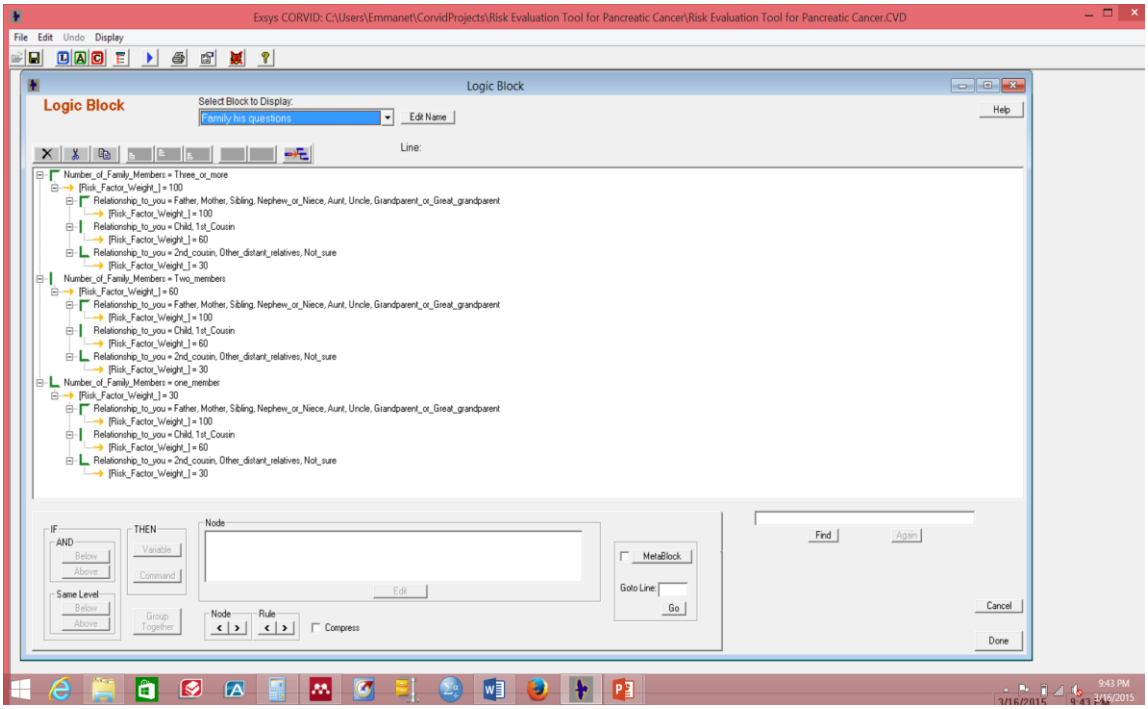



**Figure 4.11: Logic Block for Family History**

is where the algorithm is written and placed in a logical order for the CDSS to use in producing new information otherwise known as valid and reliable results. There were a total of 21 logic blocks created although the number of blocks does not signify the complexity of the design. It was easier and less confusing to program each variable in its own block. Additionally, the number of blocks does not affect the number of nodes

because the software program counts each statement as a node and computes the total of all blocks. The number of nodes allowed with the version of software used was 250 and it was exhausted.

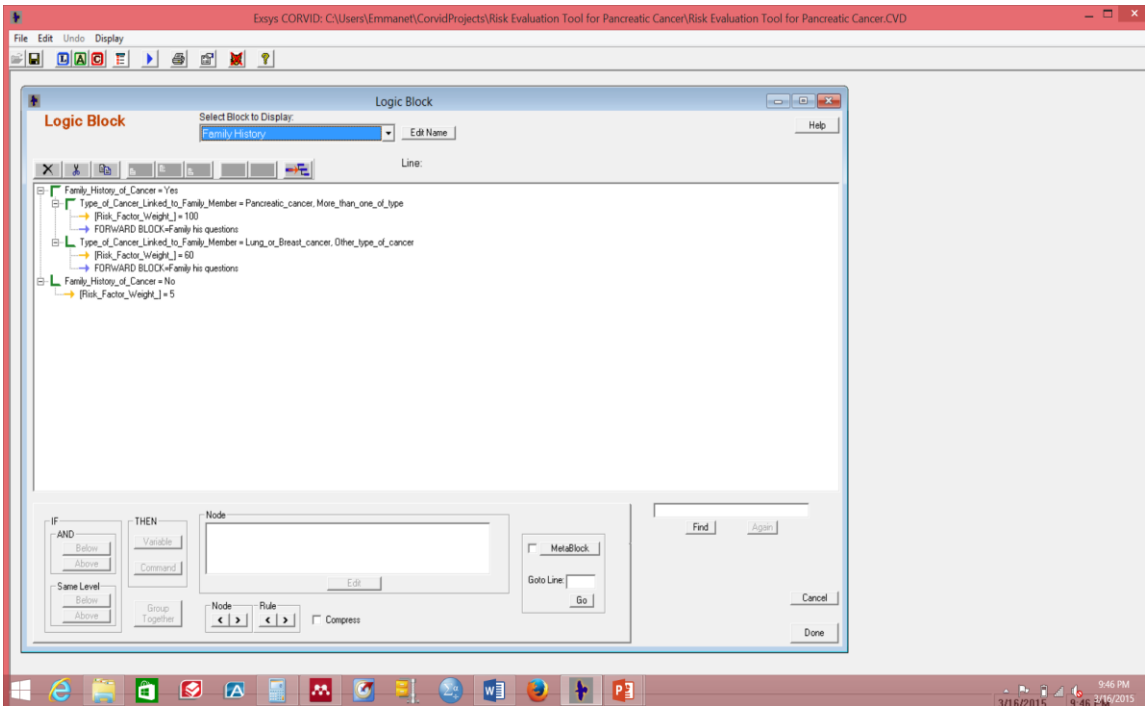



**Figure 4.12: Second Logic Block for Family History**

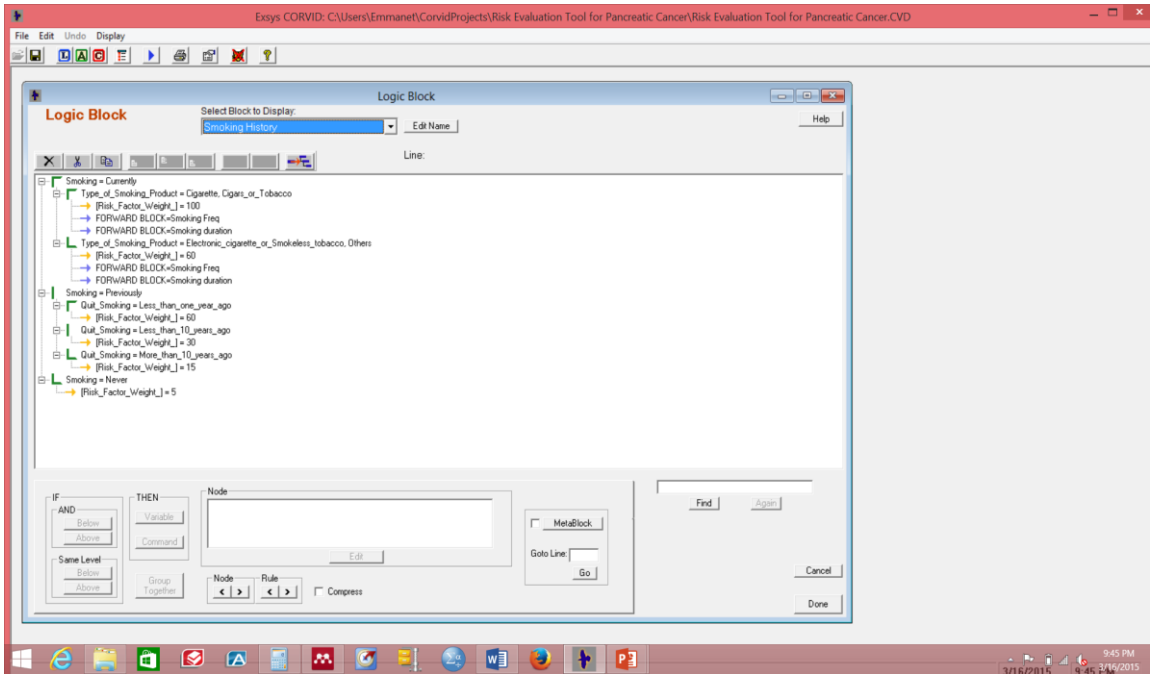



**Figure 4.13: Logic Block for Smoking History**

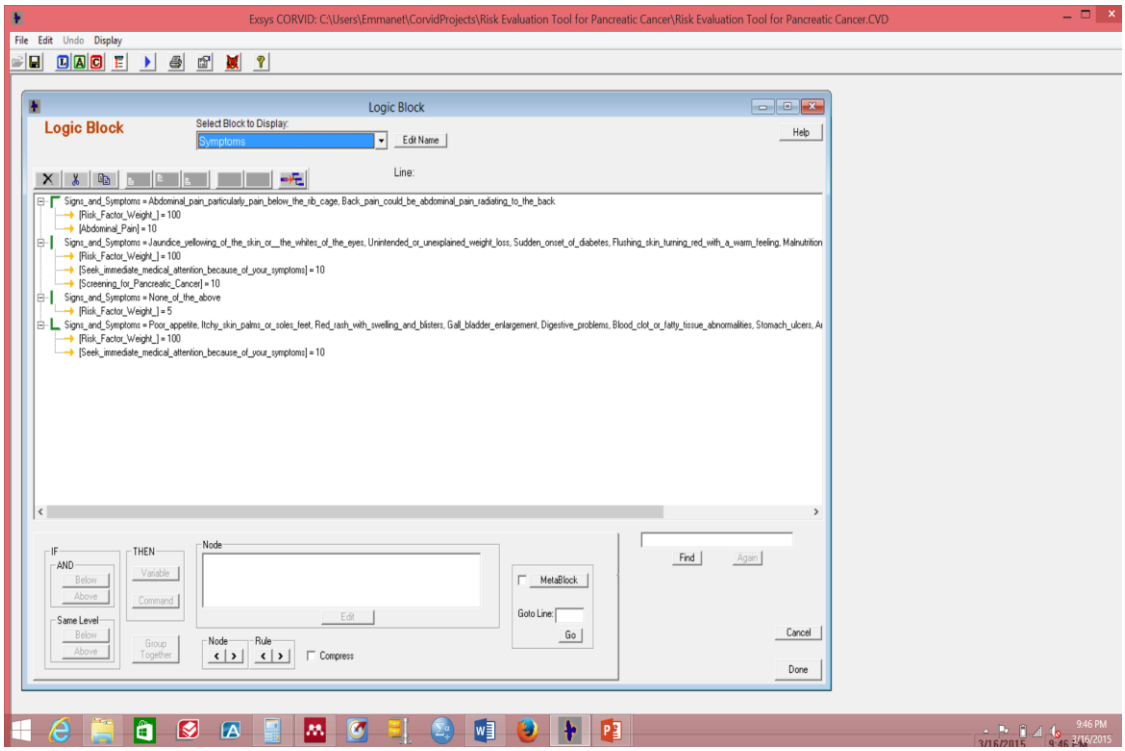



**Figure 4.14: Logic Block for Symptoms**

### *4.3.3 The Command Block*

The command block is the final step in the development of the CDSS. This is what tells the CDSS what to do and what to display in the user-interface. Without this block, the system will not run. The command block could be as simple as using just two statements and one command block or as complicated as using several statements and several command blocks. We created one command block and programmed the system to use forward chaining to allow only the needed logic blocks to be run. The reason for this is because some of the logic blocks have forward chaining to call on other logic blocks. Figure 4.15 below is a screen shot of the command block created.

