Multimodality Imaging Approach to Predict Antineoplastic Therapy Induced Cardiotoxicity

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Abstract

Cardiotoxicity, which is heart damage arising from chemotherapeutic cancer treatment, is the second leading cause of death in cancer-surviving patients. Typically, cancer patients undergo a series of extensive tests throughout their cancer treatment and beyond. Integrating existing data of available biomarkers from these routine tests can be cost-effective and prognostically important without burdening patients with additional invasive testing. Therefore, this project aims to develop an artificial intelligence model that can predict cardiotoxicity risk in cancer patients from existing CT scans to reduce the testing burden on patients while maximizing the utility of existing imaging data. Using image analysis techniques within python, the aortic wall was automatically thresholded and isolated by eliminating the aortic lumen and surrounding tissue from the mask for contrast CT scans. The resulting masks were then analyzed using PyRadiomics' feature extractor. While further modifications to the existing python program need to be made to improve the resulting masks for non-contrast images, the end goal is to use this radiomic data to develop an artificial intelligence tool for detecting important biomarkers on the aortic wall that can be used to assist cardiologists in identifying cardiotoxicity indicators. Ultimately, this tool will help automate the diagnosis of cardiotoxicity along with increasing diagnostic accuracy and precision.

Description of the Problem

An increase in the aging population within developed countries has led to higher rates of concurrent cancer and cardiovascular disease diagnoses. This can be attributed to cytotoxic agents in chemotherapeutic cancer treatments that have been shown to negatively affect the cardiovascular system, making the simultaneous treatment of these diseases difficult to treat (Albini, Adriana). This problem is extremely common as cardiotoxicity is the second leading cause of death in cancer survivors. In a study of 7,529,481 cancer patients, 394,849 (or roughly 1 in 19 people) died of heart disease. Patients who were older, male, African American, and unmarried were at the greatest risk of fatal heart disease (Stoltzfus, Kelsey C., et al).

Patients receiving cancer treatment are subject to extensive invasive and costly testing. Medical images are generally taken between intervals of every 3-6 months and can include

PET-CT, MRI, echocardiogram, chest x-ray, electrocardiogram, and various other tests. Additionally, cardiovascular disease is also known to place "significant financial burden" on patients, further reducing the state of their mental health and wellbeing (Foy, Andrew, and John Mandrola). Frequent cancer and cardiovascular disease imaging coupled with other testing, treatment, and medication can therefore place a significant strain on patients' health and finances. The estimated cost of care for various types of cancers can be seen below.

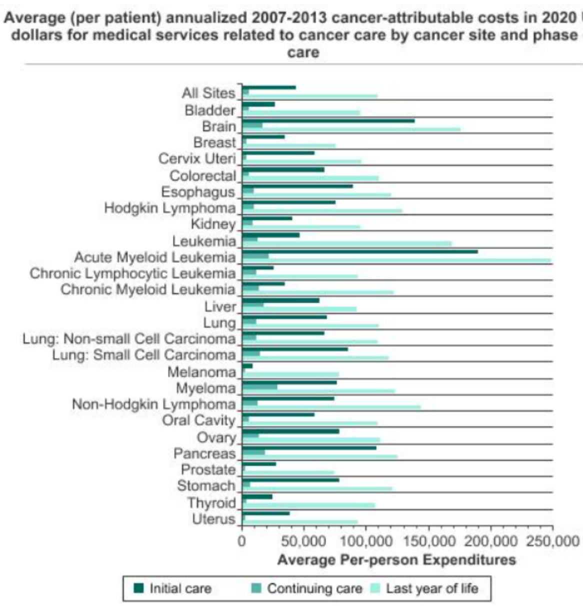

Figure 1: *Financial Burden of Cancer Care* ("Financial Burden of Cancer Care | Cancer Trends Progress Report.").

Patients suffering from cardiovascular diseases receive similar types of medical scans to those suffering from cancers located in the chest and abdomen. Additionally, estimated costs for cardiovascular disease are projected to continue growing considerably, placing an even greater strain on patients. This growth may be more significant than necessary, hence, there is a call for physicians and medical providers to optimize the use of existing tests and procedures.

The burden placed on patients suffering from both cancer and cardiovascular disease could be reduced by extracting data for both diseases from existing routine medical imaging. Currently, there is little collaboration between oncologists and cardiologists resulting in redundant and excessive imaging. If physicians in these two fields were to work closer together, expanding the interdisciplinary field of cardio-oncology, both diseases could be appropriately treated with available cardiovascular disease biomarkers being used during routine cancer medical imaging for early cardiotoxicity detection.

The question asked for this project was: given CT images of patients before and after receiving chemotherapeutic treatment, was there a way to use available cardiovascular disease biomarkers, like inflammation around the aorta, to detect cardiotoxicity? Solving this problem required the use of subject isolation techniques in combination with radiomic methods to first isolate a region of interest within an image and then extract features from that image to gain potentially diagnostic information. Therefore, this product began development of a method using image analysis for early cardiotoxicity detection, making its primary market patients with cancer and cardiovascular disease, along with cardio-oncologists.

Project Objective Statement

The objective of this project is to develop an automated program that processes and extracts aortic wall inflammation data from heart CT scans obtained from routine cancer surveillance testing. The next step will be to feed this radiomic data into a machine learning algorithm, which in conjunction with clinical data, can be used to predict cardiotoxicity risk.

The team addressed the problem by splitting up the project objective into smaller components. First, the team completed a comprehensive literature search to determine what existing methods are being tested to solve this problem. The literature search also affirmed the anatomy behind this problem by proving that data extracted by the aorta can be used to determine the risk of cardiotoxicity. Next, the team worked on a manual model of isolating the lumen from a contrast CT scan using ImageJ. Once this model was created, the macros feature in ImageJ allowed the team to automate this process. The team then replicated this code from the macros feature in ImageJ into Python. Finally, the team used PyRadiomics to extract data from the isolated aortic wall.

This approach was innovative as each step adequately prepared us for the next phase of the project. Additionally, doing article reviews every week alongside allowed the team to incorporate background information with practical application of image analysis. If the team did not start with utilizing ImageJ, then creating the final code in Python would have been infinitely more difficult. Moreover, the image analysis program produced using python itself is innovative as this is something that has not been tested before, making this a potentially novel method for the detection of cardiotoxicity as an alternative to physicians purely interpreting CT scans.

The final python program solves the problem by isolating the aortic wall in contrast images for several dozen CT scans and produces an output file with features extracted using the PyRadiomics package. The specifications of this final design included the creation of a singular program script using python, specifically the pycharm integrated development environment, that both processes and analyzes input images. This solves the initial problem of finding a way to automatically isolate the aortic wall from CT scan images of the chest.

Documentation of the Design

To achieve the final design, the team executed two separate phases of prototype development. During the Fall semester, the team used ImageJ to work on isolating the aortic wall. This initial phase was aimed at identifying the best possible way to threshold the aorta to achieve optimal results. However, due to ImageJ's non-open source nature, the team transitioned to reproducing similar results in python during the Spring semester. This allowed the team to continue with their efforts towards the final design while taking advantage of python's open-source nature. Ultimately, in python, the team was able to work more efficiently and collaboratively, leading to the final prototype being capable of processing and analyzing an entire folder of input images almost instantly.

Phase 1: ImageJ

Before delving into the team's efforts to isolate the aortic wall from a CT scan of the heart, it is essential to understand the various commands used in ImageJ. Thresholding, a technique for dividing an image into two or more classes of pixels, was primarily used to obtain the desired outcome. Typically, these classes are referred to as foreground and background. The team also utilized the 'Invert' command, which creates a reversed image, similar to a photographic negative, of the entire image or selection. Additionally, the 'Image Calculator' command was also used to perform arithmetic and logical operations between two images, such as 'AND' and 'Subtract,' which either combine or subtract two images respectively. Finally, the team also used macros, a command which automates a series of image processing steps, and batch processing, which enables the functionality of macros to be applied onto multiple images simultaneously.

Having been introduced to ImageJ in BMEG 310: Bioimaging, in the spring of 2022, the team decided to refresh their memory by reproducing a proof of concept by isolating a brain tumor in a CT scan of the brain.

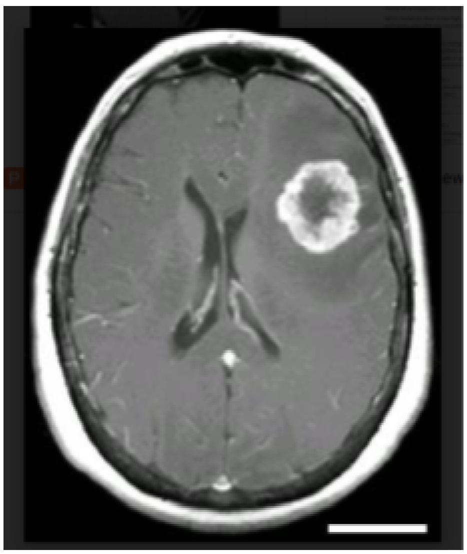

***Figure 2**: Original Brain CT Scan.*

***Figure 3**: Isolated Brain Tumor.*

With the successful completion of this task, the team then proceeded to isolate the aortic wall in a CT scan of the heart. The first objective was to threshold the image. Within ImageJ, seventeen pre-built thresholding algorithms exist, each with a slightly different algorithm being used to threshold the images. Upon experimenting with several of these pre-built-in thresholding algorithms within ImageJ, the team selected both Default and IsoData for their ability to automatically threshold images based on averaging pixel values using an iterative mechanism. Standard algorithmic outputs using the various different thresholding algorithms can be seen in the figure below.

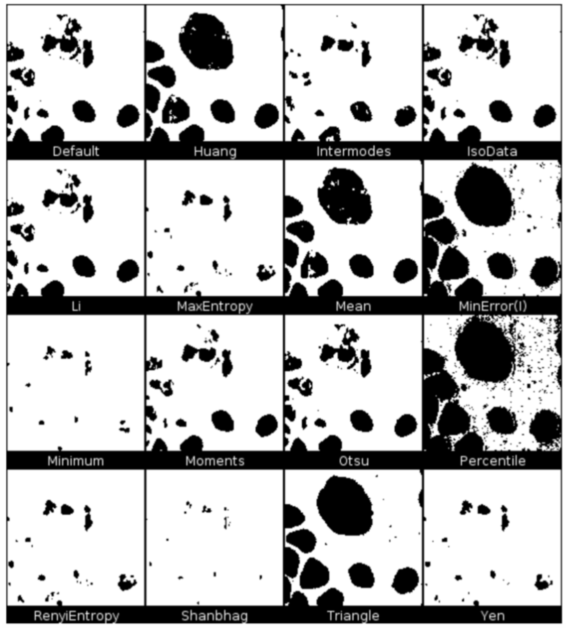

***Figure 4**: ImageJ Built-in Image Thresholding Algorithms.*

Additionally, the team explored two forms of thresholding, manual and automatic. Under manual thresholding, the two methods used were: masking and the over/under methods.

