



heartdetect

## **Seminar Group 7 Team 6** **Heart Detect**

A two-stage, analytics-based approach to  
heart disease prevention

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# Introduction to Cardiovascular Diseases (CVD) in Singapore

Zhi Hao



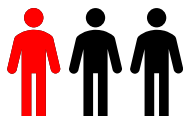
**Top 3** causes of hospitalization and death



**1 in 5** Singaporeans have 1 or more risk factors



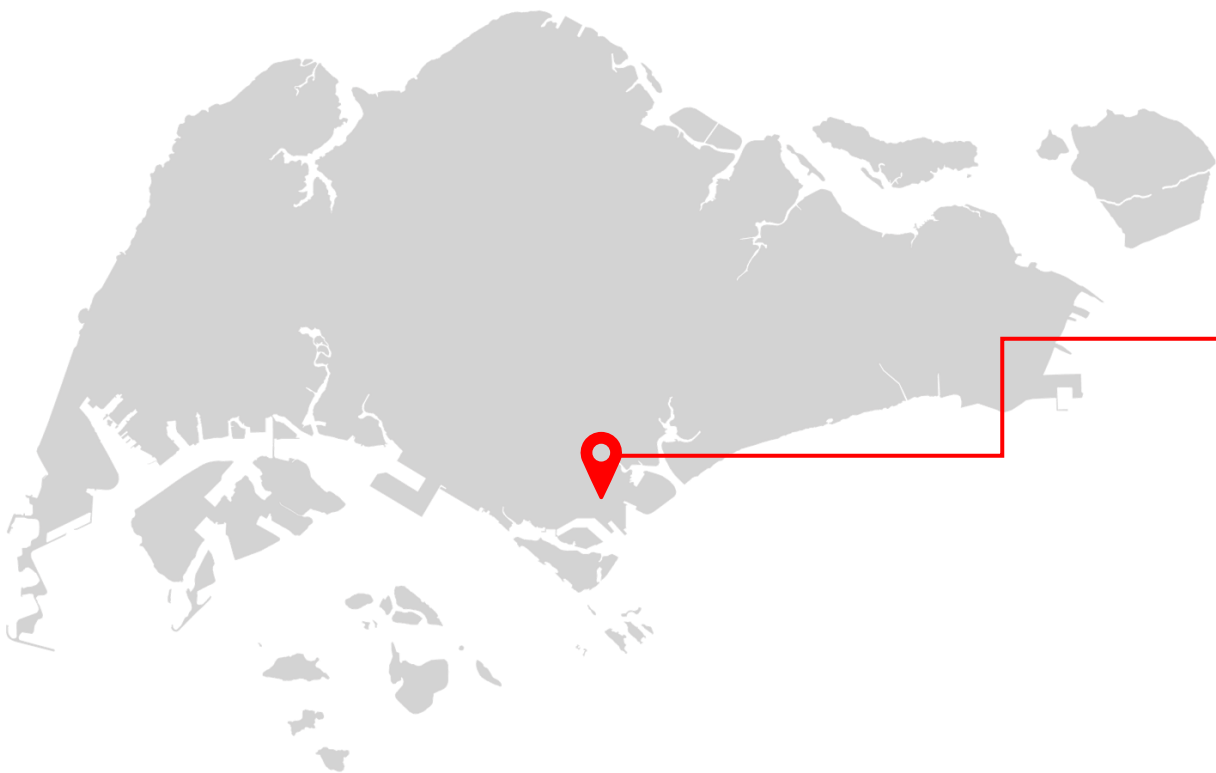
**1 in 3** Singaporeans die due to CVD



**More than 1/3** Singaporeans are not aware of risks factors



NCHS handling more than **120,000** outpatients  
Manual assessment of CVD risk levels wastes manpower





## Reduce deaths

## Prevention rather than treatment

**80%** of CVD can be prevented with the elimination of health risk behaviours  
*(Piepoli, et al., 2016)*

**Slow onset** of CVD and **long incubation periods** = **large window of opportunity** for intervention  
Symptoms are generally more serious upon diagnosis  
*(Qian, et al., 2022)*

Early intervention is critical in **preventing the onset of CVDs** and hence **increase the life expectancy** of Singaporeans

## Business Problem

Creating a prediction tool using data analytics models:

- To aid in the early detection and intervention of CVDs
- To be utilized by medical professionals at the primary care level (GPs, polyclinics)

Sources: *Piepoli, et al. (2016), Qian, et al. (2022)*

# Proposed Solution: HeartDetect

Zhi Hao

*Latest solution*

*Our proposed solution*

## Predictive Risk Score for CAD In Southeast Asians with Chest Pain (PRECISE)

- Singapore's 1st CAD risk calculator
- Estimates likelihood of patient with no known history using variables such as age, gender, smoking status, ECG changes etc.
- Particularly helpful for patients with chest pain to monitor their health status

### Limitations

- Only targets people presenting with chest pain
- Only addresses CAD (Cardiovascular Artery Disease)



heartdetect



### Stage 1: Individual Empowerment

Individuals can monitor their heart health by answering questions about their biological, medical, behavioral, genetic and environmental information.



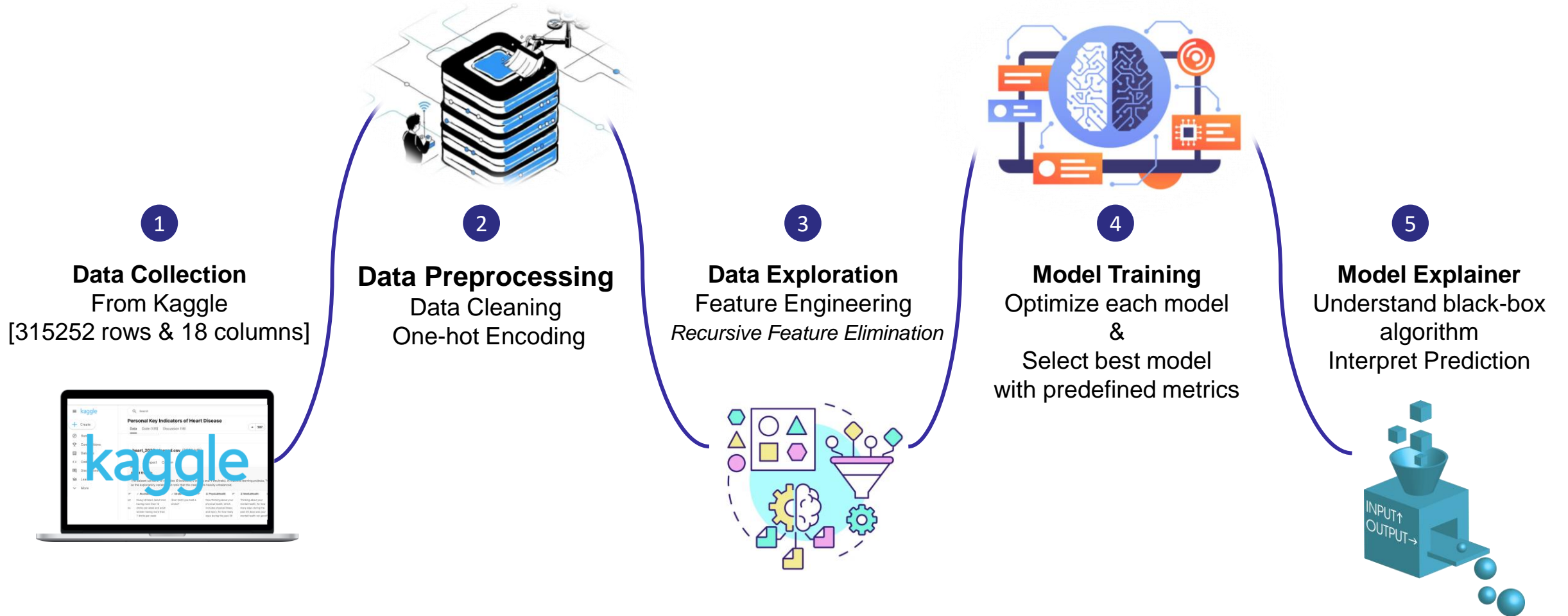
### Stage 2: Primary Medical Care

Individuals in high-risk category can visit a primary care physician (GP, polyclinic) for screening, where a data analytics model is used as a support tool for physicians during decision making