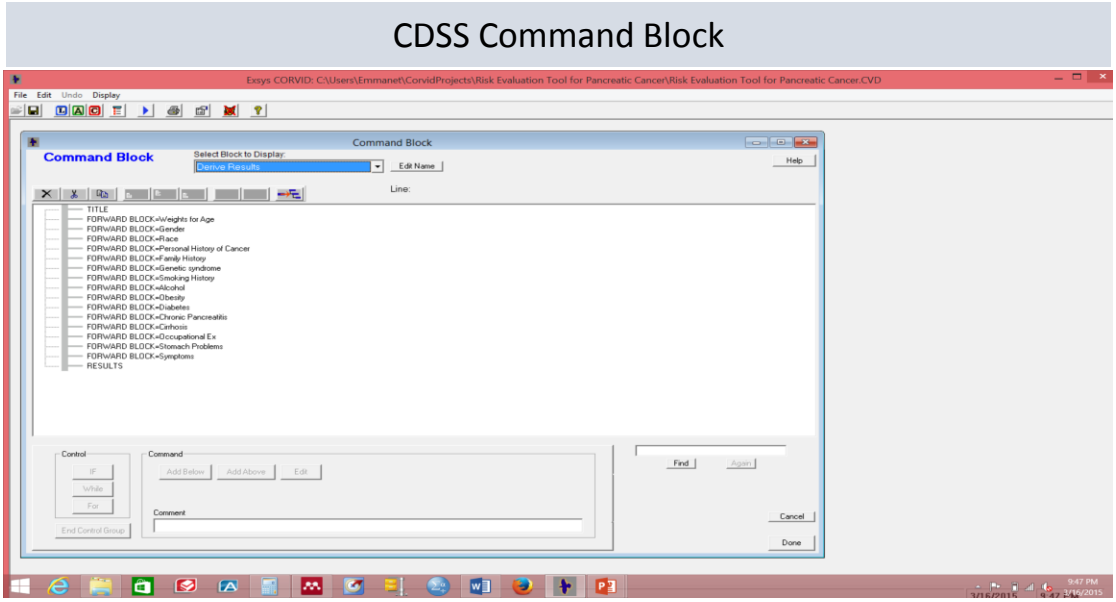



**Figure 4.15: Command Block for Results**

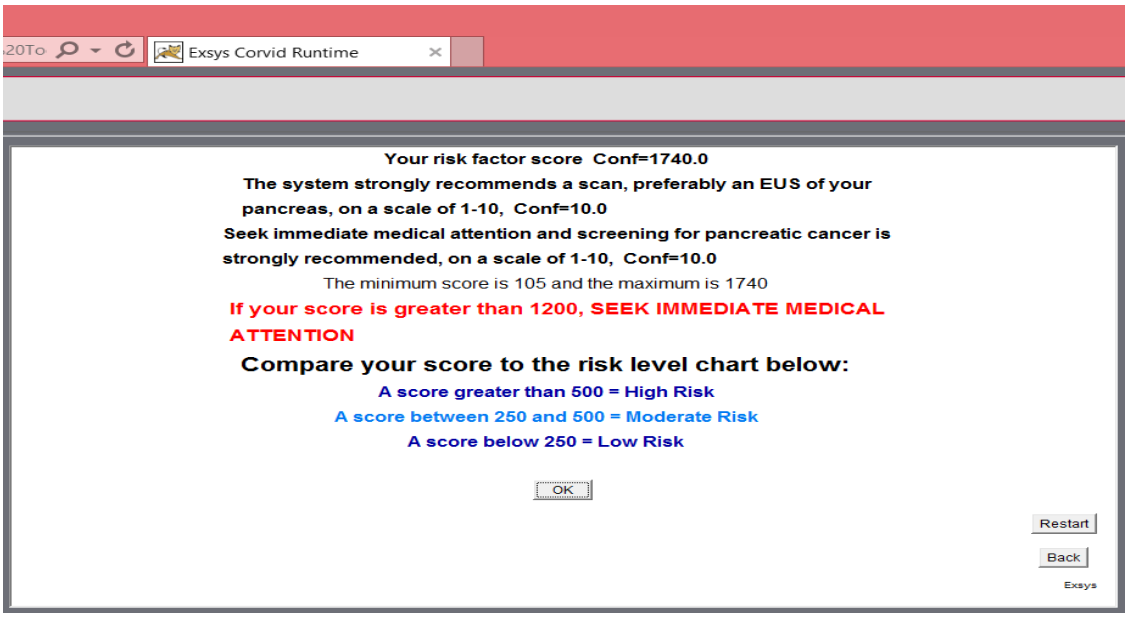
*4.3.4 The Result View*

The result view of the CDSS is the final result generated and displayed to the user after all questions have been answered. The result will vary depending on the answers provided. The system performs a summation of the total score of answers provided and displays the total score, otherwise known as the risk factor or confidence factor score to the user. The result view may also display recommendations depending on the answer provided under symptoms. The result view also displays the risk level chart showing the three levels of risk and instructions for the user to compare and identify his/her risk level.

Figure 4.16 (a) and (b) depict results with the maximum and minimum score an individual can obtain in using this CDSS. The maximum score is a high risk individual and the minimum score is a low risk individual. The system would also generate recommendations or alerts as shown on figure 4.16 (a) depending on the patient's symptom whereas, there are no additional recommendations for patients with no

symptoms and this is because, symptoms for pancreatic cancer often mimic those of other health conditions so it is important to alert users that their symptoms may need medical attention or pancreatic cancer screening.

## Examples of Results Displayed to the User




(a)

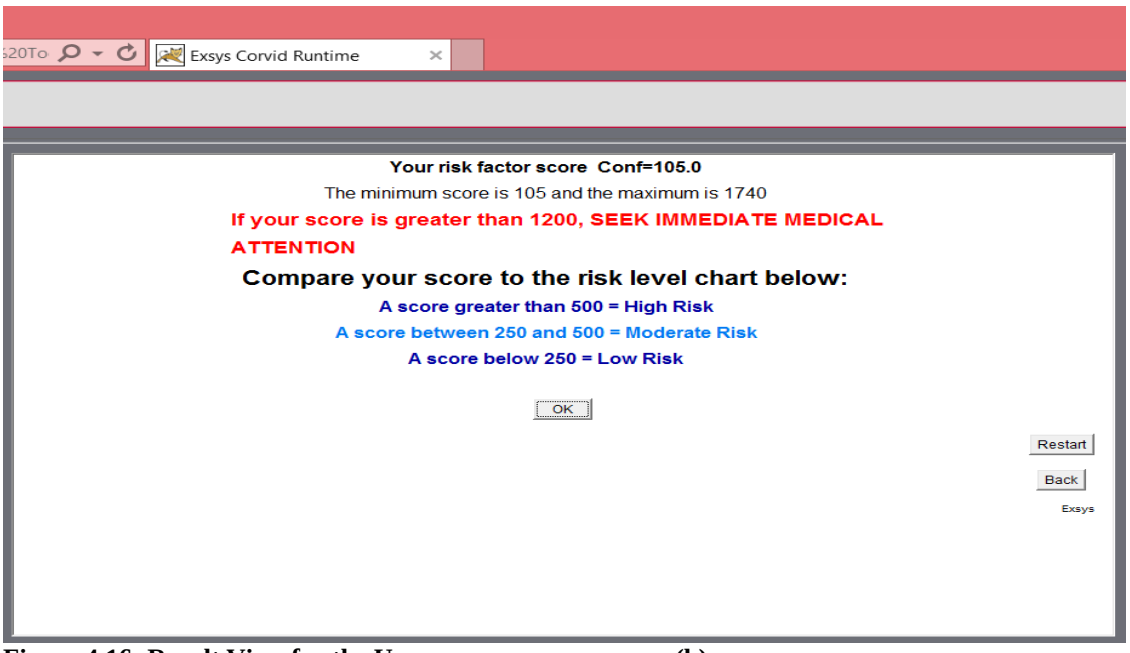



**Figure 4.16: Result View for the User** **(b)**

*4.3.5 The Order of the CDSS User-Interface and Questions*

The next few figures are screen shots depicting the pages of the user-interface. All of the possible questions are shown. The maximum number of questions is 31 and the minimum is 15. The questions are populated depending on the answers given. Some

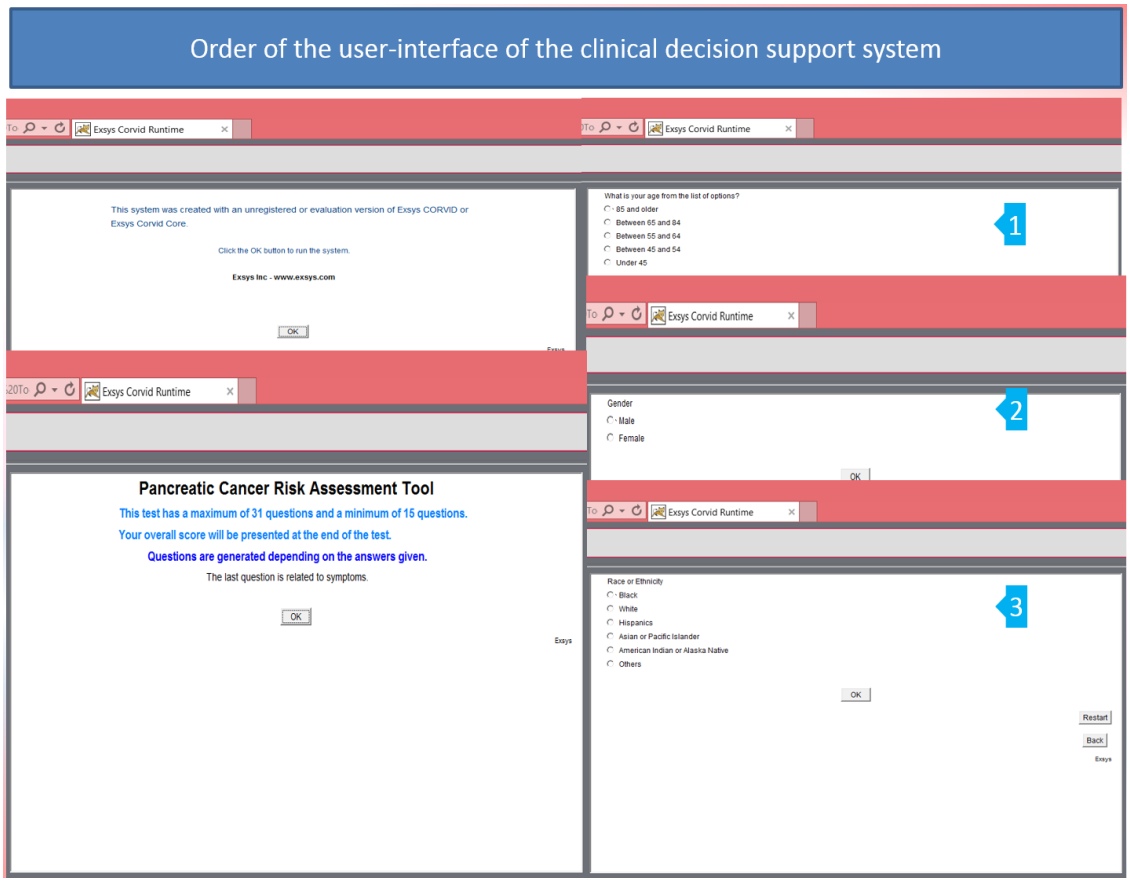



**Figure 4.17: Order of User-Interface with questions one through three**

answers with a "yes" have additional questions and answers with a "no" have the least number of total questions. Figure 4.17 shows the first five pages on the interfaces. Figure 4.22 is the last page shown with questions about symptoms and the result view generated after a computation of the total score.