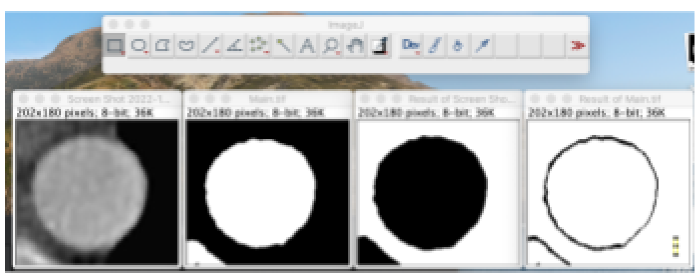

***Figure 5**: Manual Image Thresholding - Masking method.*

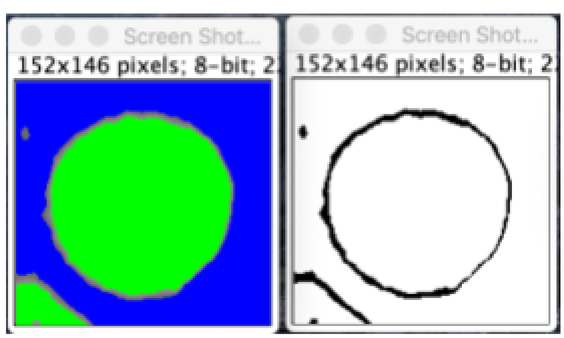

***Figure 6**: Manual Image Thresholding - Over/Under method.*

The primary difference between both methods was the number of steps involved. The masking method was a 9-step process, while the over/under method was a more simplified process that achieved a comparable outcome within just 3 steps. To enhance the efficiency of the program, the team decided to go with the over/under method. The table below summarizes the step-by-step process of manual thresholding using both methods.

Masking method	**Over/under method**
1. Convert image to 8-bit 2. Threshold image (Default) 3. Invert image 4. Open original image 5. Convert original image to 8-bit 6. Use image calculator to put the inverted image on top of the original image 7. Threshold resulting image (Default) 8. Invert image 9. Use image calculator to put the first inverted image on the second inverted image	1. Convert image to 8-bit 2. Threshold using Over/Under a. Select: Dark Background 3. Invert image

It is important to note that up until this point, all thresholding was being done by manually adjusting the slider on ImageJ. The problem with this was that the same output could not be reproduced each time due to operator variability. To minimize this human error and ensure consistent results, the team experimented with the auto thresholding feature as prior methods were manual and prone to error as the subjective thresholding values chosen during manual thresholding often gave different outputs. Using the auto feature, the team successfully isolated the aortic wall in the images shown below, ensuring the same output each time regardless of who was processing the image.

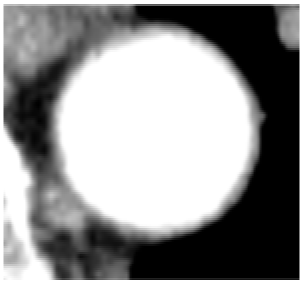

***Figure** 7: Sample Contrast Image Provided by Client.*

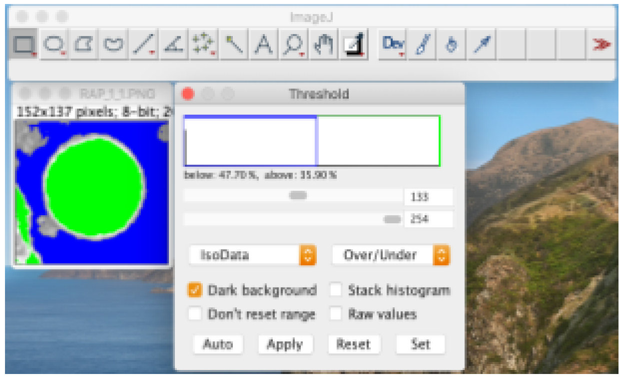

***Figure** 8: ImageJ Screen Showing Auto Thresholding.*

***Figure** 9: IsoData Auto Threshold Attempt a.*

***Figure** 10: IsoData Auto Threshold Attempt b.*

Once the aortic wall was successfully isolated, the team's next goal was to remove background noise. The tracing tool and the oval brush tool were the two ImageJ tools used in the background noise removal process, with both outputs shown below. The team found the oval brush tool to be more suitable as it provided a clearer background and was relatively easier to use. With the oval brush tool, the team created a border around the aorta and cleared everything outside that border.

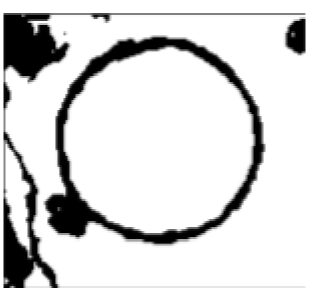

***Figure** 11: IsoData Auto Threshold Output.*

***Figure** 12: Tracing Tool Output.*

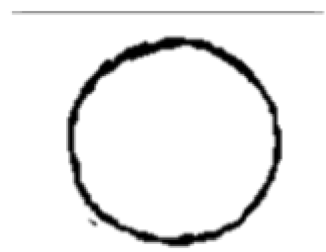

***Figure** 13: Oval Brush Tool Output.*

The step-by-step process of using both tools is further summarized in the table below.

Tracing Tool	Oval Brush Tool
1. Use wand to manually select any unwanted object 2. Edit > Fill 3. Repeat until all noise is eliminated	4. Create a border around the aorta 5. Edit > Clear Outside

The team then successfully replicated the automatic image processing method on several sample contrast scans provided by the client, as shown in the figures below. While doing so, the team observed the difference in aortic wall phenotypes among the different patients.

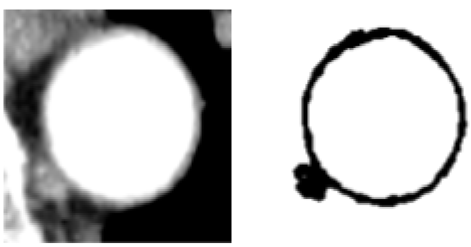

***Figure 14**: **(a)** Original image RAP1_1 **(b)** Processed image RAP1_1.*

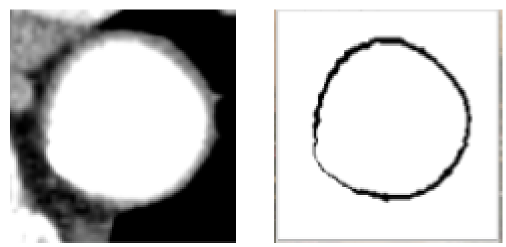

***Figure 15**: **(a)** Original image RAP1_2 **(b)** Processed image RAP1_2.*

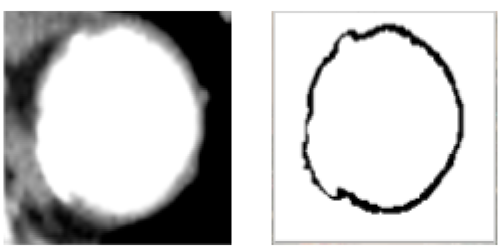

***Figure 16**: **(a)** Original image RAP1_3 **(b)** Processed image RAP1_3.*

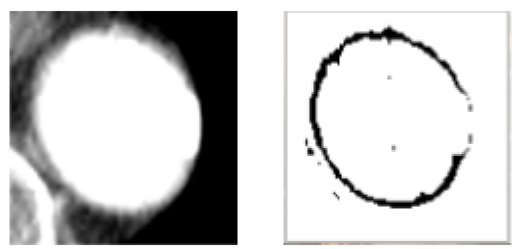

***Figure 17:** **(a)** Original image RAP1_4 **(b)** Processed image RAP1_4.*

Upon producing the output images as shown above, the team was then tasked to convert the final output back into grayscale as requested by the client. This was simply done by repeating the image calculator operation once again by adding the original image and the processed image together. A sample output of this operation can be seen in the figures below.

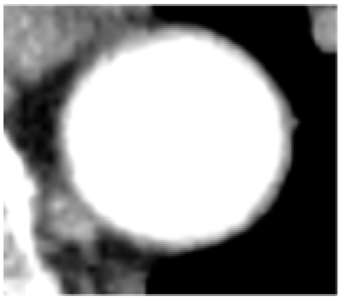

***Figure 18**: Original Image.*

***Figure 19**: Processed Image.*

***Figure 20**: Processed Image Converted Back to Grayscale.*

The next phase of the prototype development included the automation of the entire iterative process. This task was completed by using the macros feature within ImageJ. This involved recording a series of commands using the command recorder, saving the macro as a text file, and executing it by selecting the "run" icon in the ImageJ toolbar. The macros script along with the resulting output image can be shown in the figures below. The final macros script is also attached to this document as Appendix A.

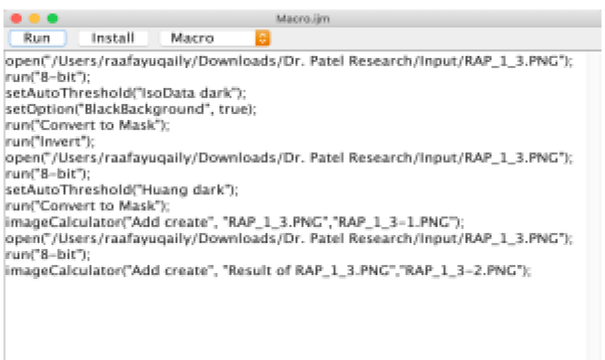

***Figure 21**: Final Script Screenshot.*

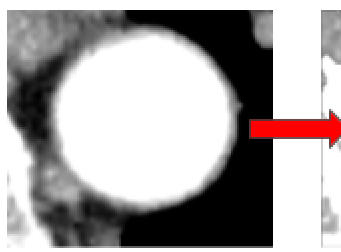

***Figure 22**: Original Image.*

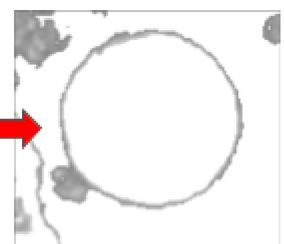

***Figure 23**: Script Output Image.*

While this image processing method could be easily executed for a single image using the macros feature, the team encountered challenges with batch processing as the script referenced the same input image multiple times. The error code, which resulted from the program's inability to distinguish between two images within the image calculator operation, can be seen in the figure below.

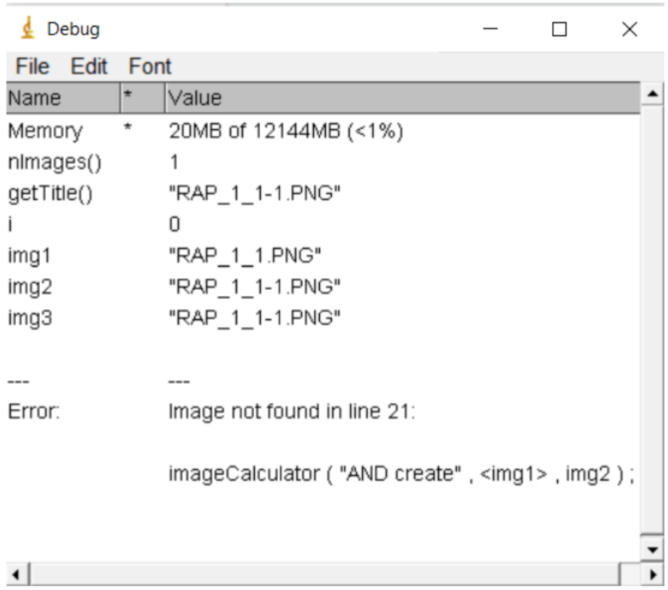

Figure 24: *ImageJ Batch Processing Debug Screen.*

The failure of ImageJ's batch processing technique, coupled with the inability of the software's use within an open-source application resulted in the team pivoting to Python.