- Extend coverage of preventive measures for heart disease
- Raise awareness of risk factors
- Maximize medical resource allocation

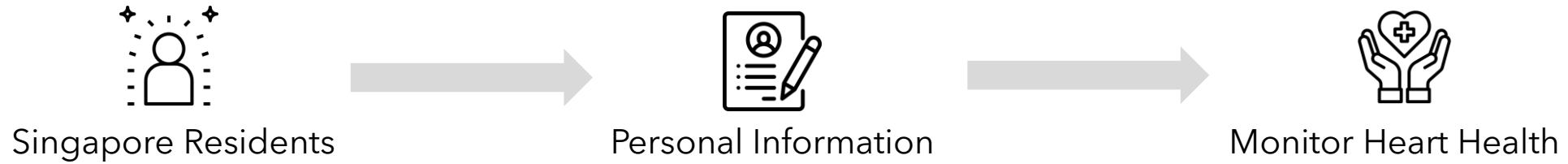
# Stage 1: *Individual Empowerment* - Overview

Jiang Lei



# Stage 1: *Individual Empowerment* - Data Overview

Jiang Lei



## Demographical Variables

**Age**  
**Gender**  
**Race**  
**BMI**



## Medical History

**Stroke**  
**Diabetic**  
**Asthma**  
**Kidney Disease**  
**Skin Cancer**  
  
\* (Ever told) (you had) a disease above?



## Lifestyle

**Smoking**  
*have you smoked at least 100 cigarettes in your entire life?*  
**Alcohol Drinking**  
*adult men > 14 drinks / week  
adult women > 7 drinks / week*  
**Physical Activity**  
*whether exercise during the past 30 days other than regular job*  
**Sleep Time**  
*how many hours of sleep get in a 24-hour period on average*



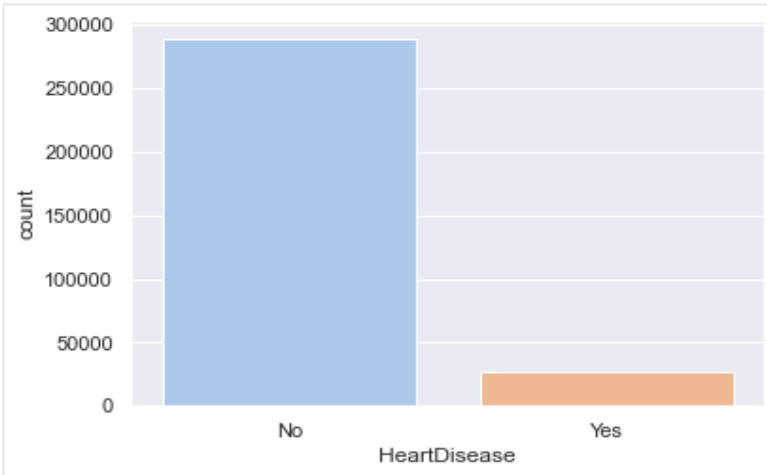
## Recent Health Condition

**Difficulty in Walking**  
**General Health**  
*Rate it with **Very Good** / **Good** / **Excellent** / **Fair** / **Poor***  
**Physical Health**  
*how many days during the past 30 was physical health **not good**?*  
**Mental Health**  
*how many days during the past 30 was mental health **not good**?*

# Stage 1: *Individual Empowerment* - Data Exploration

Jiang Lei

## Distribution of Heart Disease



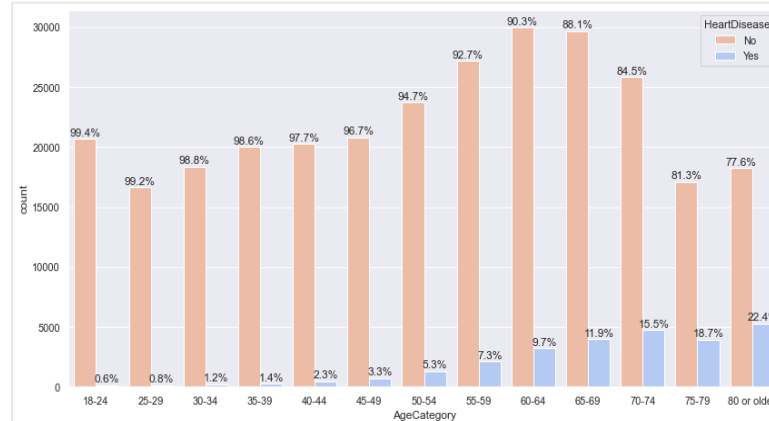
### Unbalanced Predictor Variable

91% of rows – Low risk  
9% of rows – High risk

- Algorithm-based **Sampling** Required
- Be Alert of **Overfitting** of Models

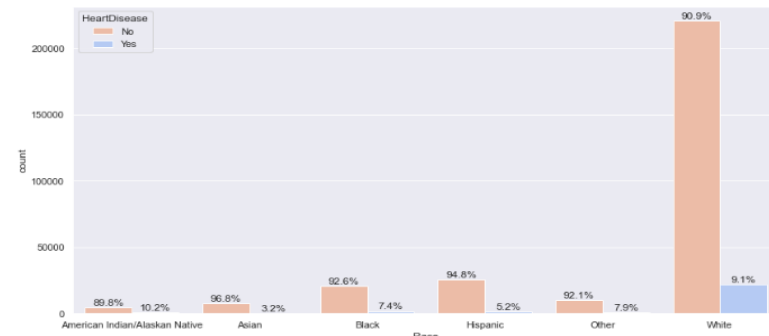


## Demographical Variable(s)



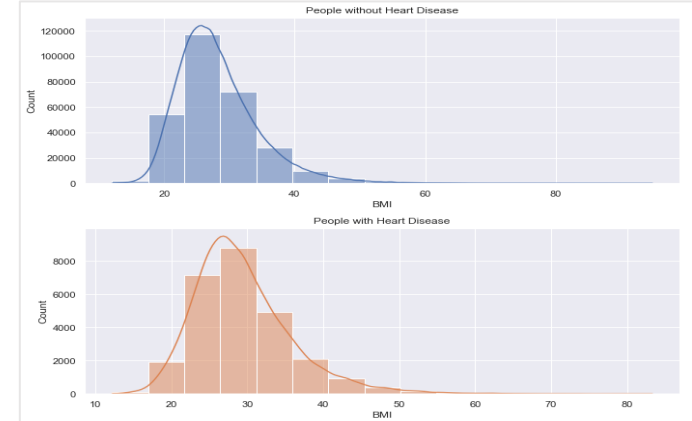
### Age VS Heart Disease

age increases, % of HD patients increases  
> 10% HD patients among 65+ people



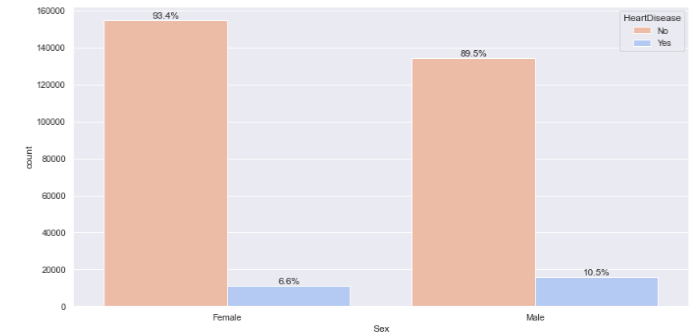
### Race / Gender VS Heart Disease

The proportion of people with heart disease is very similar across gender and race.