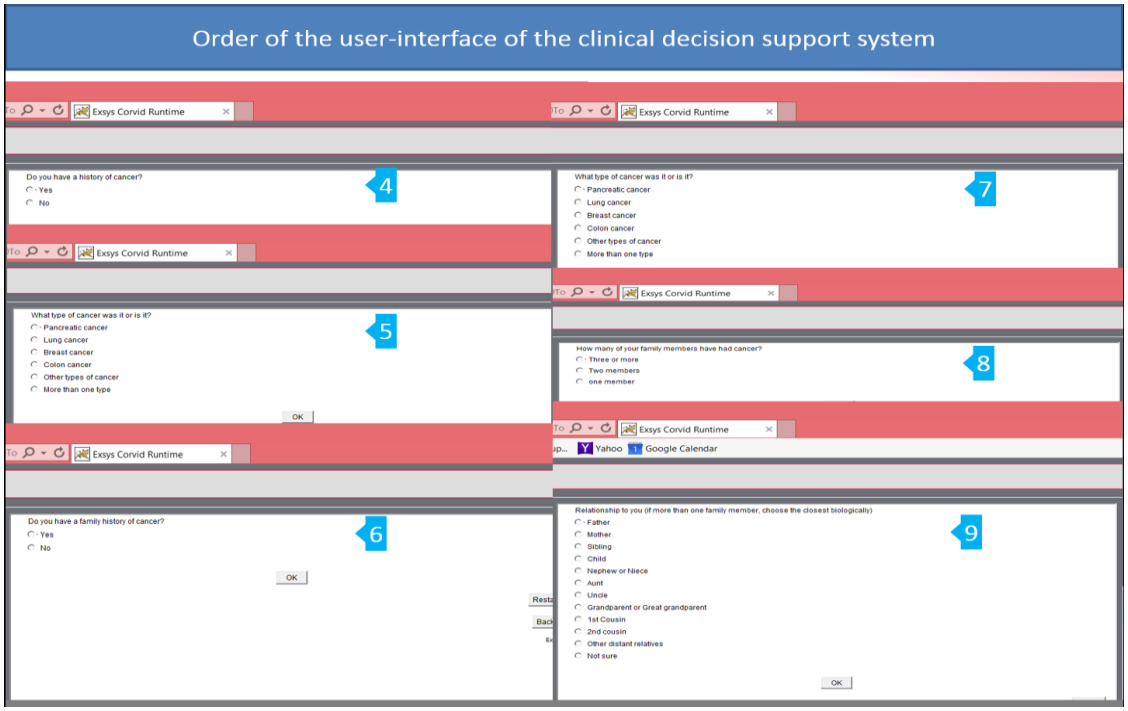



**Figure 4.18: Order of User-Interface with questions four through nine**

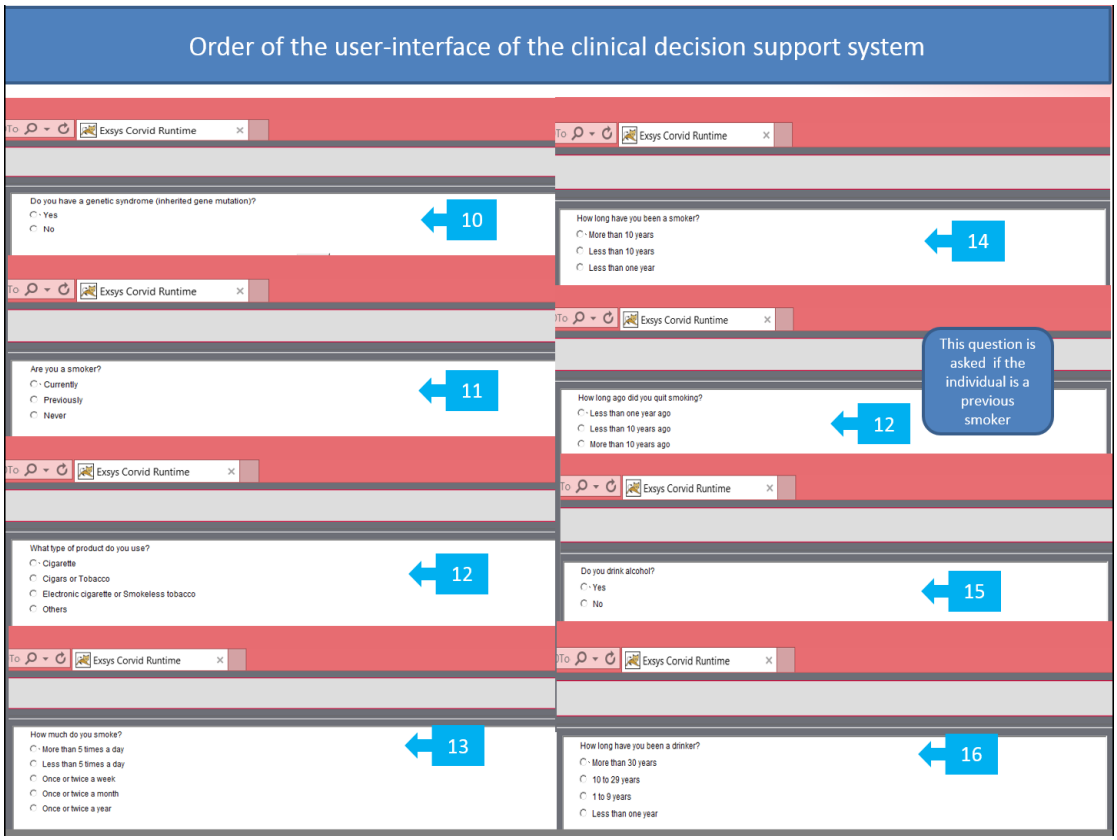



**Figure 4.19: Order of User-Interface with questions ten through sixteen**

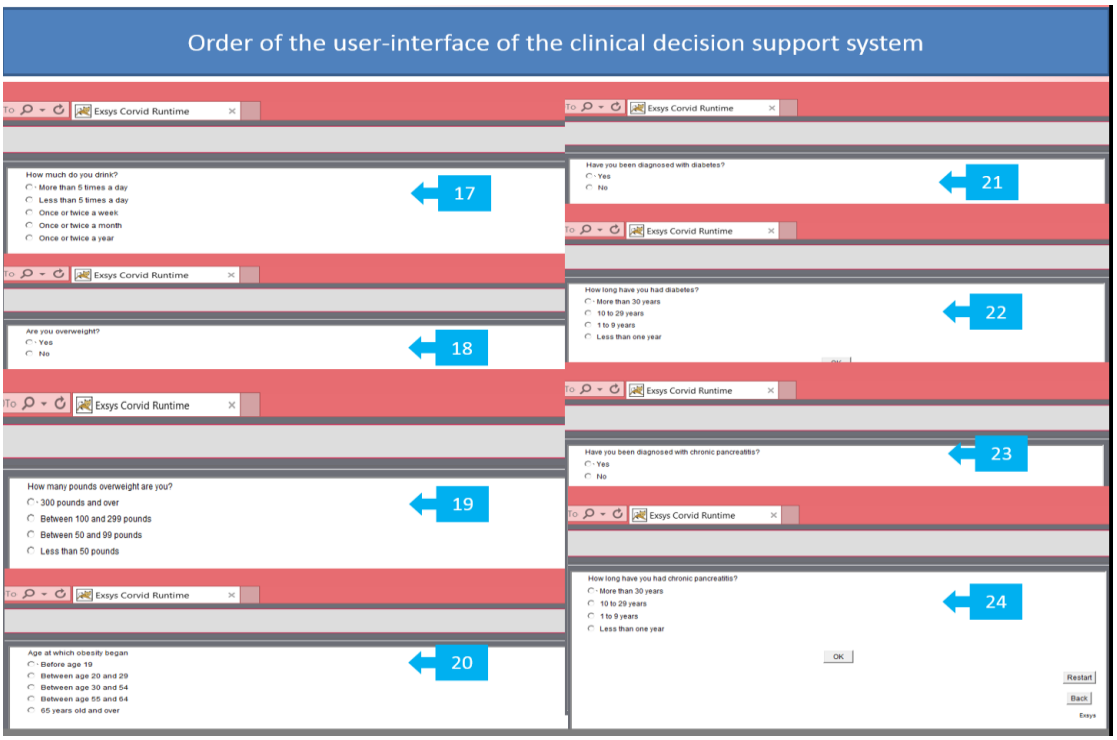



**Figure 4.20: Order of User-Interface with questions seventeen through twenty-four**

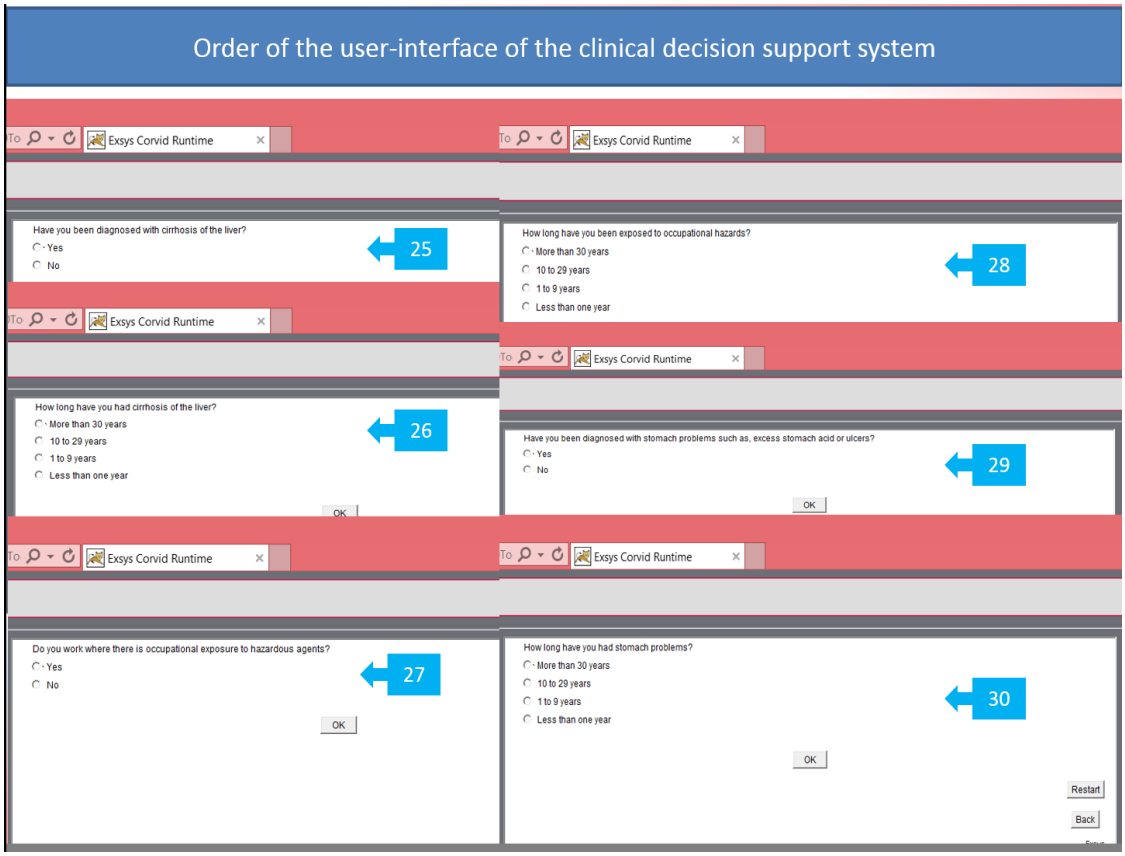



**Figure 4.21: Order of User-Interface with questions twenty-five through thirty**

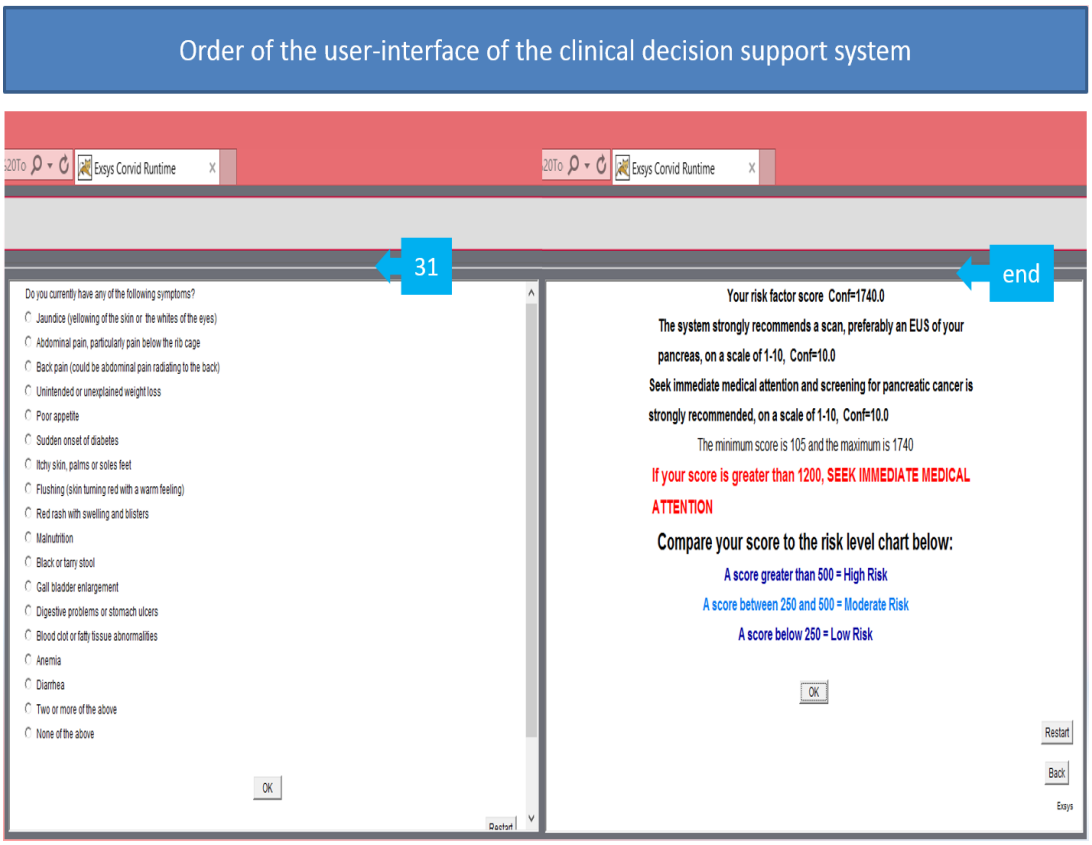



**Figure 4.22: The Last question and result view of the User-Interface**

### 4.4 Case Scenarios and Results

The CDSS was tested using nine clinical case reports and 3 patients' stories. The result will be displayed in the screen shots below. Each report and patient story was tested in two ways; 1) answering "yes" to questions in which we have no information and also providing the highest number of years on questions we have no information on, and 2) answering "no" to questions we have no information about and also providing the least number of years on questions we have no information on. Therefore, two potential results were generated and as expected, all case scenarios with "yes" answers generated a high risk score. The results for the "no" answers generated the least possible score patients in each case scenario could obtain, so it was more logical to assume this result as the actual

result for the patients. The result screen shot for each case scenario depicts that of the least possible score for the patient. This method was decided upon because none of the case reports or patients' stories have all the information needed to answer the entire risk assessment questions.

The testing phase of the CDSS was carried out to simulate actual users in order to validate the results. The questions generated are answered using the case scenarios. The CDSS analyzes the answers with the help of the inference engine to produce results and alerts as programmed in the system.