Phase 2: Python

As stated above, difficulty within ImageJ arose during attempts to batch process multiple images at once. Luckily, this process was much simpler to execute in python as initial attempts to rotate all images within an input folder by 90° were successful. The code below shows this attempt where a for-loop is used to iterate through all images (referred to as file_name) within a given folder, (referred to as in_folder_path). The code within this for-loop is responsible for executing image processing (image rotation).

```python
from PIL import Image
import os


def main():
    # path of folder containing raw images
    in_folder_path = "C:\\Users\\axelm\\Documents\\3_PET_Images_Original"

    # path of folder to contain modified images
    out_folder_path = "C:\\Users\\axelm\\Documents\\4_PET_Images_new"

    for file_name in os.listdir(in_folder_path):
        # file_name contains name of current file from in_folder_path

        # input_path appends the image's file name to in_folder_path to create a path to the image.
        input_path = os.path.join(in_folder_path, file_name)

        img = Image.open(input_path)

        # output_path contains the full path of the output (including modified file name)
        output_path = os.path.join(out_folder_path, 'invert_' + file_name)

        # modify current image with methods below
        img.rotate(90).save(output_path)

        # print output_path to console
        print(output_path)


# driver function
if __name__ == '__main__':
    main()
```

Figure 25*: Preliminary Python Script that Rotates All Images in a Folder by 90^0.*

Once it was determined that Python could perform batch processing, the next step was to replicate the entire image thresholding method previously developed in ImageJ. Slight modifications to the process were necessary due to limitations of python's image processing library. The most notable difference was the transition from IsoData to Otsu thresholding. Per the team's judgment, this decreased mask quality, but still resulted in a similar final output. The process to isolate the contrast lumen of the aorta remained unchanged from ImageJ. However, to isolate the entire aorta (including the wall), the otsu command had to be used instead. The two masks created by this process were added together to result in the final isolated aortic wall. The code to produce the final image and an example output can be seen below.

```python
# modify raw images with methods below
blur = cv2.GaussianBlur(img, (5, 5), 0)
thresh_value, thresh_image = cv2.threshold(blur, 254, 255, cv2.THRESH_BINARY)
thresh_value, otsu_image = cv2.threshold(blur, 0, 255, cv2.THRESH_BINARY + cv2.THRESH_OTSU)
otsu_image = cv2.bitwise_not(otsu_image)
masked_image = thresh_image + otsu_image
masked_image = cv2.bitwise_not(masked_image)
```

Figure 26*: Mask Creation Code.*

Figure 27*: Successful Threshold Output Using (a) Binary and (b) Otsu Commands.*

The resulting image, as shown below, was comparable to the outputs previously obtained while using ImageJ.

Figure 28. *Python Image Processing Output.*

It was then determined that for PyRadiomics to work, the final image had to be inverted. This was completed using openCV's bitwise_not operation. The inverted image can be seen below.

Figure 29. *Inverted Image Processing Output.*

At this point, all functionality from ImageJ had been redeveloped in Python with the addition of batch processing functionality. Therefore, the team began working towards improving the image analysis method. Namely, inquiries were made into blob-detection, ROI segmentation, and non-contrast isolation.

Blob-detection made use of binary conversion and otsu thresholding, similar to the original process, but further isolated the subject through openCV's findContours method. FindContours marked locations on the image where a change in color occurred and saved it as a contour. This method aimed to remove the background noise surrounding the subject. However, this method failed to mark all contours which resulted in data loss in regards to the external border of the aorta. An example output from this process can be seen below where it is compared to the otsu output.

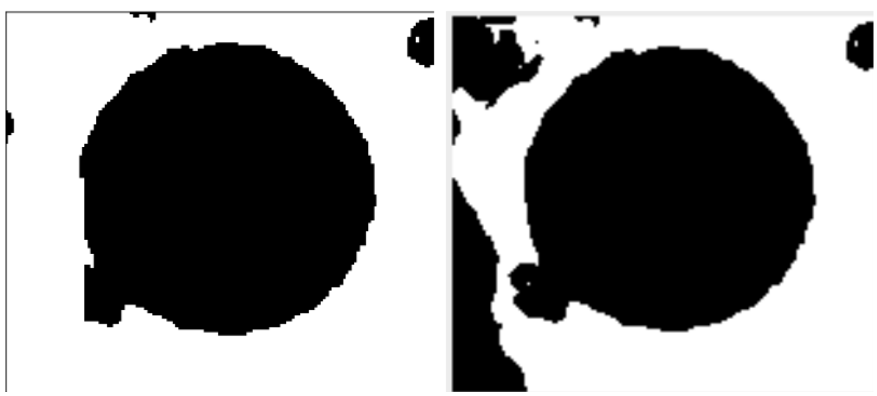

Figure 30: *(a) Blob Detection vs. (b) Otsu Thresholding.*

ROI segmentation techniques were also tested which used similar methods as blob detection but worked with the intention of cropping a full CT scan down to the region around and including the subject (the aorta). Blob-detection, while successfully able to remove background noise, also occasionally removed sections of the subject. Additionally, ROI segmentation was unable to accurately locate the aorta from a full CT scan as it was built upon the premise that the subject would be the contour of the largest area, which was not necessarily true. Ultimately, due to limitations in their inherent designs and lack of technical programming expertise, both of these functionalities were not included in the final prototype.

Non-contrast image isolation, however, was included in the final product. The current image analysis method did not work for non-contrast images so a separate method had to be created where the original image was edited to have both increased and decreased contrast versions. Otsu thresholding was then performed on both of these images to produce masks. After one image was inverted, the two images were added together to produce the final product. This method worked better for non-contrast but worse for contrast images when compared to the original process. Because of this, the two processes were split and the image thresholding method performed on an image was determined by its contrast level.

The distinction between a contrast and a non-contrast image was made by obtaining the pixel value at the center of the image. An if statement was then used to state that if the pixel value obtained was over 200, the image would be classified as "contrast," and if the pixel value of the image was under 200, it would be classified as "non-contrast."

```python
thresh = 200
if middle_pixel_value >= thresh:
    # output_path contains the full path of the output (including modified file name)
    output_path = os.path.join(out_folder_path, '(Pre) Contrast', file_name)
    cv2.imwrite(output_path, img)

    # store output path to later put in data frame. (to print to Excel and CSV)
    original_contrast_pathways.append(output_path)

else:
    # output_path contains the full path of the output (including modified file name)
    output_path = os.path.join(out_folder_path, '(Pre) Non Contrast', file_name)
    cv2.imwrite(output_path, img)

    # store output path to later put in data frame. (to print to Excel and CSV)
    original_non_contrast_pathways.append(output_path)
```

Figure 31: *Python Code to Determine Contrast Level of an Image.*

The code for non-contrast image thresholding, as well as an example output from the noncontrast processing method can be seen below as well.

```python
def non_contrast(img):
    # modify raw images with methods below
    increased_contrast = cv2.convertScaleAbs(img, alpha=6, beta=6)
    reduced_contrast = cv2.convertScaleAbs(img, alpha=0.4, beta=0)

    reduced_blur = cv2.GaussianBlur(reduced_contrast, (5, 5), 0)
    increased_blur = cv2.GaussianBlur(increased_contrast, (5, 5), 0)
    thresh_value, reduced_thresh_image = cv2.threshold(reduced_blur, 254, 255, cv2.THRESH_OTSU)
    thresh_value, increased_thresh_image = cv2.threshold(increased_blur, 254, 255, cv2.THRESH_OTSU)
    increased_thresh_image = cv2.bitwise_not(increased_thresh_image)
    masked_image = increased_thresh_image + reduced_thresh_image
    masked_image = cv2.bitwise_not(masked_image)
    return masked_image
```

Figure 32: *Image Thresholding Script for Non-Contrast Images.*

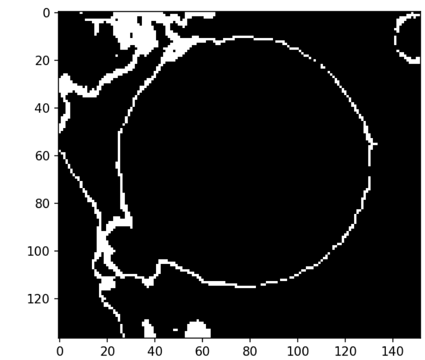

Figure 33*: Output of Aortic Wall Isolation in Non-Contrast CT Scan.*

As a product, the developed prototype was aimed to be user friendly. While no graphical user interface or web based interface was developed due to time constraints and lack of technical expertise, the team was able to reduce burden of use by making both inputs and outputs simpler to navigate and find respectively.

Due to the large number of outputs, the team decided it best to separate outputs into distinct folders within the output folder specified by the user. Namly, the product divided outputs into pre and post folders for both contrast and non-contrast images separately. Then, although PyRadiomics was run automatically from within the code for contrast images, Excel and CSV outputs were also saved for the user's convenience. These Excel and CSV files contain the pathways and labels necessary for an end user to be able to run PyRadiomics for any of the desired images. The subfolder layout, and code to create the Excel and CSV outputs can be seen below.

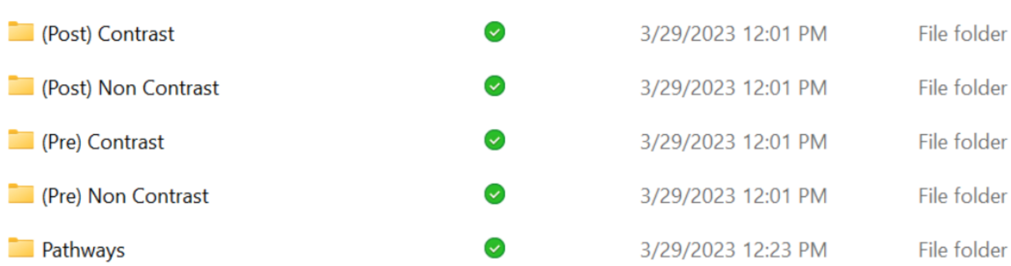

Figure 34*: Auto-generated Subfolders with Inputs and Outputs.*

```python
# Save as Excel output (Contrast and Non-Contrast output on different sheets)
with pd.ExcelWriter(out_folder_path + '\\Pathways\\Pathways Excel.xlsx', engine='openpyxl') as writer:
    df_contrast.to_excel(writer, sheet_name='Contrast', index=False)
    df_non_contrast.to_excel(writer, sheet_name='Non-Contrast', index=False)

# Save as CSV output (Contrast and Non-Contrast output in different files)
df_contrast.to_csv(out_folder_path + '\\Pathways\\(Contrast) Pathways CSV.csv', index=False)
df_non_contrast.to_csv(out_folder_path + '\\Pathways\\(Non-Contrast) Pathways CSV.csv', index=False)
```

Figure 35*: Code to Export Image Pathways to Excel and CSV Files.*

Prototype of the Final Design

The prototype of the final design is attached to this document as Appendix B. The final python script developed by the team categorizes CT scans from an input folder into contrast and non-contrast images, processes each image based on whether it is contrast or non-contrast, saves the resulting masks into their respective folders, records the file pathways of each image and corresponding mask in a csv and excel file (further separated by contrast and non-contrast), and finally runs PyRadiomics to extract aortic wall features for contrast images.

The images below prove the feasibility of the prototype by showing that the developed program is able to successfully process input images into desired masks of the aortic wall.

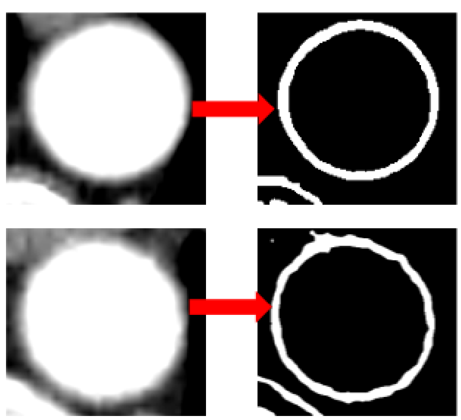

Figure 36*: Final Program Output Images.*

Proof that the Design is Functional and Will Solve the Problem

Upon implementation of the image processing method, feature extraction of the images was completed using PyRadiomics. PyRadiomics is an open-source python package developed as part of the Artificial Intelligence in Medicine (AIM) program at Harvard University for use in the extraction of radiomic features from 2D and even 3D images and binary masks. This package quantified the phenotypic characteristics such as shape and texture of our processed images by using a large panel of engineered hard-coded feature algorithms. PyRadiomics completed feature extraction using four main steps: loading and preprocessing of the image and segmentation maps, application of enabled filters, calculation of features using the different feature classes, and returning the results .