### BMI VS Heart Disease

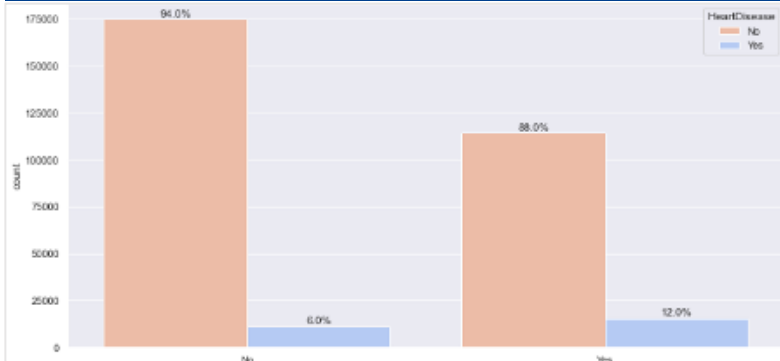
The distribution of BMI was very similar in cardiac patients and non-patients.



# Stage 1: *Individual Empowerment* - Data Exploration

Jiang Lei

## Lifestyle Variable(s)



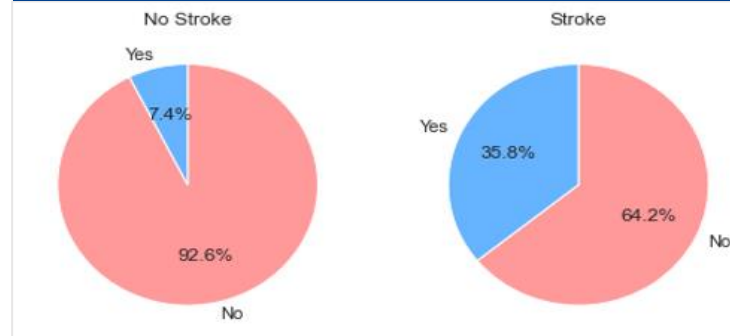
### Smoker VS Heart Disease

12% of smokers are heart patients,  
2 times of the non-smokers.

Smoking damages blood vessels, reduces the amount of oxygen in the blood, worsens heart conditions.  
(Health Hub, 2022)



## Medical History Variable(s)



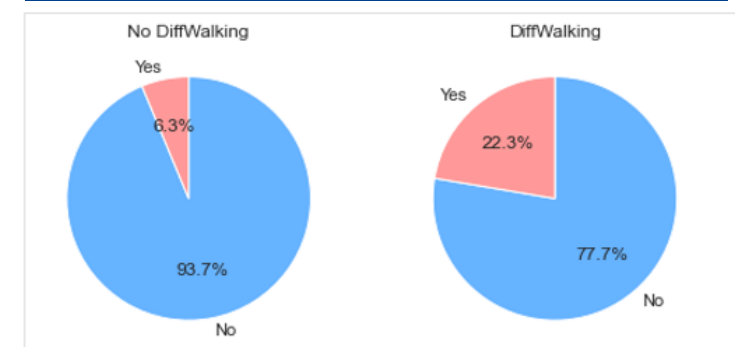
### Stroke VS Heart Disease

35.8% of stroke patients also have heart disease, 5 times of the non-stroke patients.

Similarly,  
for people have been diagnosed with **diabetes** or **kidney disease**

High blood sugar caused by **diabetes** can damage blood vessels in the heart.  
(Singapore Heart Foundation, 2022)

## Current Health Variable(s)



### Difficulty in Walking VS Heart Disease

22% of HD patients with difficulty in walking, 3.5 times of non-HD patients

People walk fast always show better cardiac status.  
(Yates, et al., 2017)



Sources: HealthHub (2022), Singapore Heart Foundation (2022), Yates, et.al. (2017)



# Stage 1: *Individual Empowerment* - Pre-Modelling

Jiang Lei



## Train-Test Split

The data set is randomly divided into training and test sets in a ratio of 7:3.

**Sampling** was required due to the disease:-non-disease imbalance distribution of 1:10.



## Oversampling by SMOTE

Synthetic Minority Oversampling Technique (SMOTE) employed to **oversample** the trainset

Generates synthetic samples for “Heart Disease - Yes” group using other variables

Overcomes the overfitting problem



## Performance Metric

**Classification Accuracy**  
Percentage of correct prediction

(**>80%**)

**ROC AUC score**  
Evaluate the performance of single model at different thresholds

(**>70%**)

**False Negative Rate**  
Error of misclassifying high-risk populations as low risk (prediction 0, truth 1)

(**<20%**)

# Stage 1: *Individual Empowerment* - Models

Jiang Lei



## Logistic Regression Model

Efficient machine learning **classification** algorithms

3 Models Trained with **Recursive Feature Elimination**  
Cleaned dataset contains up to 50 one-hot-encoding variables

Optimal Model uses **21** variables (7 features)

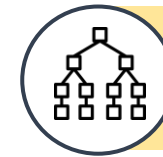


## Gradient Boosting Classifier

A more robust model **learns iteratively from each weak learner**

Model trained with **Hyperparameter Tuning**  
*Conducted on 2 parameters  
`n_estimators`, `learning_rate`*

**11** Important features are highlighted



## Random Forest Model

an ensemble of decision trees randomly selects variables and averages the prediction results

Mitigate overfitting issue  
Highly stable  
Training time longer due to complexity

**All 17** features are used

### Model Optimization



**Finding the best model based on 3 predetermined metrics**

# Stage 1: *Individual Empowerment* - Model Evaluation & Selection

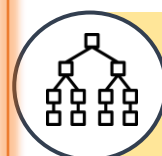
Jiang Lei



**Logistic Regression**



**Gradient Boosting Classifier**



**Random Forest**

Overall Accuracy	74.22%	87.54%	99.62%
False Negative Rate	78.46%	72.28%	1.70%
ROC-AUC Score	0.75	0.63	0.99

Lowest Accuracy  
Worst FNR & Fair Score

Poor FNR  
High Accuracy & Lowest Score

Best FNR  
Highest Accuracy & Score



**Important Features used  
in Random Forest**

1. BMI
2. Age
3. Sleep Time
4. Diabetic
5. Race
6. Difficulty in Walking
7. General Health Status
8. Gender

9. Physical Health
10. Mental Health
11. Smoking
12. Stroke
13. Physical Activity
14. Skin Cancer
15. Asthma
16. Kidney Disease
17. Alcohol Drinking