### *4.4.1 Case Report 1*

A 75 year old female presented with abdominal pain and weight loss of

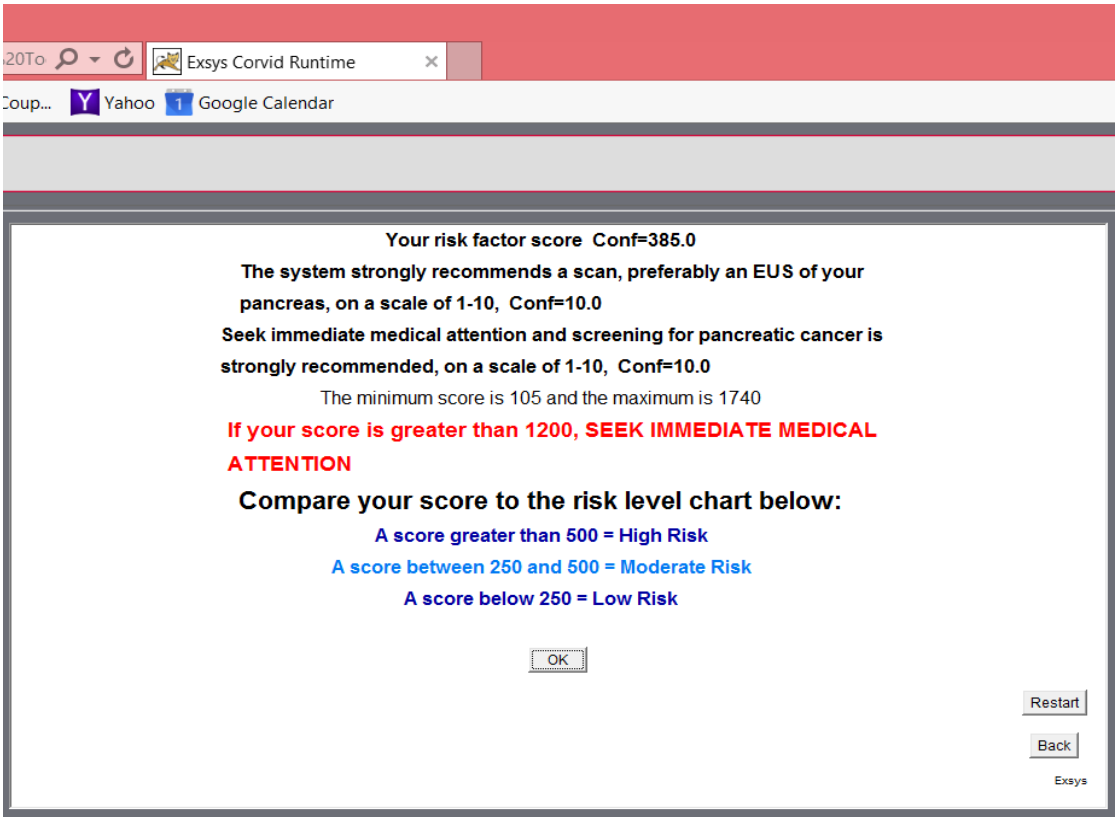



**Figure 4.23: Result for Case Report 1**

approximately 18 pounds within 2 months. Physical examination revealed upper left quadrant pain and jaundice. Serum marker CA 19-9 was 1,806u/ml and CEA was normal. CT scan showed an enhancing 4.7cm pancreatic head mass. This patient was diagnosed with inoperable carcinoma of the pancreas because the superior mesenteric vein was obstructed and encased within the tumor. No mention of the patients past medical history, family medical history and lifestyle[107].

Case report 1 has a total score of "385" which indicates this patient has a moderate risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.2 Case Report 2*

A 49 year old male diagnosed with pancreatic cancer in June of 2012. This patient was involved in a case study prior to his diagnosis. At some point he was hospitalized for obstructive jaundice. He is a non-smoker. He has a 19 year history of chronic pancreatitis. No mention of the patient's family medical history[108].

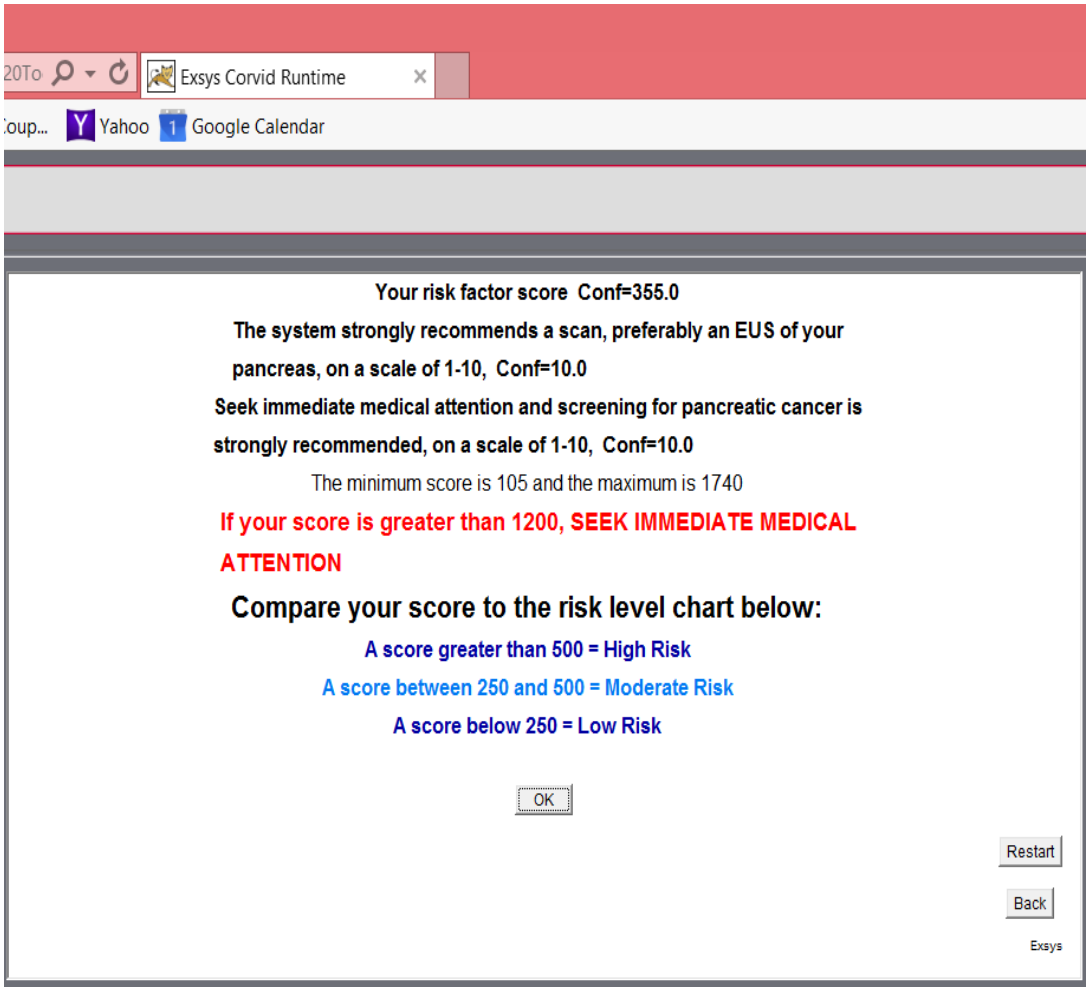



**Figure 4.24: Result for Case Report 2**

Case report 2 has a total score of "355" which indicates this patient has a moderate risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family

medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.3 Case Report 3*

A 52 year old male diagnosed with Intraductal oncocytic papillary neoplasms (IOPN), a rare form pancreatic cancer classified under IPMN. The patient had been complaining about epigastric abdominal pain radiating to his back with associated nausea for 2 years. One month prior to his diagnosis he visited the Emergency room with similar symptoms. The patient had a history of mucinous cystic neoplasm, a form of pancreatic cancer 12 years prior to this diagnosis. His past medical history was significant for alcohol and intravenous drug abuse, chronic pancreatitis, hepatitis C, and uncontrolled diabetes. He also has a family history of pancreatic neoplasm[109].