Feature classes include: First Order Statistics, Shape-based (2D and 3D), Gray Level Co Occurrence Matrix (GLCM), Gray, Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), Gray Level Dependence Matrix (GLDM), and Neighboring Gray Tone Difference Matrix (NGTDM). These feature classes are supplemented by optional filters which include: Laplacian of Gaussian (LoG, based on SimpleITK functionality), Wavelet (using the PyWavelets package), Square, Square Root, Logarithm, Exponential, Gradient (Magnitude), and 1 Local Binary Pattern (LBP) 2D / 3D.

The attached google sheet link shows the PyRadiomics output for sample CT scan images given to the team by the client. This also serves as sufficient proof that the python program is functional and is able to output the desired radiomic features. PyRadiomics Output

Future works include the improvement of image thresholding techniques for non-contrast CT scan images, complete removal of unwanted artifacts around the aortic wall, automatic region of interest segmentation to eliminate manual cropping of images, and development of a predictive machine learning framework. This can be done through the collection and analysis of clinical data in conjunction with current radiomic data to determine whether there is a significant difference in aortic wall features in healthy vs. diseased patients, helping answer the question of whether this prototype can ultimately solve the problem of detecting cardiotoxicity in cancer patients.

Engineering Standards

To develop an effective and reliable program for isolating the aortic wall from heart CT scans, along with a machine learning framework that utilizes radiomic data from the developed python program, it is important to adhere to engineering standards. These standards encompass five key areas: accuracy, precision, speed, usability, and robustness.

Accuracy is the primary standard that must be met by the algorithm. The correct identification of the aortic wall in all heart CT scans is crucial, even when scans have lower quality or resolution. The algorithm must also be capable of measuring different values of the aorta, such as its size. Without this level of accuracy, the algorithm would be unreliable and could lead to incorrect diagnoses and treatment plans.

The second standard is precision. The algorithm must generate consistent results over multiple runs, even when run on different computers or by different individuals. This ensures that the algorithm is reliable and can be used by clinicians to make informed decisions regarding their patients' health. The third standard is speed. The algorithm must be capable of processing large sets of heart CT scans quickly to enable clinicians to make diagnoses and treatment plans in a timely manner.

Usability is the fourth standard that the algorithm must meet. It should be user-friendly and easily navigable by individuals who are not familiar with computer programming. This ensures that clinicians can easily use the algorithm without requiring specialized technical knowledge or training. This can further aid patients who would like to directly use the algorithm to assess their cardiotoxicity risk by uploading their CT scans to an online application.

Finally, the algorithm must meet the standard of robustness. It must be able to handle and process CT scans of different resolutions, qualities, and anomalies that may be present in the aorta. This ensures that the algorithm is versatile and can be used in a wide range of clinical scenarios. This can also allow for the algorithm to be used to detect and diagnose various other cardiovascular diseases such as cardiomyopathy or aortic stenosis.

Before launching this product to the market, several specific engineering standards will also need to be used to both test and validate the prototype design. Upon meeting these engineering standards, the product can then seek regulatory approval. For instance, IEEE SA P7003 specifies the elimination of negative bias in the creation of any algorithm, where "negative bias" infers the usage of overly subjective or uniformed data sets or information known to be inconsistent with legislation concerning certain protected characteristics (such as race, gender, sexuality, etc); or with instances of bias against groups not necessarily protected explicitly by legislation, but otherwise diminishing stakeholder or user well being and for which there are good reasons to be considered inappropriate. (IEEE SA). Additionally, as this project aims to develop a software, software developers are recommended to follow relevant existing international standards with regard to software testing, such as the IEC 62304, the IEC 82304-1, IEC 62366-1, ISO 14971, and Food and Drug Administration guidance for off-the-shelf software use in medical devices (de Hond et al., 2022).

Background Research

Literature Review

Citations for all articles reviewed can be found under Appendix C.

1. ***Cardiotoxicity of Anticancer Drugs: The Need for Cardio-Oncology and Cardio-Oncological Prevention***

Due to the aging population of developed countries, it is increasingly common for patients to have both cancer and cardiovascular disease. In addition, cytotoxic agents in cancer treatments have shown to negatively affect the cardiovascular system. This article highlighted the need for cardiologists to assist oncologists by performing evaluations relevant to the choice of therapy to reduce or address the increasing prevalence of cardiotoxicity, naming the collaboration as cardio-oncology.

This article is relevant to our project as we are trying to predict the occurrence of cardiovascular events in patients undergoing cancer treatment, providing us with direct insight into the overlap between the two medical fields. This project also mentioned the occurrence of inflammation as a result of cardio-toxicity, something we will be actively trying to quantify through CT scans for this project.

2. ***An artificial intelligence-enabled ECG algorithm for the identification of patients with atrial fibrillation during sinus rhythm: a retrospective analysis of outcome prediction***

Atrial fibrillation (AF) is a rapid heart rate that commonly causes low blood flow. It is often under-diagnosed and associated with an increased risk of stroke, heart failure, and patient mortality. The goal of this paper was to highlight the efficiency of AI models in accurately diagnosing patients with various phenotypes of the same disease. This paper used a 12-lead ECG to identify subtle findings associated with a history of AF. To avoid ambiguity, patients who had documented AF but a missing ECG were excluded from the study. With over 180,000 patients in the dataset, the primary outcome of the study was the ability of the artificial intelligence (AI) model to identify patients with AF using AUC and ROC curves. In both the validation and testing sets, an AUC of 0.87 was achieved. Additionally, upon using multiple ECGs (where available), the AUC of the model went up to 0.9. This compared significantly better than existing biomarkers such as BNP, which is used to detect heart failure with an AUC between 0.6-0.7.

This paper directly relates to our project as we hope to extract image-based data for patients and then use it to develop an AI-based model to determine whether or not it can better assess cardiotoxicity risk in patients than current diagnostic methods. We hope to make the model effective such that it can recognize subtle biomarkers that may or may not be easily identifiable to the human eye. When we get to the analysis of our classifier, we hope to utilize similar testing methods to determine effectiveness, such as AUC and ROC curves.

3. ***Artificial intelligence in cancer imaging: Clinical challenges and applications***

This article focuses on the applications of artificial intelligence specifically in streamlining clinical workflow, finding complications that physicians might miss, and transforming image interpretation from a purely qualitative and subjective task to one that is quantifiable and effortlessly reproducible. The article continues and focuses on a multitude of artificial intelligence applications in multiple cancers: such as lung, breast, and prostate cancer. For lung cancer, AI can quantify the radiographic characteristics of the tumor's phenotype automatically and can identify biomarkers to reduce false positive test results. This allows for earlier and more accurate detection. In breast cancer, AI can use computer vision to characterize a tumor by finding the exact shape and comparing it to a database of pre-defined deep learned algorithms. For prostate cancer, AI can help with monitoring, but also detection and localization of prostate cancer.

This article relates closely to this capstone because it alludes to a large gap in artificial intelligence for cardiotoxicity diagnosis through AI or machine learning post cancer diagnosis. Our capstone helps fill this gap and allows for the further advancement of using artificial intelligence for cardiovascular risk prediction among cancer survivors.

4. ***A Novel Two-Dimensional Echocardiographic Image Analysis System Using Artificial Intelligence-Learned Pattern Recognition for Rapid Automated Ejection Fraction***

This paper discussed a novel 2D echocardiographic image analysis system using AI-learned pattern recognition that can rapidly and reproducibly calculate ejection fraction. Ejection fraction (EF) is a measurement expressed as a percentage of how much blood the left ventricle pumps out with each contraction. EF is an important criterion for certain clinical therapies and so it is important to estimate an accurate EF. Previous manual tracing approaches have been widely used for EF, but it is time-consuming and hence, visual assessments have been adopted. However, the visual assessments require practice which ultimately makes the approach subjective. Hence, a more objective and less time-consuming approach was needed. Therefore, auto EF was developed by using AI-learned pattern recognition programming trained on several thousand human endocardial tracings to mimic steps such as bridging gaps in endocardial dropout and excluding papillary muscles.

In this study, the relationship between auto and manual EFs was similar in ischemic disease patients with regional wall abnormalities as well as in the 53 patients with nonischemic cardiomyopathy. Additionally, the time requirement for auto EF was lower than the manually traced EF. Furthermore, auto EF correlated well with visual EF by expert readers. A favorable correlation was observed between auto EF and MRI with r=0.95. In conclusion, auto EF was easier to accomplish, required shorter scan times and significantly less post-processing, and was performed portably in several cases. This article backed the idea that using an automated process in 2D image analysis is more efficient and less time consuming as it reduces the risk of subjective errors due to human interpretations.

5. ***A Machine Learning Model Based on PET/CT Radiomics and Clinical Characteristics Predicts ALK Rearrangement Status in Lung Adenocarcinoma***

Anaplastic lymphoma kinase (ALK) is a gene present in an embryo that results in the development of the gut and nervous system. Mutations in this gene can lead to lung cancer that can eventually spread to other parts of the body. Certain rearrangements of this gene indicate that the patient can be treated with targeted ALK inhibitors. Traditional methods of detecting these rearrangements include fluorescence in situ hybridization, immunohistochemical staining, and reverse transcription-polymerase chain reaction, all of which require biopsy or surgical tumor specimens. The purpose of this study was to predict the ALK rearrangement status in lung adenocarcinomas by developing a non-invasive machine-learning model that combines PET/CT radiomic features and clinical characteristics.

They used two methods in extracting radiomic features from PET/CT images of 526 patients (109 positive, 417 negative) with lung adenocarcinoma. Maximum relevance minimum redundancy (mRMR) selects features with high correlation to the pathological results while retaining features with minimum correlation between them. Least Absolute Shrinkage and Selection Operator (LASSO) is a statistical formula whose main purpose is feature selection and regularization of data model by shrinking the regression coefficients sometimes to zero. From these images, 22 radiomic features were extracted. They constructed three radiomic models from these images: PET, CT and a combined PET/CT. PET/CT proved to be slightly better than PET and CT in predicting ALK mutation status, but there was no significant difference between the PET and CT models. The combined model had an advantage in predicting ALK mutation status and a higher AUC in both the testing and training groups. The combined model had an AUC of 0.87 compared to an AUC score of 0.76 from the clinical method alone in the training group. Also, in the testing group, the combined model had an AUC of 0.88 while the clinical model had an AUC of 0.74. In conclusion, a combined PET/CT radiomics-based machine learning model can be used as a non-invasive technique to diagnose ALK rearrangement for lung adenocarcinoma patients in the clinic, which can in turn aid in determining which patients can be treated with ALK inhibitors.

As seen in the methods and results of this project, machine-learning can be a useful tool when diagnosing patients. It provides a non-invasive method, and in most cases, a timesaving method which is crucial, especially when dealing with cancer patients where time is of the essence. In the long run, it may also be helpful to combine both PET and CT images in one model to optimize our successes in detecting cardiovascular diseases in cancer patients.

6. ***Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations***

Cancer and cardiovascular disease (CSV) are the most prevalent diseases in the developed world accounting for 70% of medical reasons for mortality around the globe. Evidence shows that cancer and CVD are interlinked through common risk factors. A spike in 5-year survival rates for cancer has raised concern about new cancer therapies and the unexpected CVD complications they cause. The researchers of this study held bimonthly webinars/teleconferences from 2015 to 2018 in which they reviewed literature, consensus decisions, and practical recommendations. Each one of these was ranked based on the level of evidence they provided and the grade of the recommendation. Level of evidence and grade of recommendation were both defined into 5 groups based on similar classifications from the infectious Diseases of America-United States Public Health Service Grading System.