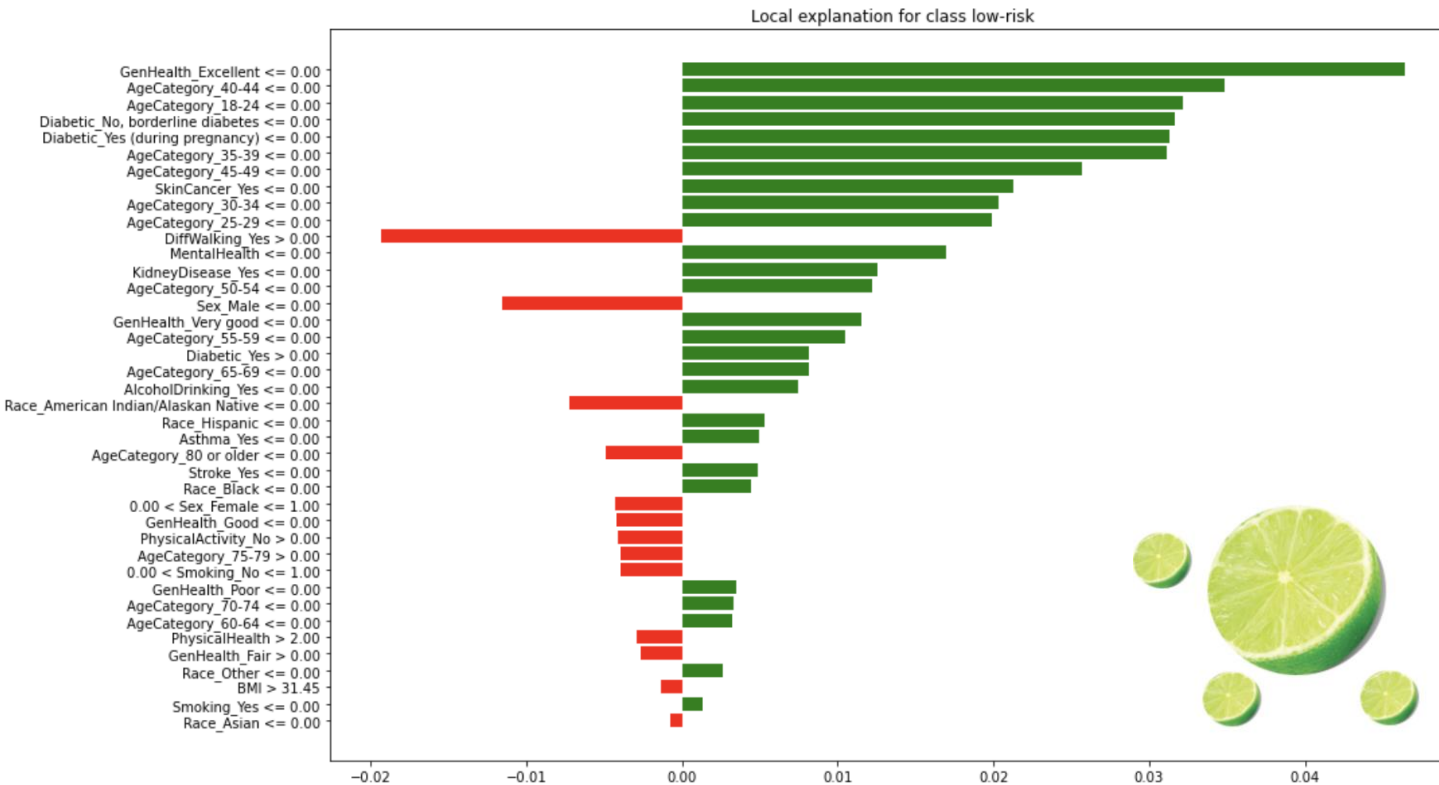
**How to build trust among end users (individuals) when interpreting predicted results (high risk/low risk)?**

# Stage 1: *Individual Empowerment* - Model Explainer

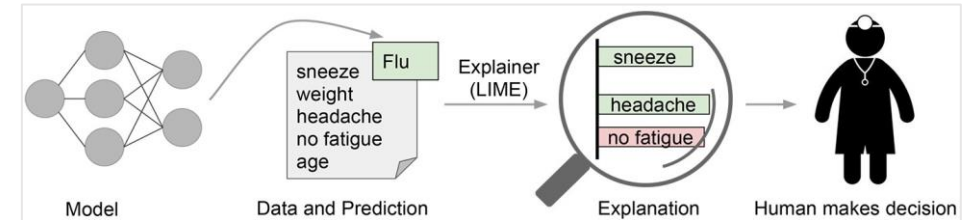
Jiang Lei

## Sample Analytic Report for An Individual

Congratulations! You are at **low-risk** for heart disease.  
However, please take note of the following factors (in red) that **negatively contribute** to your heart health.



## Local Interpretable Model-Agnostic (LIME)



## Trust in Model Using Accuracy Metrics

Test-set to measure model performance, but still different from real-world data

## Trust in Personal Predictions

Use positive & negative drivers (variables) to explain prediction results and gain user trust