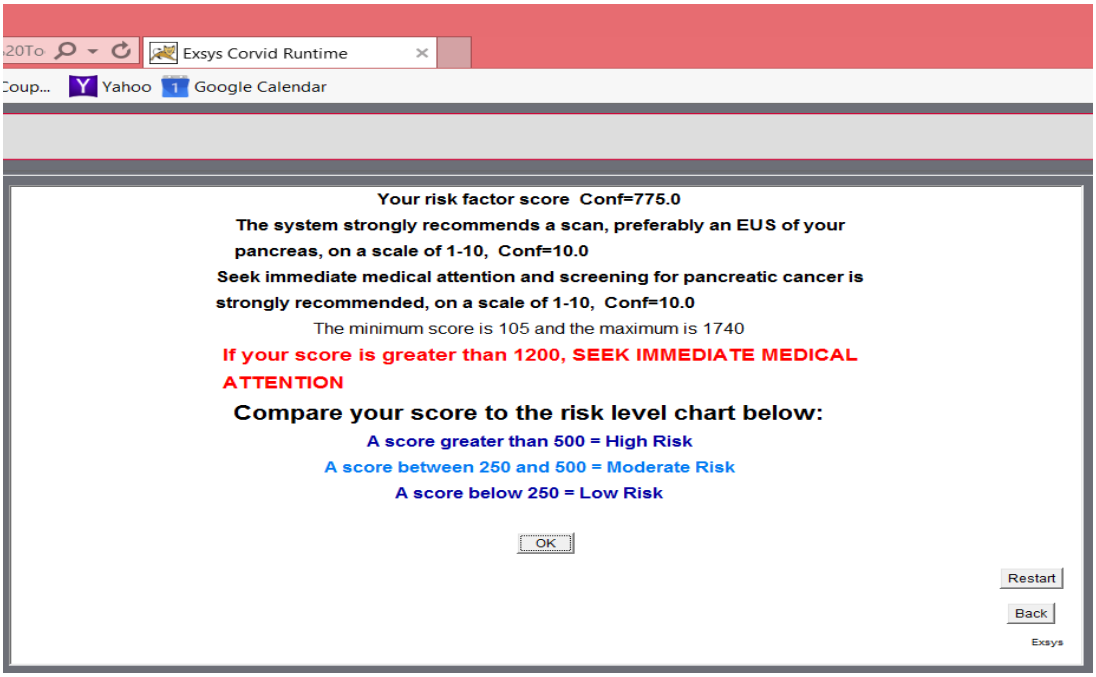



**Figure 4.25: Result for Case Report 3**

Case report 3 has a total score of "775" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.4 Case Report 4*

A 65 year female diagnosed with pancreatic adenocarcinoma following complaints of severe epigastric back pain and weight loss of approximately 22 pounds in six months. Her past medical history included an appendectomy at age 10 and arterial hypertension. She has a family history of colonic cancer (father and sister)[110].

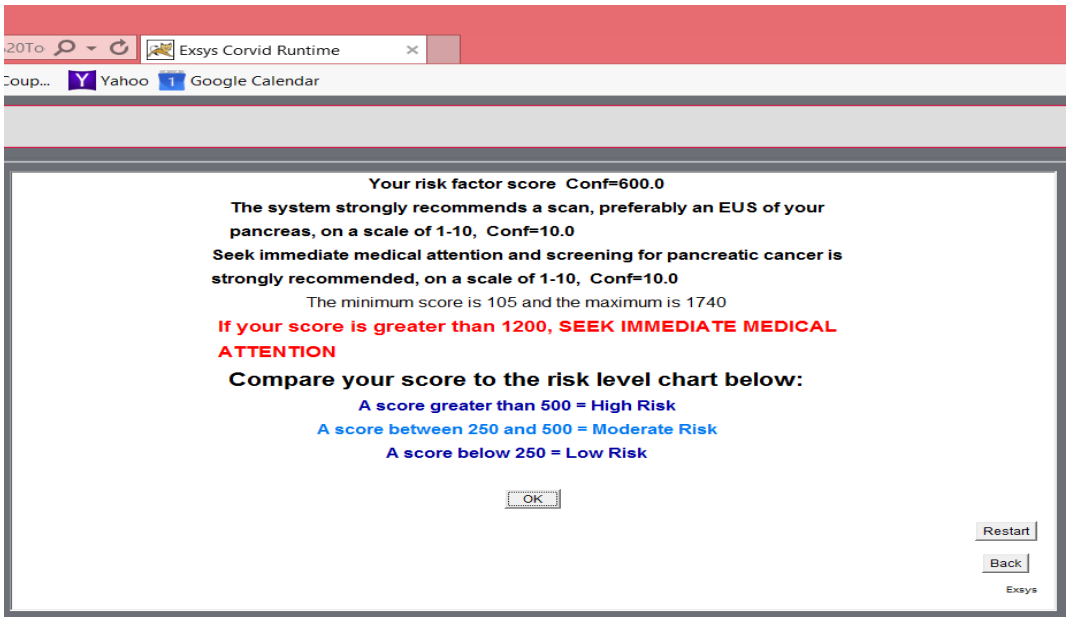



**Figure 4.26: Result for Case Report 4**

Case report 4 has a total score of "600" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.5 Case Report 5*

A 55 year old male of Jewish Ashkenazi decent seeking genetic counseling as part

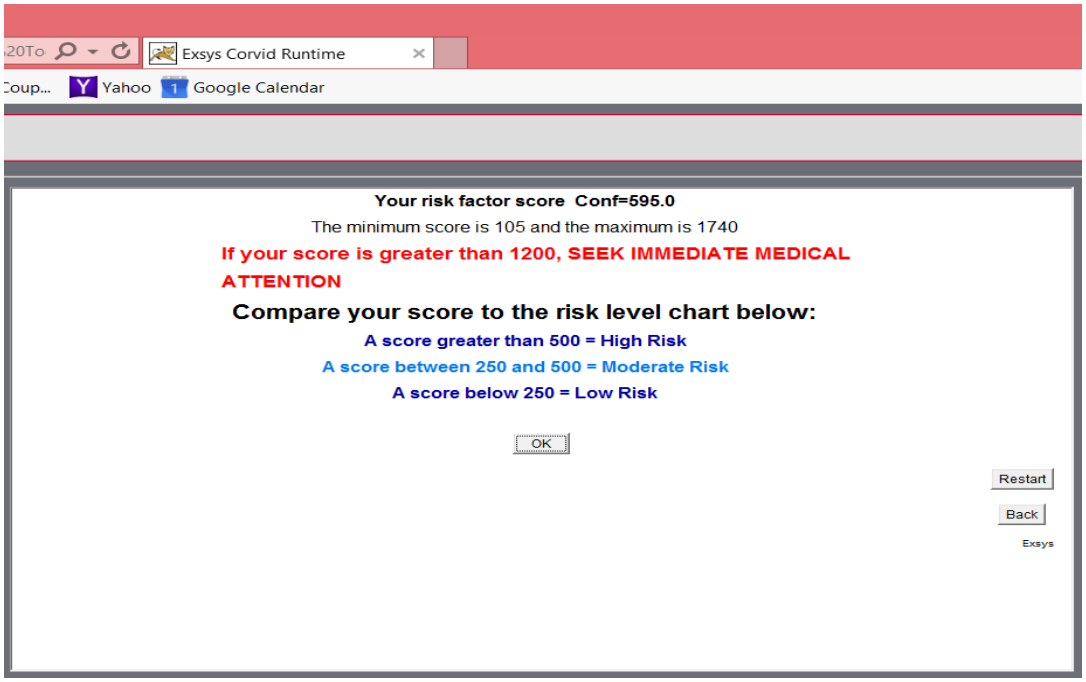



**Figure 4.27: Result for Case Report 5**

of a case study had no indication of pancreatic cancer. He was asymptomatic and healthy. He has familial gastric cancer (father, paternal uncle and paternal grandmother). He was found to harbor 3984dup4 MSH6 mutation. The gene mutation was identified to have come from his paternal side although his maternal uncle was diagnosed with colon cancer at the age of 82[111].

Case report 5 has a total score of "595" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history

and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.6 Case Report 6 and 7*

Case report 6: A 70 year old Caucasian male was diagnosed with pancreatic adenocarcinoma after presenting with abdominal distention, weight loss, icterus, along with nausea and vomiting. He was a non-smoker and only drank moderately. He had a past medical history of a stage I adenocarcinoma of the gastroesophageal three years prior and has had no recurrence of the esophageal cancer. His CEA and CA 19-9 levels were both within normal limits[112].

Case report 7: A 53 year old male diagnosed with pancreatic adenocarcinoma,

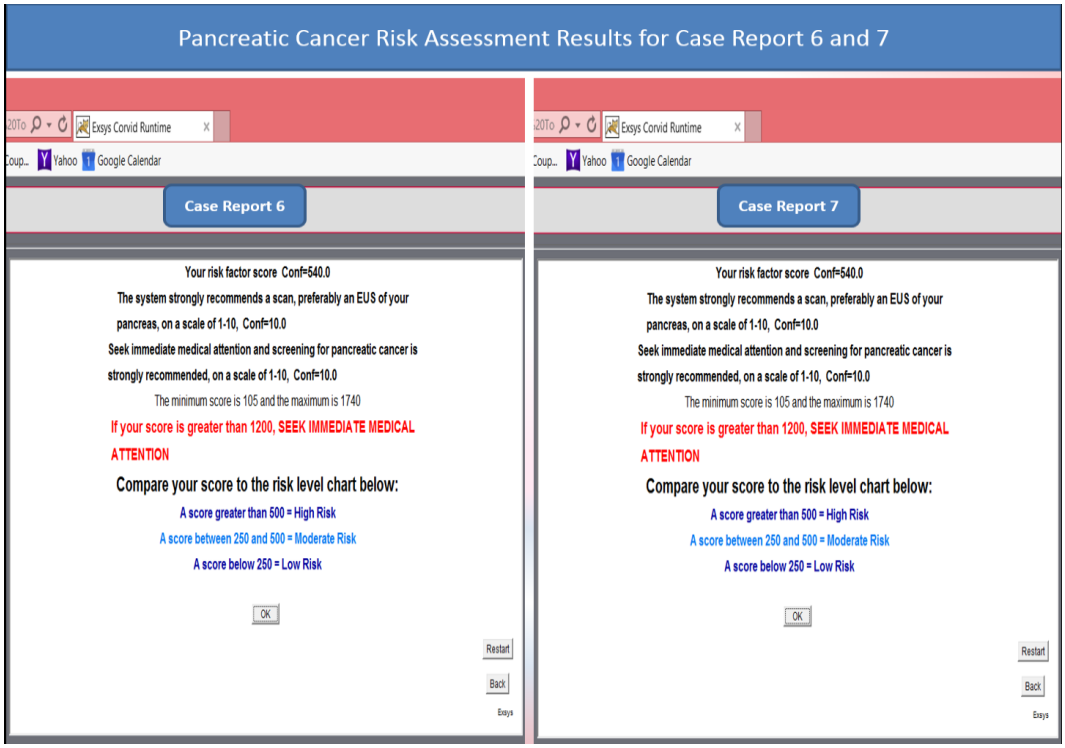



**Figure 4.28: Result for Case Report 6 and 7**

IPMN and mucinous cystic pancreatic neoplasm, although all tumor markers were normal. He has a 16-year history of recurring episodes of acute pancreatitis. His symptoms included epigastric pain, nausea and weight loss. He was a non-smoker, moderate drinker and had no history of diabetes[113].