The article was extensive and provided suggestions regarding general principles, screening before anticancer therapy, primary prevention therapy, cardiac surveillance, asymptomatic abnormalities, post-treatment guidelines, as well as uses for immune checkpoint inhibitors. Above all, this article suggests the close collaboration of cardiologists and oncologists to minimize the health risks of patients receiving anti-cancer therapies. This article detailed best clinical practice in regards to cancer patients who are receiving anti-cancer therapies. These practices were specifically aimed at minimizing the negative effect of these therapies on the heart. This article gave us a deeper understanding of our project as it described the current healthcare pathway of these patients and outlined several areas in which improvements can be made and are necessary.

7. ***Measurement of Arterial Activity on Routine FDG PET/CT Images Improves Prediction of Risk of Future CV Events***

This study determined if the use of 8F-fluoro-deoxyglucose positron emission tomography (18F-FDG-PET) could help in the prediction of cardiovascular disease (CVD). Over 500 scans from cancer free patients were analyzed with 44 participants developing CVD. It was found that there was a significant link between arterial FDG uptake and incident CVD as well as increased FDG uptake correlating with the timing of CVD incident. It was also found that the list of traditional risk factors along with addition of the arterial FDG measurements improved the previous predictions rates of CVD.

This study sets up many of the factors that prompt the creation of this capstone project. If one can measure the inflammation of arteries caused by arterial FDG uptake then one has a way to potentially diagnose CVD in patients without having to do further cardiovascular-specific scans. One limitation of this study was that the patients did not have cancer. Further research needs to be done to be sure that these results can be replicated in patients undergoing cancer treatment or having survived cancer.

8. ***Is Artificial Intelligence the New Friend for Radiologists?***

This review article talks about how artificial intelligence can be used in radiology. For AI to be effective, it needs to be able to recognize its environment, execute pattern perception, and consequently plan and operate the appropriate course of action. There are 2 different types of AI: narrow (weak) and broad (strong). Narrow AI are algorithms trained to supervise learning which includes diagnostic imaging. Broad AI performs a variety of tasks and has the ability to learn and become self-aware. AI is separated into subsets of machine learning and then deep learning. DL is separated into object detection, semantic segmentation, image processing, and natural language processing. This deep learning model is very applicable to this capstone as these methods are essential to the success of our project.

There are many clinical applications of AI. One clinical application is through the interpretation of images of breast cancer. This is made through a deep learning model that discriminates between benign and malignant tumors using MRI imaging. This application allows for improved treatment planning, dose optimization, and overall better quality of care for patients. Another application is a model that could precisely estimate wait times or appointment delays for radiography, ultrasound, CT, and MRI scans. This would analyze a patient's medical record and give a recommendation of which imaging exam is best. Some positives of AI in this situation are that data is obtained at notably lower radiation levels than previously required, resulting in image acquisition optimization with dramatically low radiation exposure as well as minimizing artifacts by applying image processing algorithms during or after reconstruction steps. One negative of AI is that algorithm compounds amplify existing inequities in socioeconomic status, race, ethnic background, religion, gender, disability, or sexual disorientation during its application, which adversely impacts equity in health systems.

9. ***A low-cost texture-based pipeline for predicting myocardial tissue remodeling and fibrosis using cardiac ultrasound***

This paper looked at using ultrasound myocardial tissue characterization as an alternative to cardiac magnetic resonance (CMR) for risk stratification in patients with left ventricular (LV) remodeling. In the study, 328 texture-based features of the myocardium were extracted from still ultrasound images and phenotypes were determined. After exploring the phenotypes determined, global LV remodeling parameters were predicted using supervised machine learning models. Separately, supervised models for predicting the presence of myocardial fibrosis using another cohort who underwent cardiac magnetic resonance (CMR) were also developed. The phenotype differentiation found that texture-based tissue feature extraction was feasible in 97% of the total 534 patients. Additionally, the inter-patient similarity analysis delineated two patient groups based on the texture features: one group had more advanced LV remodeling parameters compared to the other group. This group was associated with a higher incidence of cardiac deaths ($p = 0.001$) and major adverse cardiac events ($p < 0.001$). The supervised models predicted reduced LV ejection fraction (<50%) and global longitudinal strain (<16%) with an AUC of 0.87 in the validation set. Furthermore, the presence of myocardial fibrosis was predicted from only ultrasound myocardial texture with an AUC of 0.84. This paper ultimately showed that ultrasound myocardial tissue characterization can be used as an alternative to cardiac magnetic resonance (CMR) for risk stratification in patients with left ventricular (LV) remodeling.

Similar to using myocardial tissue characterization to stratify LV remodeling, our project is looking at aortic lumen inflammation to predict cytotoxicity risk. We certainly hope to use the methods proposed in this project to group patients with similar amounts of inflammation which can be then used to draw conclusions about different disease states. This paper also prompts us to look at how aortic lumen inflammation can be predictive of major adverse cardiovascular events or mortality in patients.

10. ***Cancer Treatment and Survivorship Statistics, 2016***

The aim of this paper was to provide statistics on the most prevalent cancers, as well as their survival rates. The most prevalent cancers among males are: prostate, colon and rectum, and melanoma, and among females are: breast, uterine corpus, and colon and rectum. The cancer types with the greatest 5-year survival rates are melanoma (92%), testicular (95%), and prostate (100%) cancers. Some common treatment plans for different cancers include surgical removal of the body part, chemotherapy, and radiation. Side effects include impairment in the function of that body part for example a side effect of colon and rectum cancer is bowel dysfunction; a side effect of prostate cancer is urinary incontinence and erectile dysfunction; a side effect of urinary bladder cancer is urinary frequency. Additionally, the number of cancer survivors continues to grow nationwide and this can be attributed to the technological advancements used in early detection and treatment.

A common effect of breast cancer and cancers in children is cardiovascular diseases. The effect of cardiovascular diseases in children is more dangerous as there is more time for the disease to manifest itself during the child's growth. This gives more purpose to our project as it is important to identify cardiovascular diseases early before they progress to more fatal stages.

11. ***Machine-Learning Algorithms to Automate Morphological and Functional Assessments in 2D Echocardiography***

139 males, 77 with ATH (Physiological hypertrophy seen in athletes) and 62 with HCM (Hypertrophic cardiomyopathy) were subject to speckle tracking echocardiography. These images were used in a machine learning ensemble which consisted of 3 machine learning algorithms: Support Vector Machines, Random Forests, and Neural Networks. The purpose of this study was to assess the diagnostic value of using a machine learning model to automatically discriminate HCM from ATH. Results suggested that the use of machine learning models can

assist discrimination of ATH from HCM. Specifically, the diagnostic ability of the machine learning model was comparable to conventional 2D echocardiographic and Doppler derived parameters.

Our project involves the creation of a program which will automatically isolate the aortic lumen. While this process can be done manually, it can be time consuming and unrealistic in a practical setting where a massive collection of images can accumulate. The purpose of an automatic process then is quite clear - to save time. The result of our project would be used to further automate the diagnostic process a physician would typically employ; it would be used in a machine-learning model, similar to the related articles, to resolve disease state. While the idea of using a combination of our project with a machine learning algorithm to automatically assess cardiac disease state seems viable, the related article demonstrated that the diagnostic value of this method could be comparable to traditional methods.

12. ***Causes of death among cancer patients in the era of cancer survivorship in Korea: Attention to the suicide and cardiovascular mortality***

This article identified cancer and non-cancer related causes of death in Korea from 2000-2016 from a population of almost 3 million. Some of the cancers reported with higher mortality rates include lung (70%), breast (77%) and liver (86%) cancers. On the other hand, some of the cancers reported with lower mortality rates include stomach (men at 39% and women at 48%), prostate (47%) and female thyroid (27%) cancers. A 20-fold increase in cardiovascular disease deaths was reported among patients with cancer from 2000 to 2016. Additionally, the risk of suicide among cancer patients was higher than that among the general population. Furthermore, treatment-related cardiotoxicity was likely to have been reported as a cancer death rather than a non-cancer death. However, this may have been because there was insufficient time to observe long-term cardiotoxicity which may have led to cardiovascular-related deaths. In conclusion, a rapid increase in deaths due to cardiovascular disease and higher mortality risks from suicide among cancer patients highlight the need to prevent cardiovascular disease and suicide in cancer survivorship care.

According to the article, some cardiovascular-related deaths may have been reported as cancer deaths which begs the question, "is there a chance that this may have happened in some cases in the United States?" Also, because there is limited time in assessing the risk of cardiovascular events, there is a need to devise a mechanism that allows us to predict these events earlier, rather than later. This makes our project more important and necessary especially when trying to efficiently minimize the risk of non-cancer deaths in cancer patients.

13. ***Electrocardiographic Predictors of Heart Failure With Reduced Versus Preserved Ejection Fraction: The Multi‐Ethnic Study of Atherosclerosis***

This article discussed the ability of ECG biomarkers to distinguish between the risk of heart failure in patients with reduced versus preserved ejection fraction. The paper brought to light that heart failure kills 40.5% of men and 59.5% of women in the adult population. It also argued that earlier detection methods for heart failure are needed as diagnosis of this condition is typically made late, upon the onset of symptoms. In this study, heart failure was defined as pulmonary edema or congestion by chest x‐ray, dilated ventricle or poor left ventricular function by echocardiography or ventriculography, or evidence of left ventricular diastolic dysfunction. They concluded that markers of ventricular repolarization and delayed ventricular activation are able to distinguish between the future risk of HFrEF and HFpEF which suggests a role for ECG markers in the personalized risk assessment of heart failure subtypes. Specifically, the markers associated with HFrEF are: Prolonged QRS duration, delayed intrinsicoid deflection, left‐axis deviation, right‐axis deviation, prolonged QT interval, abnormal QRS‐T axis, left ventricular hypertrophy, ST/T‐wave abnormalities, left bundle‐branch block. The markers associated with HFpEF are: higher resting heart rate, abnormal P‐wave axis, abnormal QRS‐T axis. Abnormal QRS‐T was associated with both forms of heart failure.

Relevant to our project, this study demonstrated specific biomarkers which are significant in the detection and classification of heart failure. Being able to accurately assess heart disease is vital for our project which aims to assess disease state within the heart based on data obtained from the aortic lumen. Further, within the discussion of this paper, mention of differences between left ventricular mass among men and women raises the question of how sex differences will play a role in our assessment of aortic lumen inflammation between both genders? This also raises the question that other than sex, what differences among patients could play a significant role in diagnosis and how this will affect our study methods. Additionally, this also prompts us to question whether these differences will extend beyond assessment, and if so, will it impact the way that we plan on isolating the aortic lumen?

14. ***Artificial intelligence-based measurements of PET/CT imaging biomarkers are associated with disease-specific survival of high-risk prostate cancer patients***

The researchers in this study seeked to prove that measurements of total volume and lesion uptake of the entire tumor would better reflect the disease's activity with prognostic significance, compared with conventional measurements. They used PET/CT scans because of their higher sensitivity and specificity compared to conventional imaging techniques. This imaging modality is especially useful for primary lymph node and bone staging of prostate cancer. Further, the study used an AI-based algorithm in order to more objectively measure - or in other words to take observer-independent measurements of - tumor detection, segmentation, and classification as PET/CT conventionally still relies on visual assessment with some semi-automated measurements. Using an AI-based algorithm also allows for more advanced measurements to be taken with limited effort as with conventional methods, SUV_{max} is the most easily obtained measurement but has limited clinical value. The researchers compared the prognostic value of a modified AI-based method derived from another study to values of other clinical data including age, Gleason score, prostate specific antigen, and treatment.