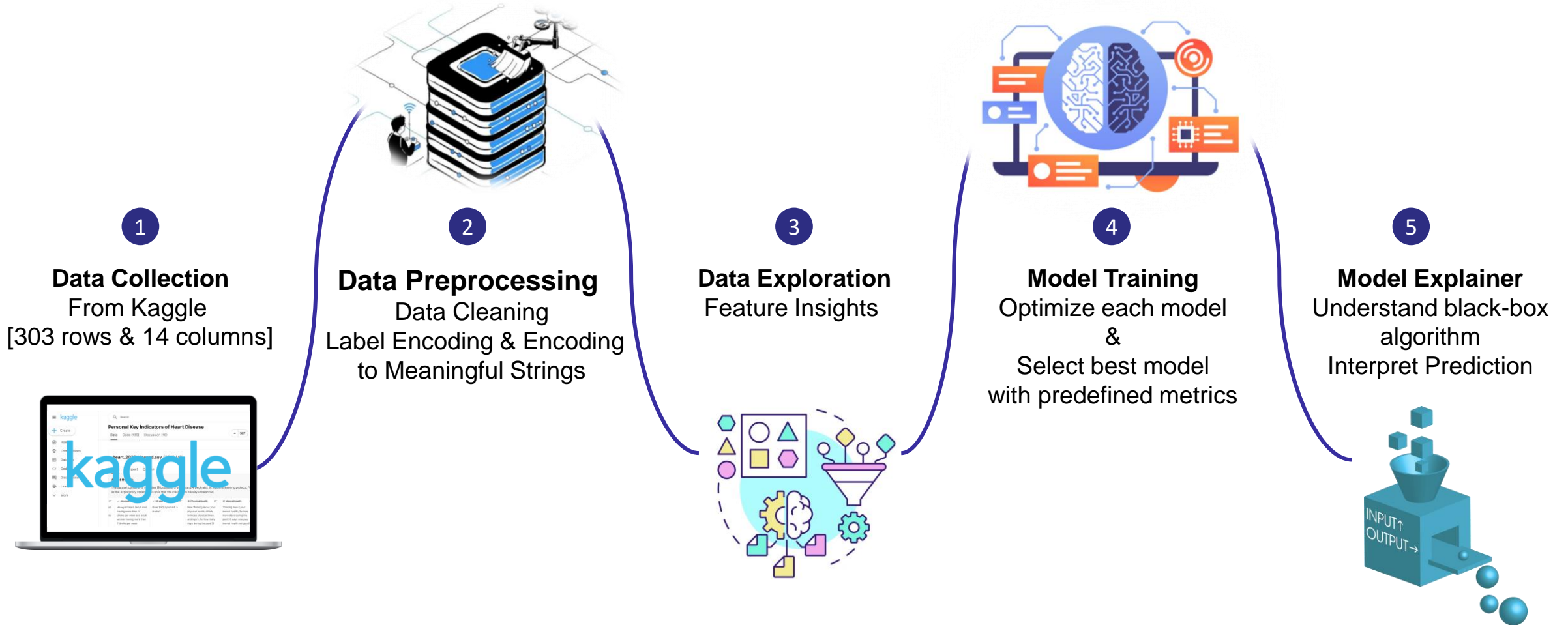
## Ensure Local fidelity

Globally important features may not be significant in the local context

Only a handful of variables directly relate to an individual prediction

# Stage 2: *Primary Care Prediction* - Overview

Jing Qiang

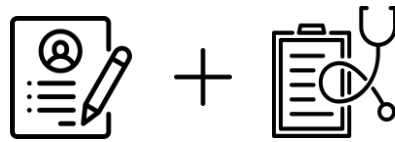


## Stage 2: *Primary Care Prediction* - Data Overview

Jing Qiang



Patients



**Personal** + **Medical**  
Information



Doctor's Evaluation  
on Heart Health



**Personal  
Variables**

**Age**

**Sex**

**Chest Pain**

*\* Are you experiencing chest  
pain?*



**Electrocardiogram  
Variables**

**Heart Rate**

**O2 Saturation**

**Rest ECG**

*\* Resting ECG Results (0-2)*



**Blood-related  
Variables**

**Resting Blood Pressure**

**Fasting Blood Sugar**

**Cholesterol**



**Other Medical  
Variables**

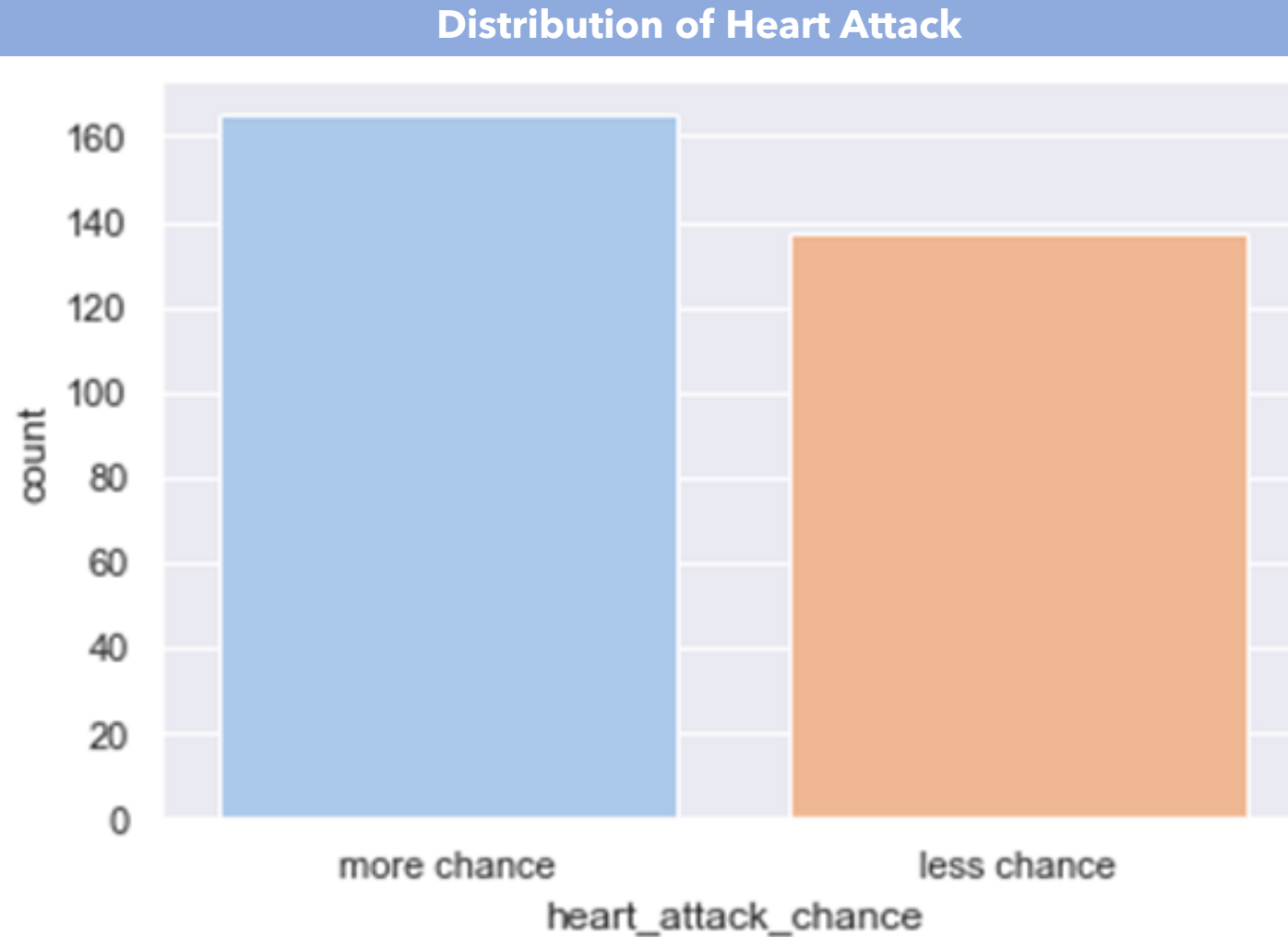
**Exercise Induced Angina**

**Number of major vessels**

*\* NOT blocked or interrupted by a  
build-up of fatty substances*

## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

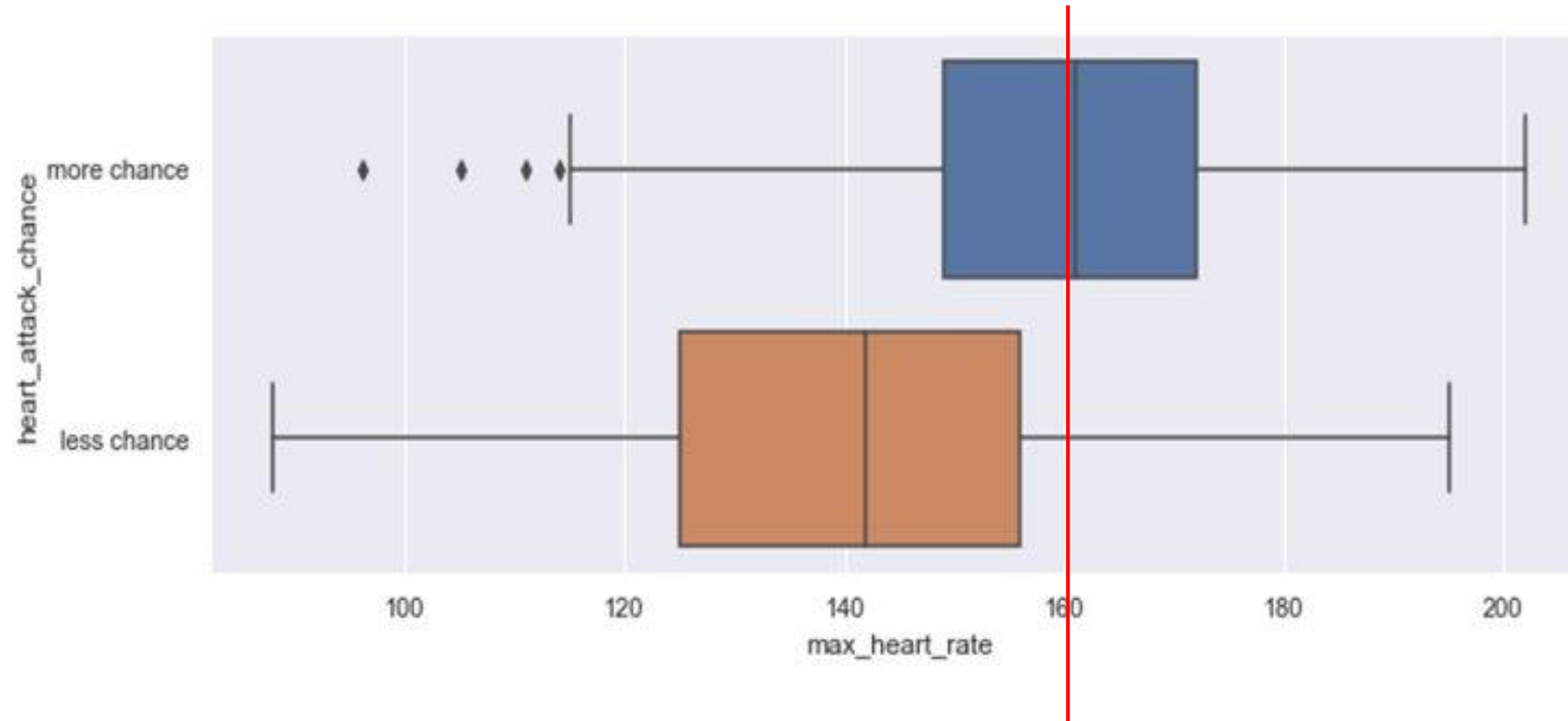


Balanced Predictor Variable

## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

Variable(s) - In-Line With Academic Research



### Max Heart Rate VS Heart Attack

The chances of heart disease **increases** when one has a **higher max heart rate** (~160bpm vs ~140bpm)  
(Perret-Guillaume, Joly, & Benetos, 2009)