Figure 4.28 shows the results for Case report 6 and case report 7. Case report 6 has a total score of "540" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

Case report 7 also has a total score of "540" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation.

Answering “no” to all missing information regarding the patient’s medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient’s symptoms as stated in the case report.

### *4.4.7 Case Report 8 and 9*

Case report 8: A 31-year old female with insulin-dependent diabetic was admitted following an episode of unconsciousness. This patient was severely hypoglycemic at admission and had been a diabetic for 12 years. No mention of the patient’s family history or other health issues[114].

Case Report 9: A 28-year old male presented with oral pain in the left mandibular

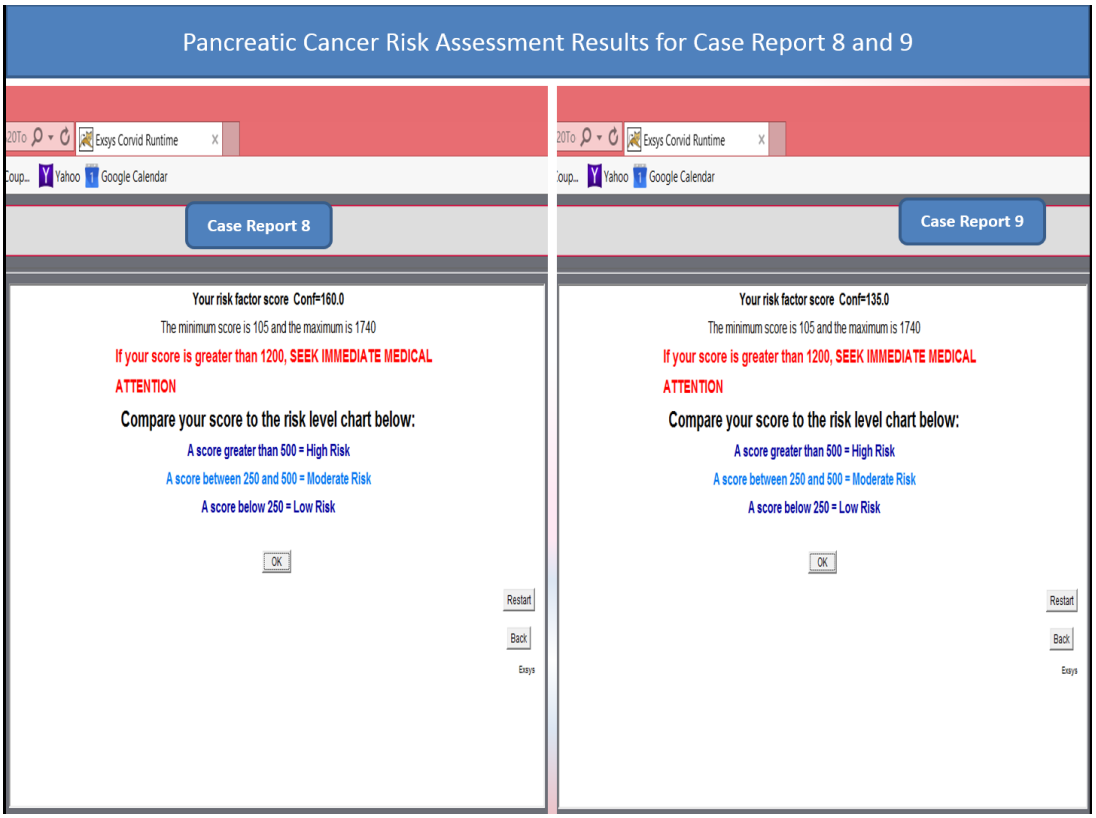



**Figure 4.29: Result for Case Report 8 and 9**

are following an extraction six months prior. The dental X-ray showed an image consistent with a piece of broken metal embedded in a distal subgingival at the mandibular left second molar. The patient had no significant previous medical history. There was no mention about the patient's family medical history[115].

Case report 8 has a total score of "160" which indicates this patient has a low risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms as stated in the case report.

Case report 9 has a total score of "135" which indicates this patient has a low risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history

and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system also presented recommendations and alerts because of the patient's symptoms as stated in the case report.

### *4.4.8 Patient Story 1*

A 60 year old Caucasian female diagnosed with pancreatic cancer after multiple visits to the hospital and her Primary care physician that lasted a period of 10 months. She first presented with diarrhea and upper abdominal pain. Three weeks later, she presented with no improvement in symptoms and weight loss. Her medical history included an 11 years history of colitis. Eventually the diagnosis was made following a PET scan that revealed a 2cm tumor in the pancreas and was considered early, however the tumor was inoperable because it was infiltrating two major veins[116].

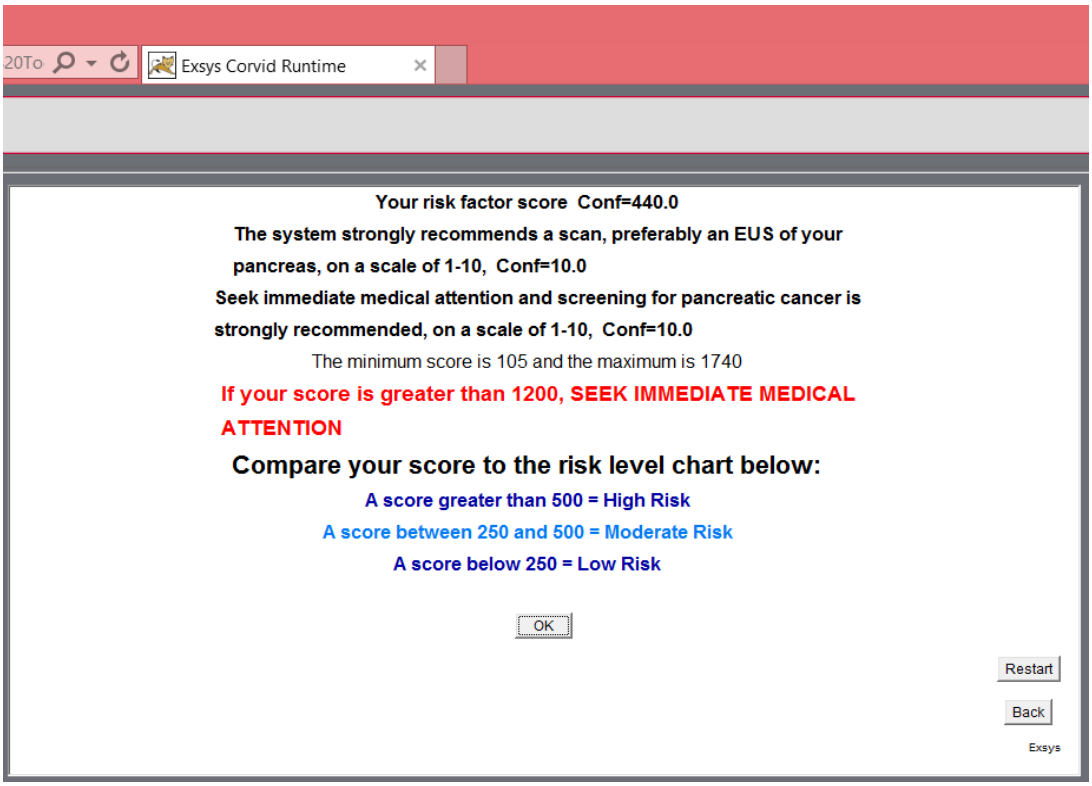



**Figure 4.30: Results for Patient Story 1**

Patient story 1 has a total score of "440" which indicates this patient has a moderate risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms.

### *4.4.9 Patient Story 2*

A 52 year old Caucasian female diagnosed with pancreatic cancer after multiple visits to her Doctors during a period of 6 months. She first presented with flu-like symptoms and an ear infection but progressively got worse with the addition of other symptoms including, abdominal pain, weight loss and diminishing hearing. She was a past smoker, and worked where she was exposed to occupational hazardous agents. She also has a family history of lung cancer (father)[117].

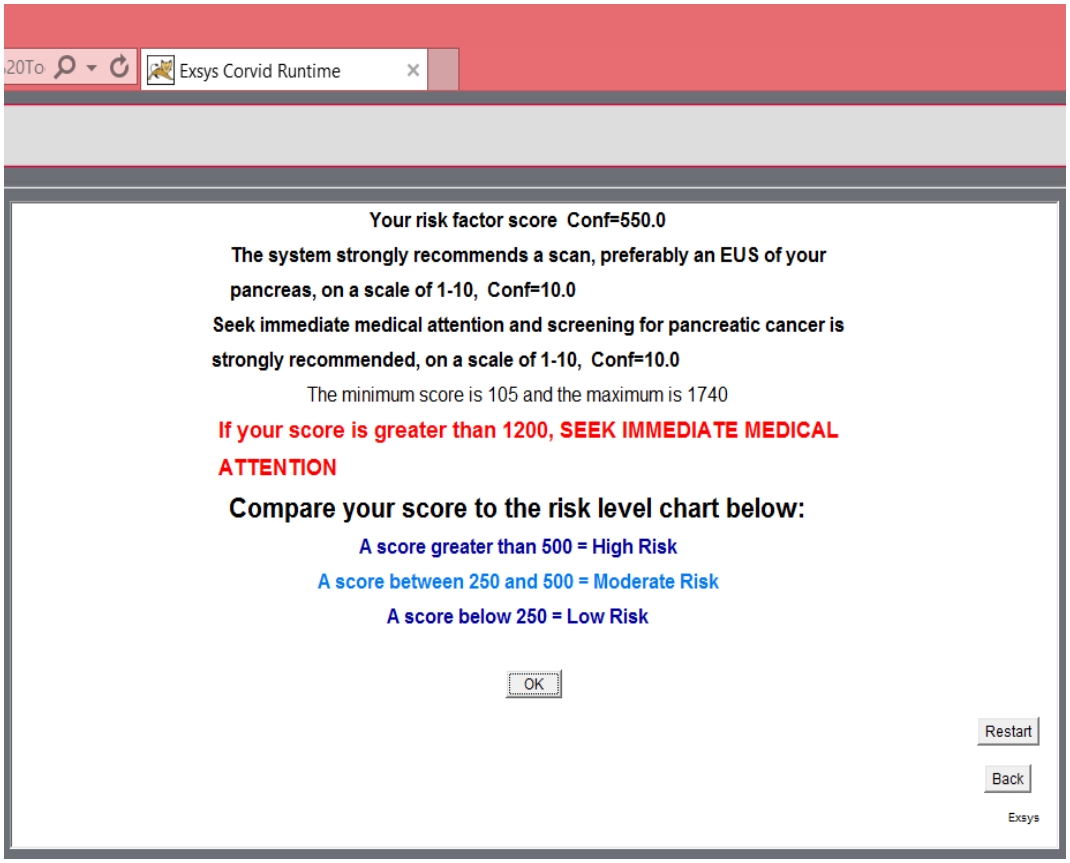



**Figure 4.31: Results for Patient Story 2**

Patient Story 2 has a total score of "550" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms.