The algorithm used was trained on 143 PET/CT scans and applied to 304 prostate cancer patients. It should be noted that the examined group underwent imaging from different cameras than the group used to train the AI. The algorithm failed to perform automated measurements in 5% of patients due to artifacts such as hip prosthesis. Of 285 patients, 23 died of prostate cancer, 18 of which received palliative treatment. A univariate Cox analysis showed that three of the volumetric measurements (lesion volume, TLU, and fraction) made automatically by the AI-based algorithm as well as age were significantly associated with disease-specific survival. This is in contrast to the other PET/CT measurements (SUV_{max} and SUV_{mean}), PSA (logarithmic), and Gleason score. 95% of the scans were accurately identified by the AI-based algorithm and the automated quantification it performed was significantly associated with disease-specific survival for those who received non-curative treatment.

This article proves what many previous articles have made apparent, that the use of AI or machine learning in image analysis appears to be a viable solution for increased accuracy in diagnosis and determination of further treatment plans. Further, this article shows us that it is unnecessary to create an algorithm from scratch if we are able to find one of similar purpose. If we are able to modify such an algorithm for our project, it would not only make creating that algorithm easier but it would also serve as a baseline of what the algorithm should already be capable of producing.

15. ***Clinical utility of automated assessment of left ventricular ejection fraction using artificial intelligence–assisted border detection***

The researchers in this study investigated the clinical viability of automating the assessment of left ventricular ejection fraction. The automation of the left ventricular ejection fraction was completed using an artificial intelligence-assisted border detection technique. The use of AI for this purpose has the potential to decrease both time consumed and the skill necessary for image analysis. Specifically, This article tested the Siemens AutoEF software to determine whether it correlated with visual assessments of EF, manual planimetry, and cardiac magnetic resonance (CMR). Ninety-two Echocardiograms were analyzed where visual assessment by expert and novice readers correlated more closely with manual planimetry using Simpson's method than did AutoEF. The correlation values were $R = 0.86$, 0.80, and 0.64 for expert reader, novice reader, and AutoEF Respectively. From these results, the researchers determined that the automatic quantification of EF requires significant improvement before it can compete with visual assessment for clinical use.

This article shows that current efforts for similar goals to our project are being researched but with unviable results. This taught us that while machine learning has promising results, it can not always be successful and better than manual techniques. Therefore, we need to ensure the predictability of our work with outstanding classification rates.

16. ***PET Scan with Fludeoxyglucose/Computed Tomography in Low-Grade Vascular Inflammation***

The article PET Scan with Fludeoxyglucose/Computed Tomography in Low-Grade Vascular Inflammation discussed the assessment of low-grade inflammation in patients with chronic inflammatory diseases. The researchers in this study combined PET and CT as to combine their respective strengths - high sensitivity and excellent spatial resolution. Vascular uptake of Fludeoxyglucose (FDG) allowed for the visualization of several diseases such as atherosclerosis, as F-FDG accumulates in sites of acute and chronic inflammation. Also, FDG PET/CT is useful In the evaluation of large vessel vasculitis and indolent primary aortic malignancies.

Chronic inflammatory diseases are associated with a high incidence of cardio-vascular events. Being able to assess the degree to which inflammation has occurred in our structurally isolated aortic lumen may be able to give insight into the cardiac disease state of a patient. Although our project does not directly use FDG-PET/CT, understanding how/why this imaging modality is useful in the assessment of low-grade vascular inflammation will undoubtedly affect the way in which we approach the assessment and isolation of the aortic lumen.

17. ***Applications of artificial intelligence in oncologic 18F-FDG PET/CT imaging: a systematic review***

This Literature review compared different applications of artificial intelligence with 18F-FDG PET in a clinical setting. The first application analyzed was AI used for the characterization of malignant pulmonary nodules, tumor detection and delineation, differentiation of lung cancer subtypes, lung cancer staging, and response assessment for lung cancer. One study was able to focus on tumor detection, decreasing the rate of false positives from 72.8% to 4.9%. The second study analyzed head and neck cancer through automated deep learning algorithms to produce a model that differentiates malignant and non-malignant lymph nodes. Pancreatic cancer was also analyzed which the scientist created a CAD model for. The first step used segmented ROI with simple linear interactive clustering on a CT scan, followed by dual thresholding principal component analysis to extract pancreas features. Lastly, the model performed pancreatic cancer classification by hybrid feedback-support vector machine-random forest. This model was 96.47% accurate.

Some anticipated challenges when using artificial intelligence are that medicine is rapidly changing and the algorithms made will have to reflect those changes. It is very hard to ensure that your model is valid and reliable based on the current changes in medicine. This review is relevant to this capstone because we will also face some of these challenges listed here. We need to design our project with continuous improvement in mind so that we ensure our final output is the most up to date.

18. ***A Cognitive Machine Learning Algorithm for Cardiac Imaging: A Pilot Study for Differentiating Constrictive Pericarditis from Restrictive Cardiomyopathy***

This article focused on using machine learning algorithms to differentiate constrictive pericarditis from restrictive cardiomyopathy in cardiac imaging. This was done by using multidimensional attributes of speckle tracking echocardiography (STE) data sets derived from patients with known restrictive cardiomyopathy (RCM) and constrictive pericarditis (CP). An associative memory classifier (AMC) based machine learning algorithm was developed using the clinical and echocardiographic data of 50 patients with CP and 44 with RCM. The AMC had an AUC of 89.2% which further improved (96.2%) upon the addition of 4 echocardiographic variables. In conclusion, using machine learning algorithms in cardiac imaging may aid assessments and support the quality of interpretations especially for novice readers with limited experience.

According to this article, using a machine learning algorithm to detect or predict cardiovascular events has been proven to be accurate and effective. Additionally, this article makes a software suggestion that can be used for the machine learning algorithm necessary in the latter part of our project. The software used in the article is the associative memory classifier (AMC) which may be helpful to explore when we get to that stage in our project.

19. ***Artificial intelligence-enhanced electrocardiography in cardiovascular disease management***

Electrocardiograms (ECGs) are low-cost, simple rapid tests used for diagnosing various heart diseases. They are standardized and reproducible, but their interpretations are subject to human expertise and level of experience. The purpose of this article was to summarize the current and future state of the AI-enhanced ECG in the detection of cardiovascular disease in at-risk populations, discuss its implications for clinical decision-making in patients with cardiovascular disease and critically appraise potential limitations and unknowns. Automated AI models have been adapted to analyzing the routine 12-lead ECG which mimics human-like interpretation but with greater diagnostic fidelity. Deep-learning methods applied to ECG use neural networks with many layers to learn a function between a set of inputs (e.g. wave morphology like Q T R S) and outputs (e.g. ECG rhythm or ejection fraction). The problem with this is that humans cannot understand how the network makes the association between inputs and outputs. However, this reduces human error as the model is not subject to human interpretation. The effectiveness of the AI model in ECGs was shown in one project where an AI model created from a dataset of >70000 patients and >80000 ECGs produced an AUC score of 98%, sensitivity of 87% and specificity of 99% when 828 ECGs were tested. 80% of the tests matched the gold standard. The ECG has been used in detecting asymptomatic cardiovascular diseases like left ventricular systolic dysfunction, silent atrial fibrillation (AF), hypertrophic cardiomyopathy, and hyperkalaemia. One of the modern applications of wearable and mobile ECG technologies is the deep neural network in the Apple watch that helps detect AF passively from photoplethysmography (PPG) which is an uncomplicated and inexpensive optical measurement method that is often used for heart rate monitoring purposes. PPG is a non-invasive technology that uses a light source and a photodetector at the surface of the skin to measure the volumetric variations of blood circulation.

Some challenges faced with AI include the need for a large sample set to develop this mode. It may not be feasible to get a large amount of data if the condition is rare or if the model needs to be developed immediately. Additionally, if the data for the model is obtained from high-quality databases with meticulously obtained ECGs, it may not be accurate when applied to real-world clinical applications. Furthermore, the infrastructure to integrate AI–ECG results into electronic health records and make them available at the point of clinical care is not widely available. Finally, there exists a barrier to approval by regulatory bodies. A legal framework to support AI-based clinical decision-making has not yet been established.

The pandemic has highlighted the need for rapid, point-of-care diagnostic testing. Hydroxychloroquine or azithromycin for the treatment of the infection resulted in a marked increase in the use of these medications. They have the potential to prolong myocardial repolarization and increase the risk of dangerous ventricular arrhythmias which has led to the FDA to approve the use of mobile devices to monitor QT interval in patients taking these medications. The impact of COVID on patients with cardiovascular diseases raises the need for a more timesaving method in detecting these diseases. Furthermore, a deeper understanding is needed of how the coronavirus impacted patients with the risk cardiovascular of events.

20. ***Application of artificial intelligence in cardiac CT: From basics to clinical practice***

This article focuses on the advancement of artificial intelligence (AI) and AI libraries to allow for their increased use with cardiac CTs. Artificial intelligence techniques can be separated by their purpose with a few examples being image improvement, diagnostic classification, object detection, and more. Image improvement is focused on reducing noise and creating more images. One negative to this process is that when you reduce noise in the image, the quality of the processed image decreases. For diagnostic classification, there was a pre-specified amount of categories created to split patients, or the automation would give a percent likelihood that the image would fit into any of the categories. Object detection focused on finding specific objects in the scan and giving exact coordinates. The article further explained that CAD is a large problem in the United States that needs to be diagnosed early through non-invasive testing. This can be done by detecting hemodynamic changes caused by the disease in the coronary artery. One study reviewed had the goal of automatically detecting functionally significant coronary artery stenosis through a rest CCTA, as measured by a fractional flow reserve (FFR). To complete this goal, they segmented the LVM, using an auto-encoder, collected the significant details, and then classified the areas into stenosis or no stenosis.

This paper is relevant to our capstone project because we hope to use a similar methodology of machine learning to isolate the aortic wall and determine cytotoxicity risk. One of the largest goals stated throughout the paper is that the AI should perform tasks at similar or higher accuracy than state-of-the-art prediction studies in cardiac CT. This should also be taken into careful consideration when completing our automation process. If the total process time is longer than it would take for a physician to read the scans and come up with a similar prognosis, then the algorithm would be ineffective.

Results of the Patent Search, Prior Art, Assessment, and Patentability

Machine learning algorithms have been successfully used in similar projects in the past. For example, they have been used to discriminate between Hypertrophic cardiomyopathy (HCM) and Atherosclerosis (ATH). Three different algorithms were used: support vector machines, random forests, and neural networks. This model was comparable to conventional 2D echocardiographic and Doppler derived parameters (Narula, Sukrit et al.).

Several other solutions and technologies have also been developed that may be helpful for our project. For example, a machine learning model to classify diseases such as cardiovascular disease was recently patented by (Gheorghita et al). Another patent which uses a machine learning algorithm to generate at least one indicator to predict the risk of radiation induced toxicity was also recently filed by (Kamel et al). Furthermore, extensive research has also been done on using machine learning to predict the type of cancer in patients based on non-invasively obtained radiological datasets (Buckler, Andrew J., et al). In addition to predicting an oncoming pathological event, supplementary work has also been done on predicting the time for these events to occur (Buckler, Andrew J., et al). Moreover, machine learning techniques have also been used for several reasons on CT images like an algorithm that was recently developed to identify structural anatomical features in a non-contrast CT image (Regent, L. E. E., et al.). A method was also developed and patented to correct for possible motion artifacts in these CT cardiac images by (Edic et al).

An extensive summary of 30 unique patents related to this project, along with their respective key claims, which was conducted earlier in the Fall 2022 academic semester, can be viewed using the link below:

BMEG 455 Cardio Patent Search

As observed in the prior art search above, although there are several machine learning algorithms patented for different cardiovascular diseases, there is none specifically patented for the detection and diagnosis for cardiotoxicity. Additionally, there is currently no patented solution available to solve the problem of specifically processing and isolating the aortic wall from CT scans of the heart. Therefore, it is safe to say that there is not much competition in the marketplace with regards to this project's prototype and if filed with adequate documentation, the methods proposed within this report could be patented in the future.