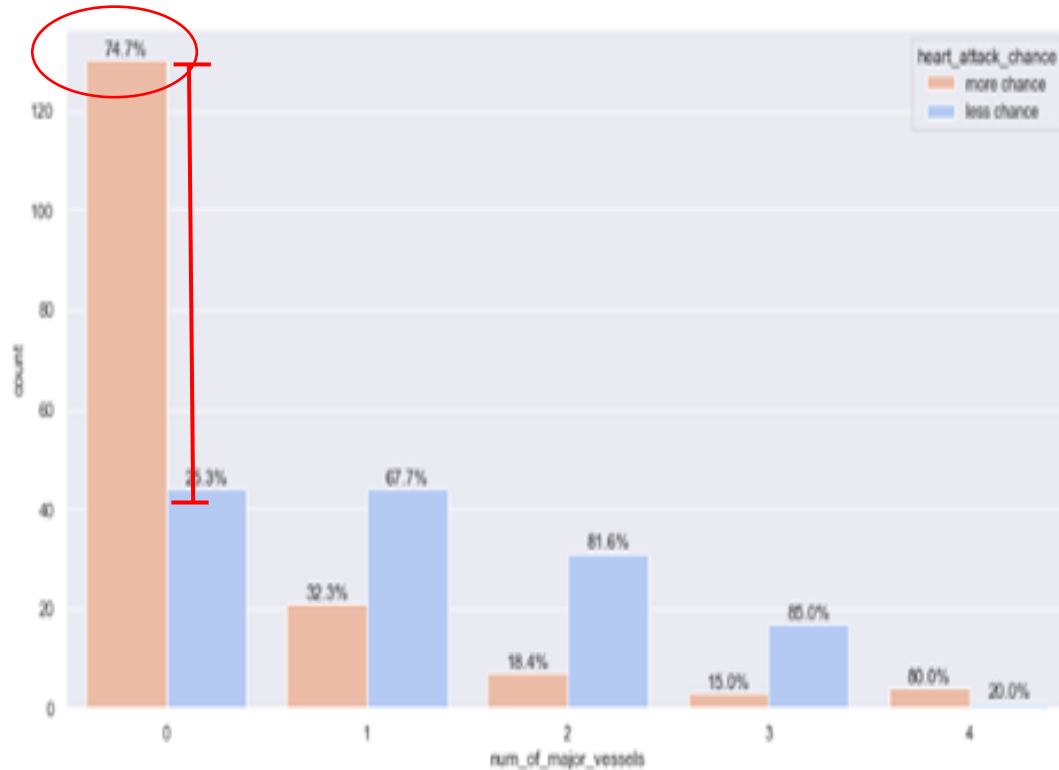
Sources: Perret-Guillaume, Joly, & Benetos (2009)



## Stage 2: *Primary Care Prediction* - Data Exploration

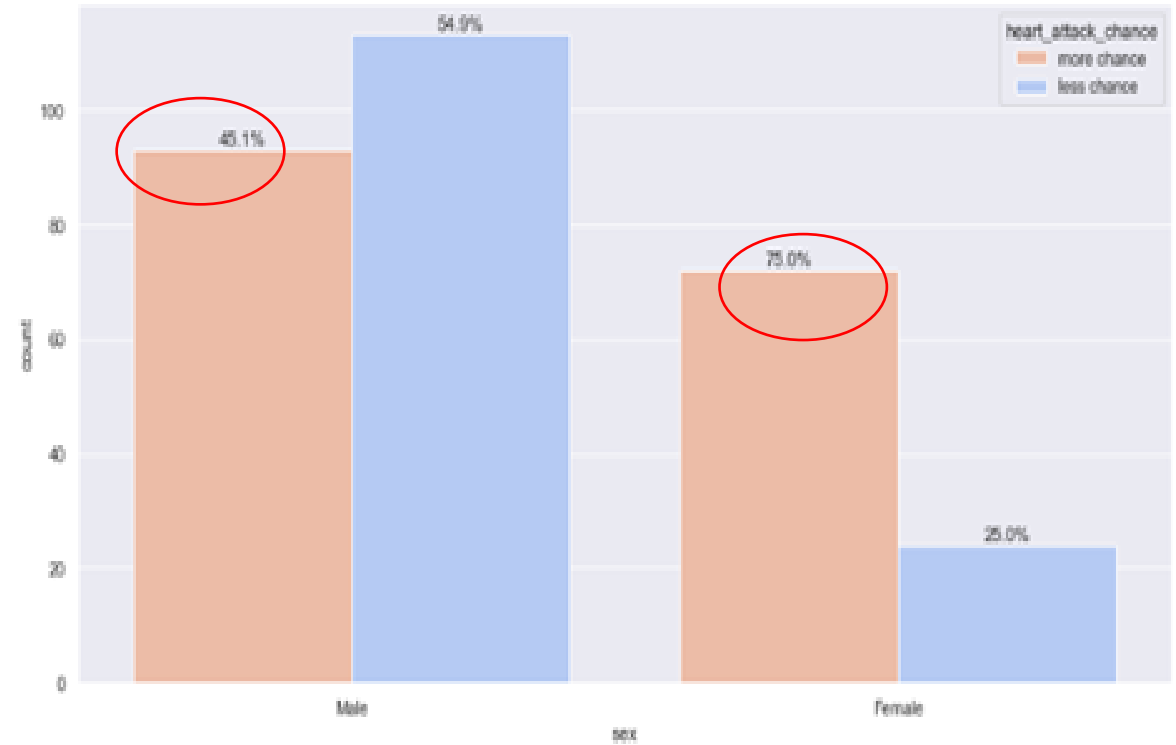
Jing Qiang

### Variable(s) - In-Line With Academic Research



#### Number of major vessel VS Heart Attack

The more **blood vessels detected** (*not blocked or interrupted by fatty substances*) **by fluoroscopy**, the **lower** the **chance** of having a high risk of heart disease.



#### Gender VS Heart Attack

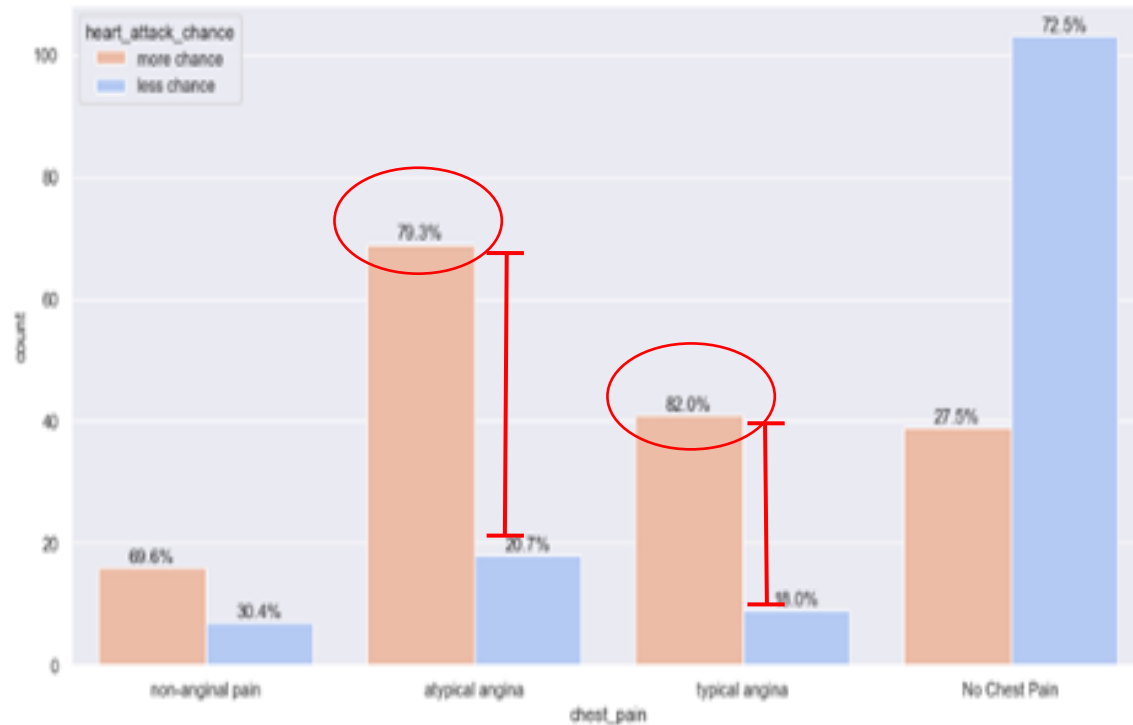
**Females** are shown to be at a **higher risk** of a heart attack (*females' 75% vs males' 45.1%*)  
(Carauna, 2018)

Sources: Carauana (2018)

## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

### Variable(s) - In-Line With Academic Research



#### Chest Pain VS Heart Attack

Those with **chest pain** has a **greater than 69.6%** of having a higher chance of heart attack  
(Singapore General Hospital, n.d.)