*4.4.10 Patient Story 3*

A 72 year old Caucasian female was diagnosed with pancreatic cancer following

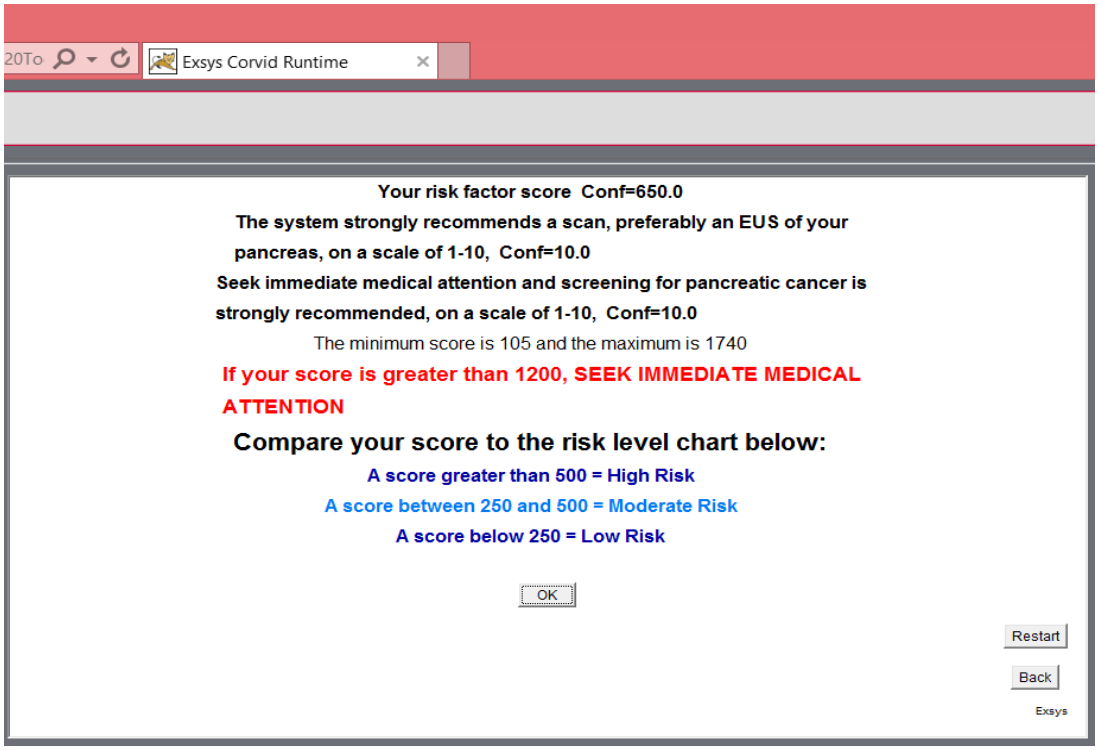



**Figure 4.32: Results for Patient Story 3**

multiple visits with varying symptoms after three years. The patient has a family history cancer. Her brother had cancer of the lymph node and was diagnosed with pancreatic cancer 10 years later. Her nephew also had a pancreatic cancer diagnosis. They were both fit and healthy, non-smokers and did not consume alcohol. This patient presented with stomach and bowel problems for three years before her diagnosis. Two years prior to her diagnosis, she was diagnosed with diabetes and during that time she experienced intense itching on her legs and arms. The patient's medical history included hypertension. The patient was active, a non-smoker and did not drink. One year before her diagnosis she started experiencing abdominal pain radiating to her back. Her symptoms progressively

got worse and included, poor appetite, diarrhea, weight loss, rectal bleeding followed by dehydration and jaundice and fluid retention in her abdomen[118].

Patient story 3 has a total score of "650" which indicates this patient has a high risk of developing pancreatic cancer. This is the least possible score for this patient because answers with the least weighted score for each question with missing information in the case reports were chosen as the correct data for this patient. The system requires a holistic approach in order to provide a more reliable result for the user. Accurate information for each individual is required for every question generated by the system. The results generated are personalized and tailored to each individual's situation. Answering "no" to all missing information regarding the patient's medical history, family medical history and lifestyle habits, such as, smoking will therefore, provide the least possible risk level. The results also show that the system presented recommendations and alerts because of the patient's symptoms.

### 4.5 Results' Conclusion

The results for the case scenarios show that 58% of those tested had high risk for developing pancreatic cancer, 25% were moderate risk and 17% were low risk which also translates to seven high risk patients, three moderate risk patients and two low risk patients. All except three cases had pancreatic cancer diagnosis and of those diagnosed with pancreatic cancer, six were high risk patients and three were moderate risk patients. One of the high risk cases was a healthy individual with no diagnosis of any sort. The other two cases with low risk had diagnosis of other sort and not pancreatic cancer.

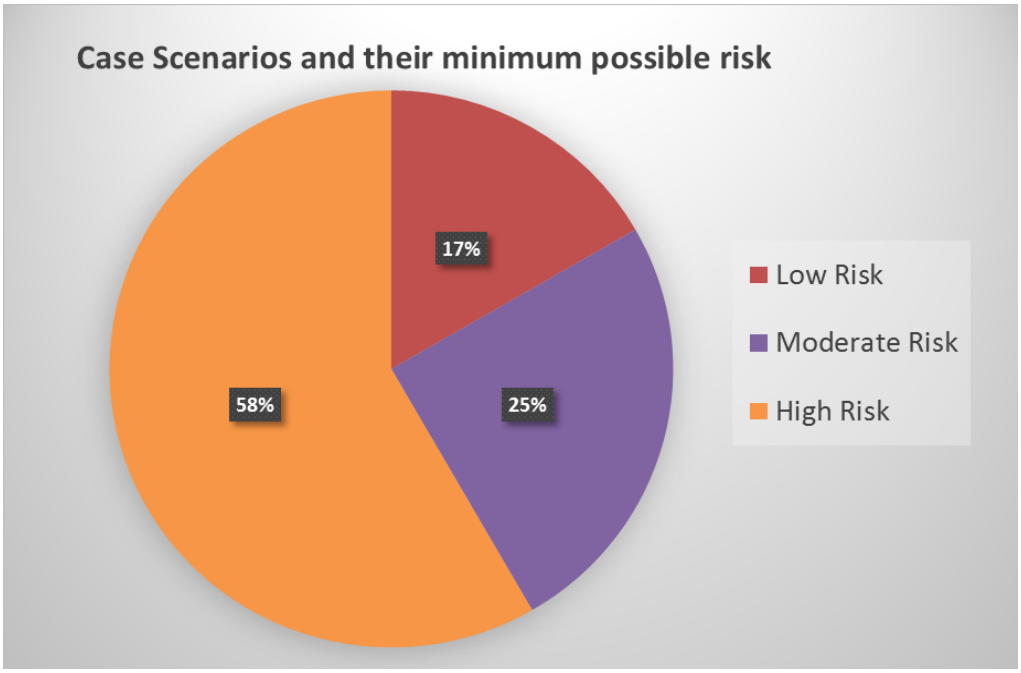



**Figure 4.33: The results of the 12 case scenarios as a whole**

For reference, "case report 5" was the healthy individual with no diagnosis; however the result show that this individual has at least a high risk for developing pancreatic cancer. Figure 4.33 depicts the overall minimum score which also represents the results with a "no" answer for all 12 case scenarios.

The results showed that it is possible to develop a CDSS that can identify high-risk individuals and other risk levels for pancreatic cancer. The results also show that the system is an easy-to-use system that can provide a heuristic approach in the diagnosing pancreatic cancer earlier than later. This system can enlighten individuals on relevant information about pancreatic cancer risk factors and symptoms. The effectiveness of the CDSS and the impact it will have in reducing the number of misdiagnoses and delayed diagnoses of pancreatic cancer in patients were undetermined. However, it is our claim that it will add some value to the quality and safety of patient care. The gap that exists between what is known about pancreatic cancer and finding a systematic approach for early detection of the disease is one that most researchers feel an urgent need to merge.

We believe that the use of CDSS for pancreatic cancer will pave the way for merging this gap.

This study was conducted with several questions in mind and to answer all questions, the proposed CDSS will require further studies. Embracing CDSS by the majority of health care settings is possible but highly unlike if more studies are not carried out to prove its relevancy. Although, there are limitations such as the cost of implementing a CDSS within an organization's system and interoperability challenges, the benefit of implementation of a CDSS will surpass these challenges and eventually will become cost-effective for an organization. For example, the cost of malpractice lawsuit in the event of medical errors could be prevented if the use of CDSS is adopted. Additionally, the general population will experience some benefits in using this system in providing and suggesting relevant information to their health care providers which could aid in timely and accurate diagnosis within a shorter period. The overall benefits of the use of CDSS, as shown in previous studies are reasons to believe this CDSS could be essential, particularly for those with a high risk of developing pancreatic cancer.

CHAPTER V

# DISCUSSION AND CONCLUSION

## 5.1 Summary

*Introduction:* Pancreatic cancer has the worst prognosis in all of medicine with a median survival of less than 6% five year survival. The reason for this may be due to the aggressive nature of pancreatic cancer and the onset of symptoms late in the stage of the disease. Early diagnosis and treatment of pancreatic cancer is a problem because symptoms are very similar to symptoms for other illnesses and they often appear only late in the stage of the disease, while treatment is difficult because the tumors are the most resistant to therapy. Though there are treatment options for pancreatic cancer, they present very little hope in the survival of the disease because surgery, which provides the best treatment option has only about 20% to 25% five-year survival[106] with a high risk of complications and a high rate of recurrence of pancreatic cancer.

*Statement of Problem and Significance of Study:* The two main problems are; advanced stage diagnosis accounts for more than 85% of all pancreatic cancer diagnosis and there is lack of a known method for early diagnosis. The high mortality rate and the low survival rate of pancreatic cancer is largely due to late detection of the tumors. The little to no knowledge about the biology and etiology of pancreatic cancer can present some challenges in finding a systematic approach in diagnosing patients with pancreatic cancer at the very early stages of the disease. The goal of this study was to develop a CDSS that can be used as a risk assessment tool by the general population and health care providers to determine risk levels for pancreatic cancer. The use of a CDSS was proposed and its

significance has been shown in other studies related to other types of illnesses to improve workflow in an organization, reduce medical errors, improve patient care and reduce overall cost for the establishment and patient. Although, literatures to support the benefits of using CDSS in pancreatic cancer diagnosis are unavailable, this study hopes to shed some light into the possibilities of its benefits and potential in identifying the risk levels of individuals and in reducing misdiagnoses and delayed diagnoses.

*Literature Review:* The review of literature suggests there is little knowledge about the biology of pancreatic cancer, the pathology of the disease, specific genetic markers, and methods of accomplishing early detection of the disease. Because pancreatic cancer generally does not present symptoms at an early stage, relying on symptoms is not an option; however, it is believed there may be biological signs of the tumor at the early stage before physical symptoms begin to manifest. Scientists believe that a breakthrough finding of the specific gene responsible for pancreatic cancer will be made and its location on a chromosome will be identified just as it has been discovered in other types of illnesses. Specific biological and molecular markers for pancreatic cancer have not been identified and whether the use of biomarkers such as CA19-9 and CEA are reliable is yet to be fully accepted. As regards the causes of pancreatic cancer, smoking poses the strongest environmental risk. Genetic syndromes and familial pancreatic cancer have a genetic predisposition with increased elevated risk for developing pancreatic cancer. A synergistic effect of smoking and familial pancreatic cancer has been reported to highly elevate the risk of developing pancreatic cancer. Other risk factors such as, chronic pancreatitis, obesity, diabetes and cirrhosis have also been linked to pancreatic cancer.