Anticipated Regulatory Pathway

The regulatory process for every medical device depends on its classification as defined by the Food and Drug Authority (FDA), which is based on the level of control necessary to provide reasonable assurance of its safety and effectiveness to the general public. The FDA specifically regulates all food, cosmetics, and electronic devices that produce radiation, drugs, biological products, and medical devices.

Since this project makes use of a computer program and a supplementary machine learning algorithm, the FDA does not currently classify this as a medical device that is able to "treat, diagnose, cure, mitigate, or prevent disease or other conditions" ("U.S. Food and Drug Administration"). This is because the FDA's traditional paradigm of medical device regulation was not designed for adaptive artificial intelligence and machine learning technologies. However, under the FDA's current approach to software modifications, the FDA anticipates that many of these artificial intelligence and machine learning-driven software changes to a device may need a premarket review.

In a proposed framework, the FDA envisions a "predetermined change control plan" in premarket submissions. In this potential approach, the FDA would expect a commitment from manufacturers on transparency and real-world performance monitoring for artificial intelligence and machine learning-based software as a medical device, as well as periodic updates to the FDA on what changes were implemented as part of the approved pre-specifications and the algorithm change protocol. This approach could allow for the FDA's regulatory oversight to embrace the iterative improvement power of artificial intelligence and machine learning-based software as a medical device, while assuring patient safety (Center for Devices and Radiological Health).

As such guidance on AI/ML tools has not yet been finalized by the FDA, for the scope of this paper, our prototype can be classified as a low to medium risk, class II medical device. Our prototype would be classified as a class II device because of it being a potential moderate risk to patients if an incorrect diagnosis is provided, prompting healthcare providers to alter treatment plans which may ultimately harm the patient.

All class II devices are subject to general controls that are applicable to class I devices such as good manufacturing processes, standards and reporting adverse events to the FDA, registration, and general recordkeeping environments. Class II devices are also subject to special conditions such as specific labeling requirements, device-specific mandatory performance standards, and device specific testing requirements (Office of the Commissioner).

A 510(k) application is to be completed in which adequate evidence is to be presented that can prove that the machine learning algorithm is effective by comparing it to an already approved ML algorithm for a similar use. While this might be slightly difficult as there are not many analogous products that work specifically for cardiotoxicity, there are various similar products available in the market for the detection of other cardiovascular diseases such as hypertrophic cardiomyopathy.

The figure below outlines the FDA medical device approval process that can be referenced to better understand the regulatory process for bringing a medical device to market.

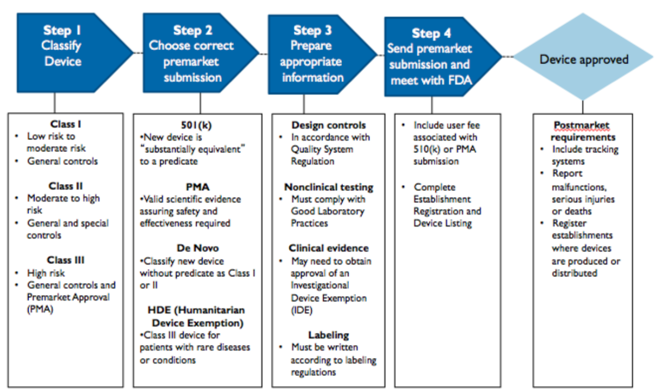

Figure 37: *FDA Medical Device Approval Process.*

Reimbursement

The solution developed in this project is to be used directly in conjunction with medical imaging. While ultimately intended to be used with the integration of multiple imaging modalities, this project focused on CT imaging. Under Medicare Part B (medical insurance), diagnostic tests such as X-rays and CT scans are covered (Medicare Coverage of Cancer Treatment Services). Due to the relationship our product has with this covered medical expense, it could be reasonable to assume that any expenses related to the use of our product would also be covered by medicare. This is because our product is simply an extension of using CT scans, providing patients additional diagnostic information that will aid in disease detection and diagnosis.

Cycle of Care

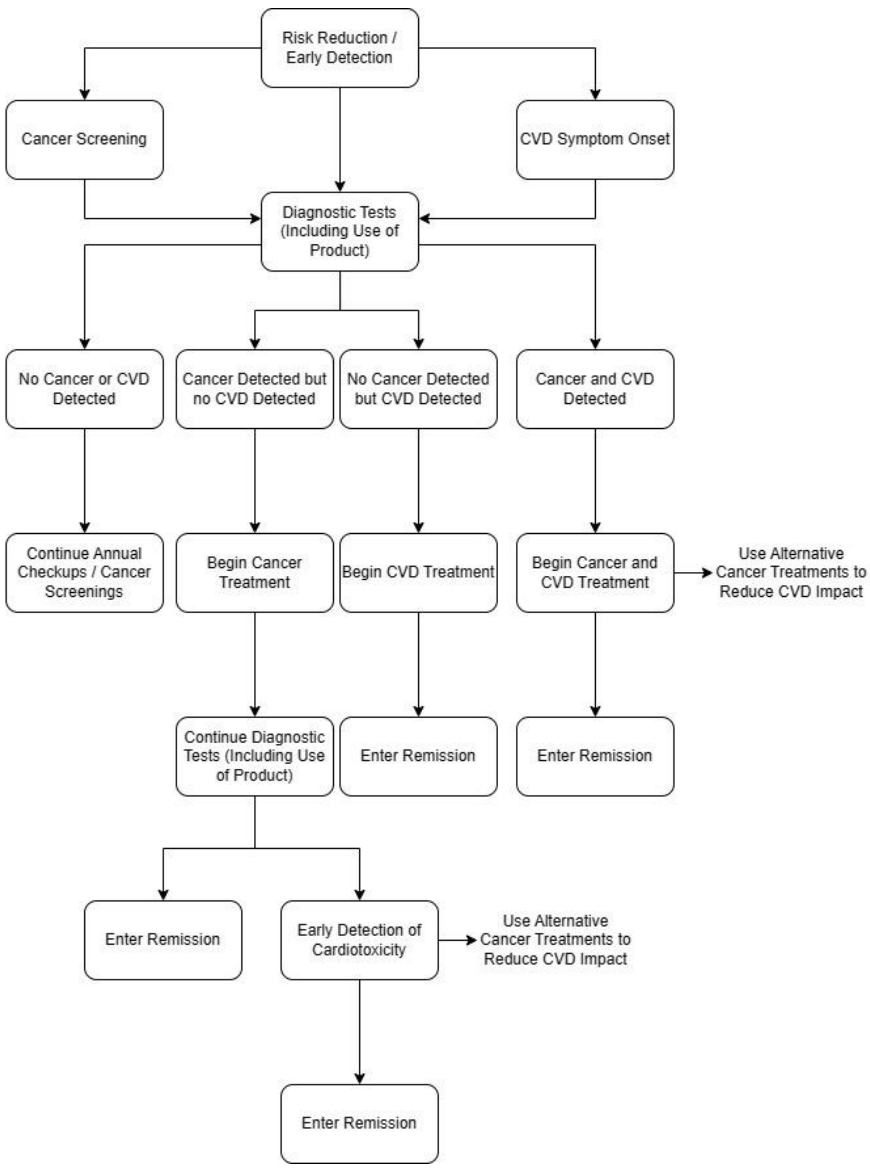

Figure 38*: Cycle of Care.*

Coding for the Device

Within inpatient settings, diagnoses and procedures are specified by ICD-10 (International Classification of Disease, 10th revision) codes. More specifically, our product would be defined by ICD-10-PCS or the procedure coding system. The product developed in this project is a process which could be implemented within the CT scan procedure to further increase the extracted diagnostic information. Furthermore, this product has especially relevant use within the analysis of CT scans taken of the chest. CT scans of the chest and abdomen fall under ICD-10-PCS BW24ZZZ ("Find A Code").

The American Medical Association also maintains Current Procedural Terminology (CPT) codes. Diagnostic procedures of the chest involving CT imaging are defined by CPT 71250, 71260, 71270. CPT 71250 and 71260 are described as diagnostic procedures in which the provider performs a CT examination of the thorax with or without the use of contrast material respectively. CPT 71270 outlines a similar procedure but where images are first taken without contrast material and then followed by more imaging with contrast material ("CPT code lookup"). While our prototype could be integrated within any of the existing codes mentioned above, one could also apply for a completely independent code specific to the intended functionality of this project's developed prototype.

Ethics

The fundamental canons of ethics decided by the National Society for Professional Engineers applies to this capstone project. The first cannon is to "hold paramount the safety, health, and welfare of the public." In this project, the team used CT scans from real patients to test and develop a program using python. While creating this code, the team had to ensure that what we are doing is going to have a positive effect on our consumers. The second canon is to "perform services only in areas of their competence". This cannon is very easily followed as this capstone was designed to be within the scope of the team's area of expertise. These two canons were most paramount to our success in this project, however, it is important to note that all other canons of ethics were followed as appropriate.

Another major ethical consideration for this project was to ensure that we are following all of HIPAA regulations. HIPAA is the Health Insurance Portability and Accountability Act of

1996 which requires by federal law that sensitive patient data is protected from being disclosed without their consent. As the team is using CT scans of real patients, it was vital to ensure patient privacy. This was accomplished by having Kenneth, an undergraduate student within the Research Apprenticeship Program (RAP) at WVU, manually access patient medical records using a secure workstation at the Heart and Vascular Institute (HVI) to crop all identifying information from the CT scans. Kenneth then coded the CT scans using a key generated by our client. All images were then shared with the team using an encrypted sharepoint folder.

Estimated Cost of Manufacturing

In manufacturing a machine learning algorithm, there are several factors that can affect the estimated cost of production. These include research and development expenses, storage space, cost of equipment such as computers, as well as ongoing maintenance and support costs. It is also important to note that since this project does not aim to develop a device with physical components, it is challenging to provide an actual dollar value for a single "unit item." However, a rough estimate, based on reasonable assumptions, can place the cost of a comparable machine learning project around $51,750 to $136,750 (Incze, 2019).

To begin with, research and development plays a crucial role in developing such a machine algorithm. The expertise of several professionals such as engineers, data scientists, and software developers would be required. As of 2022, the average yearly salaries of these professionals stand at $102,000 for software engineers and $120,000 for data scientists. As such, the cost of recruiting these specialists would be factored into the estimated cost of manufacturing.

Additionally, the cost of obtaining and storing the CT scans needed to train and test the algorithm would also be accounted for. This includes the cost of purchasing or acquiring the scans, as well as the storage space required to hold them on a shared drive or an external hard drive.

Furthermore, the cost of equipment such as computers used to run the algorithm would need to be included in the cost of manufacturing. The cost of advanced computers that can handle coding programs range from $600 to $2,000. Depending on the complexity of the algorithm, high-end computers with powerful processing capabilities may be required, which can drive up the cost of manufacturing.

Lastly, given that the algorithm may require periodic updates or debugging, the cost of maintenance and support would be factored in. This includes the cost of maintaining the software and hardware components of the algorithm, as well as providing technical support to users who may encounter issues while using the algorithm. The hourly pay for technical support personnel can be as little as $65/hour to as much as $100/hour for individuals with more experience.

When healthcare providers or facilities adopt the machine learning algorithm this project aims to develop, they will likely incur an upfront cost in the form of a monthly subscription fee. This subscription cost will grant them access to the algorithm, which they can easily access and use by simply uploading patient CT scans. The algorithm will then process the scan, isolate the aortic wall, provide radiomic features of importance, and identify a given patient's risk of developing cardiotoxicity.