#### Rest ECG VS Heart Attack

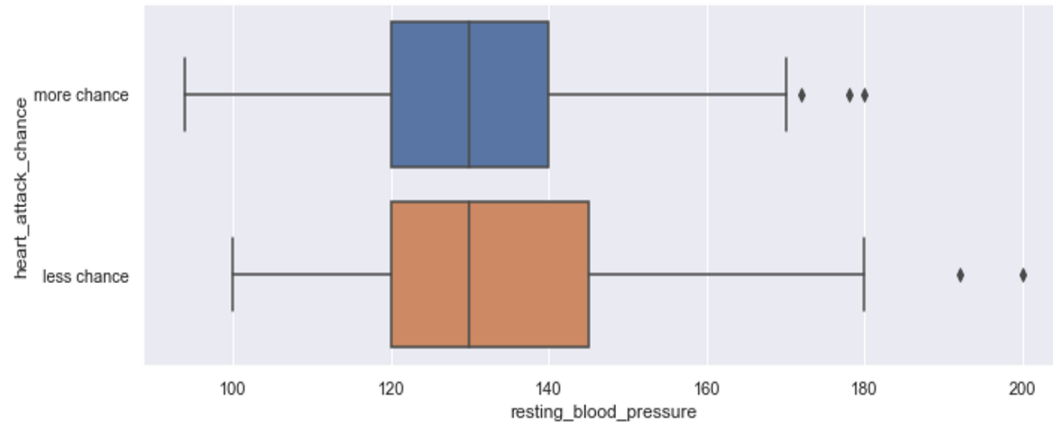
Those with **ST-T wave abnormality** has **17.3% more chance** of higher risk of heart attack  
(Beckerman, et al., 2005)

Sources: Singapore General Hospital (n.d.), Beckerman, et al. (2005)

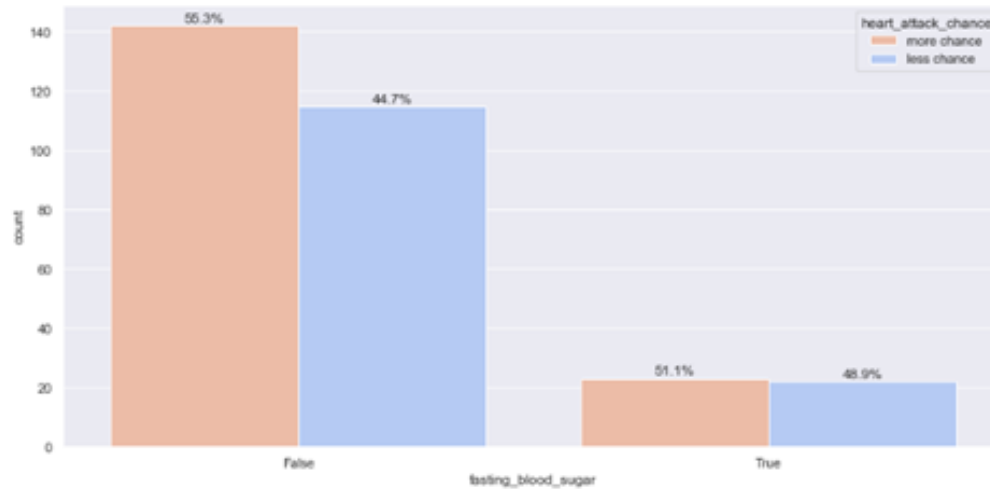
## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