Researchers believe that damage to the pancreas can eventually lead to pancreatic cancer. Chronic pancreatitis is one problem that could cause lesions in the pancreas and potentially become malignant tumors. Other risk factors like alcohol, diet and coffee are still debatable risk factors because studies have not been consistent in their findings. Besides risk factors, several studies have focused on genetic factors that may be responsible for pancreatic cancer and some have conducted studies on technological advancement, such as computer aided detection, imaging technology, biomarkers for pancreatic cancer and in this study, the use of a CDSS. Specific genes responsible for pancreatic cancer are still under investigation; however, it is believed that certain genes responsible for breast cancer and some other forms of cancer may play a role in pancreatic cancer development. Gene mutations such as, KRAS is an oncogene. It is the most studied mutation for pancreatic cancer. It has been reported that KRAS is found in almost all pancreatic adenocarcinomas. KRAS is known to be present in the early stages of the progressively PanIN pathway of the transformation of normal cells into pancreatic cancer cells. Approximately, 95% of pancreatic adenocarcinomas result from KRAS gene mutations but the functional role of KRAS in the formation of pancreatic cancer is still unknown.

The symptoms related to pancreatic cancer usually manifest late in the stage of the disease and they develop when the tumor is big enough to cause pressure to surrounding or nearby tissues, block the bile duct or have metastasize to other organs. Once the tumor metastasizes to other organs it severely reduces the chances of survival and this is what needs to be prevented. Signs may include jaundice, pain, bowel obstruction, loss of appetite, unexplained weight loss, diabetes and others. Jaundice is a

critical symptom for pancreatic cancer diagnosis and sudden onset of diabetes has been reported in some patients. All the symptoms associated with pancreatic cancer could be mistaken for other types of illnesses making diagnosis more difficult. The most reliable method of diagnosis is through the use of imaging technology and a biopsy. EUS is one of the most recommended for detecting lesions in the pancreas less than one centimeter in diameter.

The use of CDSS for clinical diagnosis and management of pancreatic cancer patients is an area that is lacking studies and literature. Even though CDSS have been widely studied in connection with other types of illnesses and is believed to be an effective method for improving the quality and safety of patient care, it is still not widely adopted by many healthcare settings. Several studies show that CDSS can reduce medical errors, improve workflow, aid clinicians in providing better medical decisions about their patients at the very moment of patient care, and many other benefits that could potentially be cost-effective in an organization[87,119]. CDSS has been around for over 30 years but the outcomes for using CDSS is an area that needs further exploring[87]. The development, proposal and potential benefits have been reported and tracked in previous studies, however, retrospective studies showing the actual effects on patient care is lacking.

*Research Methodology and Results:* This study utilized multi-method approach by conducting both a quantitative study and a quasi-experimental study. The steps followed in carrying out this study were; a review of literature, review of existing data, data analyses of HCUP NIS data, design and development of a CDSS and testing of the CDSS using multiple case scenarios. The results of this study found that it is possible to develop

a CDSS that could identify high risk individuals for pancreatic cancer and it is possible to develop a CDSS that can enlighten the user about pancreatic cancer risk levels. In order to know how impactful the CDSS will be in reducing the number of misdiagnoses and delayed diagnoses, more studies will need to be conducted.

## 5.2 Conclusion

More than 85% of pancreatic cancer diagnoses are made during the late stage of the disease. The difference in survival of pancreatic cancer found at an early stage and at an advanced stage is highly significant. Pancreatic cancer incidence rate have been on the rise in the past 20 years. The review of literatures suggests that the increase in incidence of pancreatic cancer may be due to the present-day extended life span as compared with decades ago.

This study aimed at finding the possibilities and capabilities associated with the use of CDSS as a potential risk assessment tool for pancreatic cancer by the general population and health care providers. In this study, the proposed CDSS was developed to aid in identifying high risk individuals for pancreatic cancer and to aid making an earlier diagnosis. Because pancreatic cancer is often diagnosed at an advanced stage and because the symptoms could often result in delayed diagnosis or misdiagnosis, the aim for the proposed CDSS was to mitigate this problem and reduce the length of time it takes for a diagnosis to be made. The CDSS that was developed in this study provided insight to the possibilities of adopting such a system in a health care setting and other public/private organizations that support the awareness of pancreatic cancer. Our results show that the CDSS is able to provide consistent results that are valid and reliable in identifying the

risk level of individuals, particularly high risk individuals. The use of knowledge-based and evidence-based CDSS design was the most practical for this study because of the abundance of knowledge in published literatures and reported statistical data on pancreatic cancer. The research design used followed a step-by-step process that incorporated all findings from relevant publications from 2001 to date. Basically, the study design follow this pattern in order: simple literature review, research questions, extensive literature review, data analyses and interpretation, design method for the CDSS and a functional CDSS. The most relevant and most current information about pancreatic cancer were reviewed and used to develop the parameters for the CDSS. Testing of the CDSS was carried out to simulate actual users and to identify errors in the design, to update the system to function more like an expert and to ensure the validity and reliability of the results it produced. Although, testing on actual users was not carried out, multiple case scenarios were used to test the system. Our findings point in a positive direction. In addition, the CDSS is believed to have met proposed criteria of a successful CDSS using the four features as described in a study by Kawamoto et al. These features include a) a computer-based system b) the CDSS results presented at the time and location of decision-making, c) CDSS results are automatically produced as part of the clinicians' workflow and d) actionable CDSS results provided[120].

What is known about pancreatic cancer is that, it has a high mortality rate and poor prognosis due to lack of early symptoms and resistance to treatment, there is lack of proven scientific methods to detect lesions in the pancreas early. With these in mind, the design of the CDSS was directed towards the possibility of using it in identifying high risk individuals and in reducing delayed diagnoses or misdiagnoses in patients. Some

patients have reported sudden onset of type II diabetes and when medical attention was sought, their diagnosis was delayed for quite a while because all symptoms including blood test results were mistaken as comorbidity for diabetes. Rather than suspecting pancreatic cancer as the cause of the type II diabetes and perhaps conduct more testing to eliminate pancreatic cancer, that was not the case. To prevent cases like this, the use of CDSS as shown in this study is beneficial. This study has shed some light on the possibility of adopting the use of CDSS whether integrated into existing health informatics of whether it is a standalone system. CDSS has been shown in other areas to improve the overall quality of patient care and if the use of CDSS in pancreatic cancer diagnosis and management can bring about lower mortality and higher survival rate, then it has made a significant contribution in patient care. Saving a life and finding avenues for other diseases to be cured or prevented by employing this methodology presented in this study, out ways the cost of establishing and maintaining the proposed system. Some may argue that it is not necessary to establish a system that can screen individuals on a regular basis because pancreatic cancer is not the most prevalent carcinoma and the discovery of IPMTs reduced the fear people had about pancreatic cancer , however, it is better to be prophylactic than have a diagnosis of the disease at an advanced stage. In conclusion, it is our claim that the CDSS will be able to distinguish between the three risk levels created in this study, identify individuals correctly based on the information provided, make the necessary suggestions to individuals based on their symptoms, and provide the user relevant information necessary for a better quality of care.

### 5.3 Discussion

The use of technologically advanced techniques in identifying malignant tumors in the pancreas at the very beginning stages of the tumors will provide possible breakthroughs in understanding the biological features of pancreatic cancer. Understanding what the trigger for mutations are and discovering methods of predicting when mutations could occur may lead to an accepted technique for early diagnosis of pancreatic cancer patients. This study developed a CDSS used to find the possibilities and benefits both clinicians and patients could experience. Although due to limitations, the developed CDSS was not technologically complex enough to identify malignant tumors in the pancreas; it is not our belief that it is an impossible task to develop one. The CDSS used in this study can provide consistent suggestions to the user based on the patient's entire data and this is essential in stimulating the interest of researchers, and in leading researchers in the direction of creating more complex CDSS for clinical trials targeted towards pancreatic cancer diagnosis. The development of a CDSS that could aid clinicians across board, even those with the least experience such that no patient will ever have to experience a delay or misdiagnosis of pancreatic cancer is one of the reasons for this study. The CDSS developed in this study was tested using multiple case scenarios to simulate an actual patient and a clinician and we have proven two of the three hypotheses posed. In order to prove the third hypothesis, clinical trials over several years and a more comprehensive CDSS is needed. A better software program to build the CDSS is also needed.

Because the pancreas is a very delicate organ and a difficult to reach organ during treatment, the chances of having significant impact in the mortality of the disease is not

currently promising however, with all the findings and research being conducted to determine a systematic approach for early detection of malignant tumors in the pancreas, there is hope that someday, a breakthrough technique for early detection will be discovered. Our hope is that the use of CDSS can become a diagnostic tool used to reduce the diagnostic devastation associated with pancreatic cancer. Discovering all aspect and functionalities of the genetic component related to pancreatic cancer and other biological component responsible for the onset of pancreatic cancer will also be influential in leading researchers towards an early diagnostic technique. Also, the need for more awareness and more funding for research in pancreatic cancer should be highly considered even though the number of new cases of pancreatic cancer in comparison to some forms of cancer is low. Research in pancreatic cancer is one area that has not received much attention and funding when compared to other types of cancer, such as, breast cancer and lung cancer. Let's not forget that pancreatic cancer has the highest mortality and the most aggressive and resistant to treatment.

### 5.4 Future Directions

There are several studies that could be done to contribute to or lead to breakthroughs in pancreatic cancer diagnosis. Case studies over an extended number of years and studies to include a large subset of subjects will be needed to formulate the accurate and precise weights or risk factor scores for the three different risk levels used in this study. A risk factor reference chart is required in designing a more valid and reliable CDSS for pancreatic cancer risk assessment. Development and implementation of a more complex and technologically advanced CDSS with interoperability functions and other

significant features are needed. Additionally, developing a well-designed CDSS that is integrated with advanced computer aided detection (CAD) with high sensitivity and high specificity for tumors in the pancreas could provide answers and possibilities in identifying malignancy very early on in a patient. The CDSS can produce results based on the readings of the highly sensitive and specific CAD and the built-in expert knowledge and evidence. Discovering the specific biomarkers for pancreatic cancer and incorporating the results aspect into the CDSS to analyze and produce suggestions for clinicians will be important for future directions. The application of image processing and visualization, and biomarker testing within a CDSS are highly recommended. The combination of both an automated reader and biological tests within a clinical decision support system represents a technologically advanced CDSS that could be developed in the near future to resolve the problem with early diagnosis and management of pancreatic cancer patients. Fundamental questions are yet to be answered but with persistent and consistent studies, problems will be resolved. Questions that came up during the course of this study but with no definite answers are; can there be an imaging technique that will produce, detect and read the results of the imaging rather than been read by a radiologist? Can there be an imaging technique with high sensitivity and specificity to detect the smallest possible lesions in the pancreas even before it is possible for a radiologist to identify? In other words, if the lesions are too minute for a radiologist to detect or interpret by looking at the imaging result, can a state-of-the-art technique take over the place of the radiologist to interpret the imaging result and identify the lesions as early as possible? Other questions developed as progress was made with the literature review,

however the focus and decision for this study resulted from the limitations that currently exist with the use of CDSS for pancreatic cancer diagnosis.

This study has provided insight into so many different aspects of pancreatic cancer related research. In this study, a CDSS was developed and tested using multiple case reports. However, the holistic aspect to ensure the validity and reliability of the CDSS was not utilized due to limited resources of patients' data. Future directions should include a case study to represent the general population and to identify the precise parameters for the three risk levels and the best weighting for each variable in order to obtain a more accurate result. To accomplish this, an approved IRB will need to be obtained, funding will be needed and both clinicians and patients should be recruited for the study. In addition, a more complex and comprehensive CDSS should be developed, however developing a CDSS with such potential will require the use of a software package that has unlimited privileges unlike the academic evaluation package of Exsys Corvid used in this study. Hence, a software program with more capabilities should be obtained. A subject matter expert in developing the future CDSS and knowledge from experts in the subject area of pancreatic cancer are needed. All relevant resources to ensure the accuracy, reliability and validity of future CDSS should be leveraged to the fullest potential such that the study can provide a great deal of contribution in the area of pancreatic cancer.

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