In addition to providing users unlimited access to the algorithm, the monthly subscription fee will also cover access to maintenance and support personnel. This will ensure that users have access to technical assistance when needed and can report any issues they may encounter while using the algorithm. The subscription will also cover access to any future software updates that may be made to the algorithm, including but not limited to applicability to other cardiovascular diseases. This is important as it ensures that the algorithm remains up-to-date and can continue to deliver accurate and precise results.

By adopting a monthly subscription model, healthcare providers and facilities will be able to enjoy predictable and manageable costs for accessing the algorithm, maintenance, and support. This will help minimize any sizable one-time upfront costs and ensure that providers can effectively budget the cost of using the algorithm within their practice's finances.

Potential Market and Impact

Commercially, this machine learning algorithm could be either independently licensed and sold as a product or added as part of an existing artificial intelligence-enabled software package. The primary market for this invention would be the healthcare industry, specifically organizations and professionals within the cardiology and oncology segment, with the current global oncology market valued at over $305 billion ("Oncology Market Size"). Specific entities that may be interested in commercializing this invention and serving as distribution channels for this product can include software companies focused on organizing patient data and developing data-driven diagnostic tools, medical device companies focused on producing CT machines or other cardiac imaging modalities, along with pharmaceutical companies either focused on developing new anti-cardiotoxicity drugs or improving existing chemotherapeutic treatment options.

Additionally, while the customers purchasing this product will primarily be healthcare organizations such as hospitals, cancer treatment centers, and cardiology clinics etc, the end users will be physicians, who will be using the technology to aid in developing treatment plans, and patients, who will directly benefit from the diagnostic information provided by such a product.

Research suggests that incorporating such artificial intelligence (AI) products within existing diagnostic workflows can make healthcare a lot cheaper, effective, and more equitable (Marr, Bernard). This is because AI tools can not only help with early disease detection and prediction, but can also improve the interpretation of patient scans by augmenting the work of physicians in diagnostically challenging cases.

Regardless of how ingrained AI will become in other professions and industries, the healthcare sector is to play a major role in the $15.7 trillion economic boost provided to the global economy as a result of AI (Bresnick, Jennifer.). This includes major stakeholders such as healthcare providers, pharmaceutical and life science corporations, and consumers.

However, it is also important to state some major challenges that the industry will face: patient confidentiality and security regulations. Due to laws in place such as HIPAA, organizations' ability to apply machine learning to datasets will be limited. Additionally, healthcare organizations will also face backlash from employees regarding modifying workflows over fears of job loss. However, as technology continues to become deep-rooted in the modern economy, adequate steps will need to be taken to address these growing concerns.

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Appendix A: Final ImageJ Macros Script

```
open("C:/Users/axelm/Documents/1 School/1 Senior Year/BMEG 455 - Senior
Design/ImageJ/RAP_PET images/RAP_1_1.PNG");
run("8-bit");
setAutoThreshold("Minimum dark");
//run("Threshold...");
setAutoThreshold("IsoData dark");
//setThreshold(133, 255);
setOption("BlackBackground", false);
run("Convert to Mask");
open("C:/Users/axelm/Documents/1 School/1 Senior Year/BMEG 455 - Senior
Design/ImageJ/RAP_PET images/RAP_1_1.PNG");
run("8-bit");
run("Invert");
setAutoThreshold("IsoData dark");
//run("Threshold...");
setAutoThreshold("Minimum dark");
//setThreshold(48, 255);
run("Convert to Mask");
imageCalculator("AND create", "RAP_1_1.PNG","RAP_1_1-1.PNG");
selectWindow("Result of RAP_1_1.PNG");
open("C:/Users/axelm/Documents/1 School/1 Senior Year/BMEG 455 - Senior
Design/ImageJ/RAP_PET images/RAP_1_1.PNG");
run("8-bit");
imageCalculator("Subtract create", "Result of RAP_1_1.PNG","RAP_1_1-2.PNG");
selectWindow("Result of Result of RAP_1_1.PNG");
```

Appendix B: Final Python Script

```
import cv2
import matplotlib.pyplot as plt
import os

import numpy as np
import pandas as pd


def main():
   # path of folder containing raw images
   in_folder_path = "C:\\Users\\pwu00\\OneDrive\\Desktop\\RAP-KW"

   # path of folder to contain modified images
   out_folder_path = "C:\\Users\\pwu00\\OneDrive\\Desktop\\Output"

   # create folders inside out_folder_path to store contrast and non-contrast separately
   os.makedirs(out_folder_path + '\\(Pre) Contrast', exist_ok=True)
   os.makedirs(out_folder_path + '\\(Pre) Non Contrast', exist_ok=True)
   os.makedirs(out_folder_path + '\\(Post) Contrast', exist_ok=True)
   os.makedirs(out_folder_path + '\\(Post) Non Contrast', exist_ok=True)
   os.makedirs(out_folder_path + '\\Pathways', exist_ok=True)
   os.makedirs(out_folder_path + '\\Pathways', exist_ok=True)

   # create lists to save file pathways
   original_list = []
   mask_list = []

   for file_name in os.listdir(in_folder_path):
      # file_name contains name of current file from in_folder_path

      # input_path appends the image's file name to in_folder_path to create a path to the image.
      input_path = os.path.join(in_folder_path, file_name)

      # load image and convert to grayscale
      img = cv2.imread(input_path)
      img = cv2.cvtColor(img, cv2.COLOR_BGR2GRAY)

      # Find middle pixel value
      height, width = img.shape
      middle_pixel_value = img[height // 2, width // 2]

      # Re-save original image segregating Contrast and non-contrast
      thresh = 200
      if middle_pixel_value >= thresh:
         # output_path contains the full path of the output (including modified file name)
         output_path = os.path.join(out_folder_path, '(Pre) Contrast', file_name)
         cv2.imwrite(output_path, img)
```

```
            # store output path to later put in data frame to print to Excel
            original_list.append(output_path)

        else:
            # output_path contains the full path of the output (including modified file name)
            output_path = os.path.join(out_folder_path, '(Pre) Non Contrast', file_name)
            cv2.imwrite(output_path, img)

            # store output path to later put in data frame to print to Excel
            original_list.append(output_path)

        # run processing method dependent on image type
        if middle_pixel_value >= thresh:
            masked_image = contrast(img)

            # output_path contains the full path of the output (including modified file name)
            output_path = os.path.join(out_folder_path, '(Post) Contrast', '(mask) ' + file_name)

            # store output path to later put in data frame to print to Excel
            mask_list.append(output_path)

        else:
            masked_image = non_contrast(img)

            # output_path contains the full path of the output (including modified file name)
            output_path = os.path.join(out_folder_path, '(Post) Non Contrast', '(mask) ' + file_name)

            # store output path to later put in data frame to print to Excel
            mask_list.append(output_path)

        # print image to screen
        # plt.imshow(masked_image, cmap="gray")
        # plt.show()

        # save the image
        cv2.imwrite(output_path, masked_image)

    # write output paths and binary label to Excel file
    label_list = np.repeat(255, len(original_list))
    df = pd.DataFrame({'Original': original_list, 'Mask': mask_list, 'Label': label_list})
    with pd.ExcelWriter(out_folder_path + '\\Pathways\\Pathways.xlsx', engine='openpyxl') as writer:
        df.to_excel(writer, index=False)


def contrast(img):
    # modify raw images with methods below
    blur = cv2.GaussianBlur(img, (5, 5), 0)
    thresh_value, thresh_image = cv2.threshold(blur, 200, 255, cv2.THRESH_BINARY)
```

```
    thresh_value, otsu_image = cv2.threshold(blur, 240, 255, cv2.THRESH_OTSU)
    otsu_image = cv2.bitwise_not(otsu_image)
    masked_image = thresh_image + otsu_image
    masked_image = cv2.bitwise_not(masked_image)
    return masked_image


def non_contrast(img):
    increased_contrast = cv2.convertScaleAbs(img, alpha=6, beta=6)
    reduced_contrast = cv2.convertScaleAbs(img, alpha=0.4, beta=0)

    # modify raw images with methods below
    reduced_blur = cv2.GaussianBlur(reduced_contrast, (5, 5), 0)
    increased_blur = cv2.GaussianBlur(increased_contrast, (5, 5), 0)
    thresh_value, reduced_thresh_image = cv2.threshold(reduced_blur, 200, 255, cv2.THRESH_OTSU)
    thresh_value, increased_thresh_image = cv2.threshold(increased_blur, 200, 255, cv2.THRESH_OTSU)
    increased_thresh_image = cv2.bitwise_not(increased_thresh_image)
    masked_image = increased_thresh_image + reduced_thresh_image
    masked_image = cv2.bitwise_not(masked_image)
    return masked_image


# driver function
main()
```

Appendix C: Literature Review Citations

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Appendix D: RAP Abstract (Kenneth Wang)

Background: Due to advancements in anticancer therapy, patients with cancers are living longer. However, many patients treated with anticancer agents are susceptible to cardiotoxicity, which is heart damage arising from chemotherapeutic cancer treatment and the second leading cause of death in cancer survivors.

Purpose: The purpose of this project is to develop an artificial intelligence model that can predict cardiotoxicity risk in cancer patients to reduce the testing burden on patients while maximizing the utility of existing imaging data.

Methods: This project will utilize computed tomography (CT) scans from patients undergoing cancer treatment at Ruby Memorial Hospital. Upon collecting this imaging data, we used various image analysis techniques such as thresholding to isolate the aortic lumen, which will be used to measure inflammation around the aorta. Additionally, radiomic techniques will also be utilized to extract data, such as the area of the aortic lumen, from the processed image scans.

Results: We were successfully able to manually isolate the aortic lumen using ImageJ software. The final image 1(b) below utilized two separate images which were thresholded and placed on top of each other. The first image had thresholding values of (145,255) and the second image had thresholding values of (0,110).

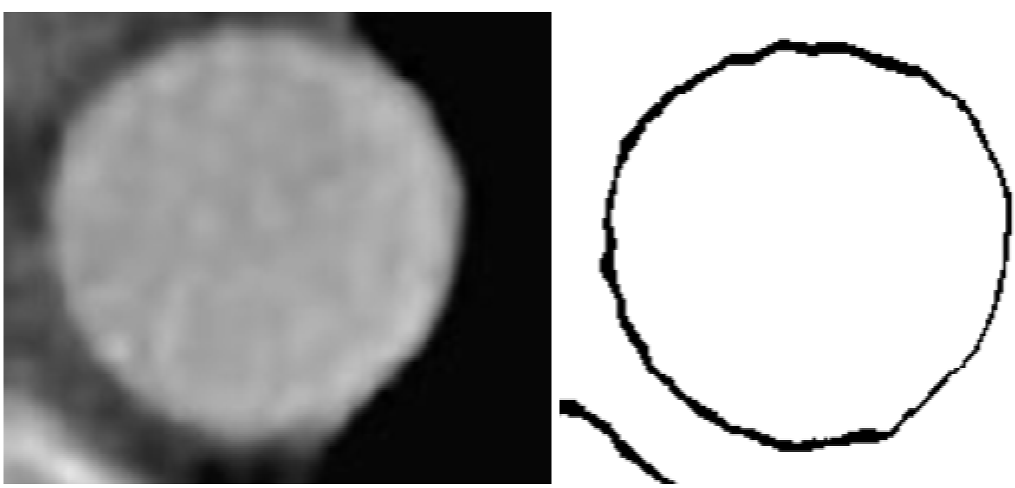

Image 35: *The image above shows (a) non-contrast CT scan focused on the aorta and (b) thresholded CT scan using ImageJ to* isolate the aortic lumen.

Future Works: We hope to optimize the thresholding values used to isolate the aortic lumen along with using scripting features to automate the lumen extraction process such that a batch of images can be automatically processed. We then hope to use the processed images to build a model to determine if aortic inflammation can be used to predict cardiotoxicity risk.