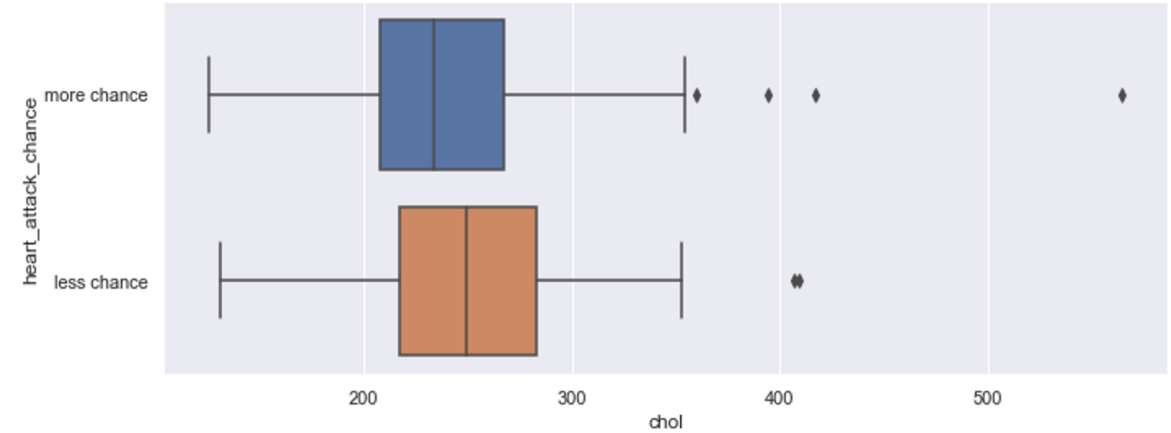
### Variable(s) - No Significant Impact



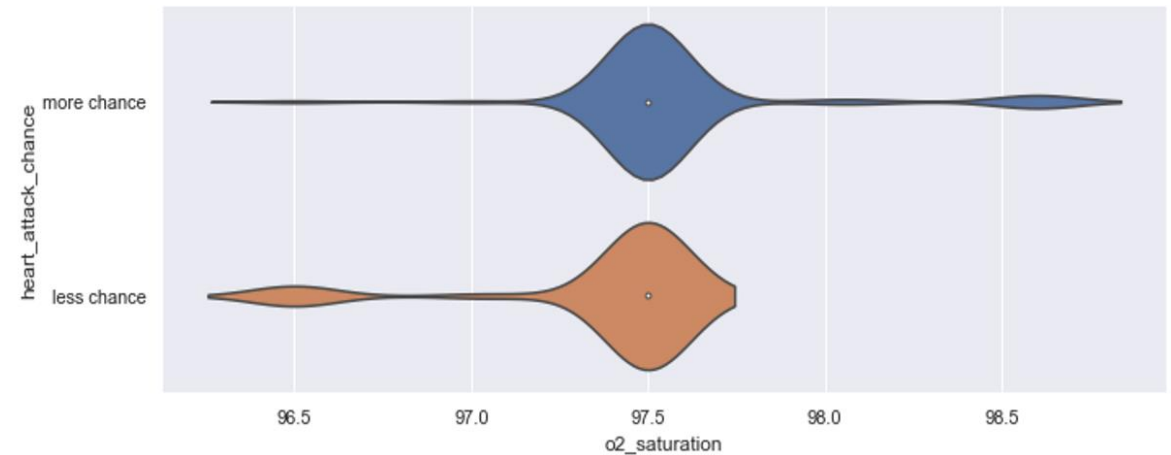
Heart Attack Chance VS Heart Attack



Fasting Blood Sugar VS Heart Attack



Cholesterol VS Heart Attack

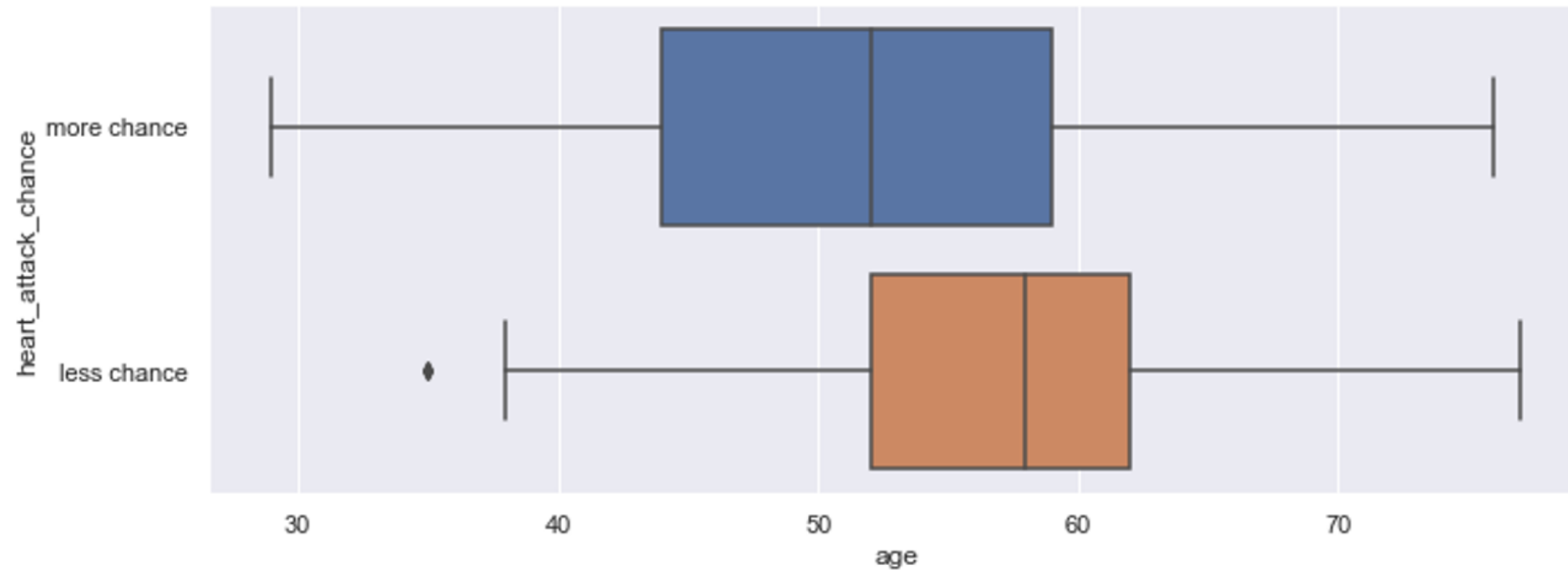


O2 Saturation VS Heart Attack

## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

Variable(s) - Contradicts Current Research



### Age VS Heart Attack

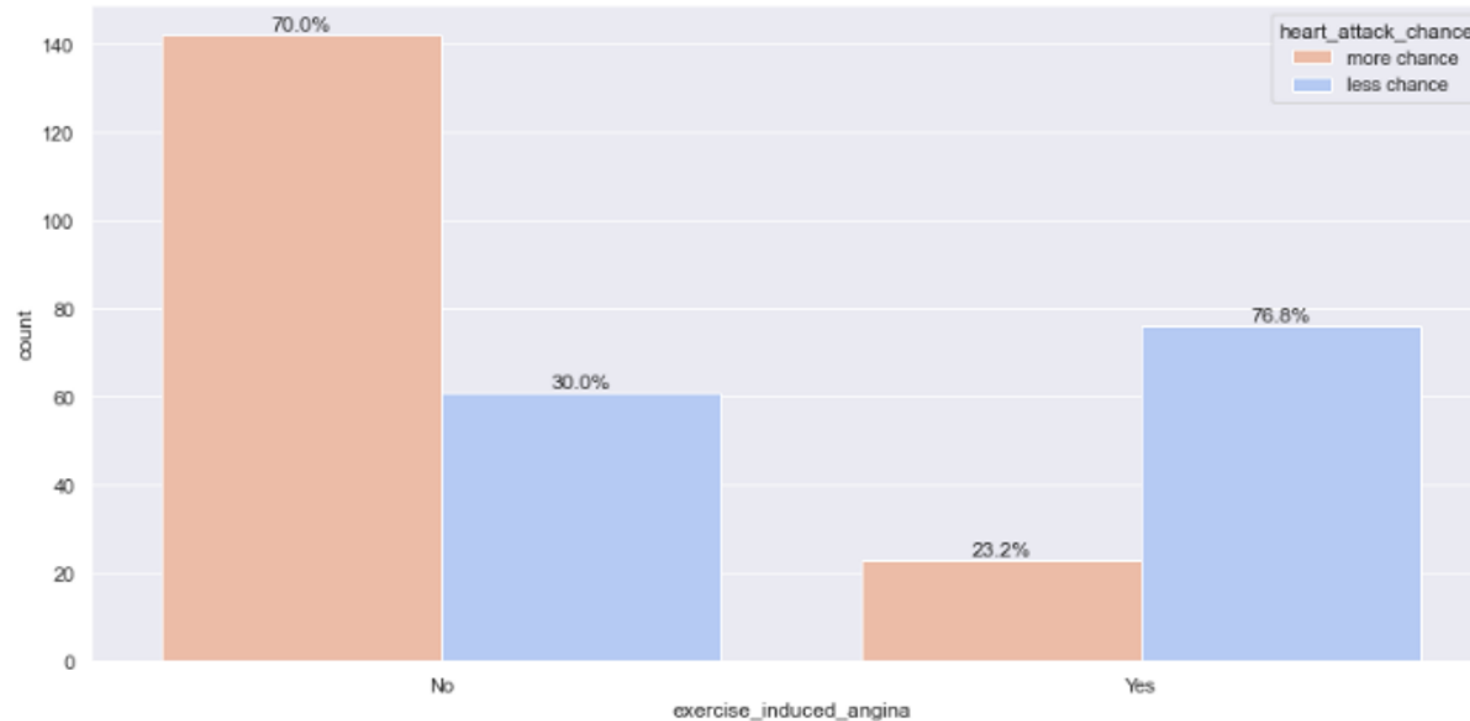
The **younger** you are, the **higher** the **risk** of you getting a heart disease, which contradicts existing research (Rodgers, et al., 2019)

Source: Rodgers, et al. (2019)

## Stage 2: *Primary Care Prediction* - Data Exploration

Jing Qiang

### Variable(s) - Contradicts Current Research



### Exercised Induced Angina VS Heart Attack

Having exercise-induced angina is a common complaint of cardiac patients (Brown & Oldridge, 1985), but our exploration shows **not having exercise-induced angina** means one have is at a **higher risk** of heart disease.

Source: Brown & Oldridge. (1985)

## Stage 2: *Primary Care Prediction* - Pre-Modelling

Jing Qiang



### Train-Test Split

The data set is randomly divided into training and test sets in a ratio of 7:3.

**Cross Validation** was required due to the small size of the dataset.



### Cross Validation (5-fold)

5-fold Cross Validation is employed to **evaluate** analytical models on the limited train dataset sample.

It splits the train dataset into **5 groups**, using 4 groups to train the model and 1 group to validate the model. This is repeated for all possible combinations of the 5 groups.

Overcomes the limited dataset problem.



### Performance Metric

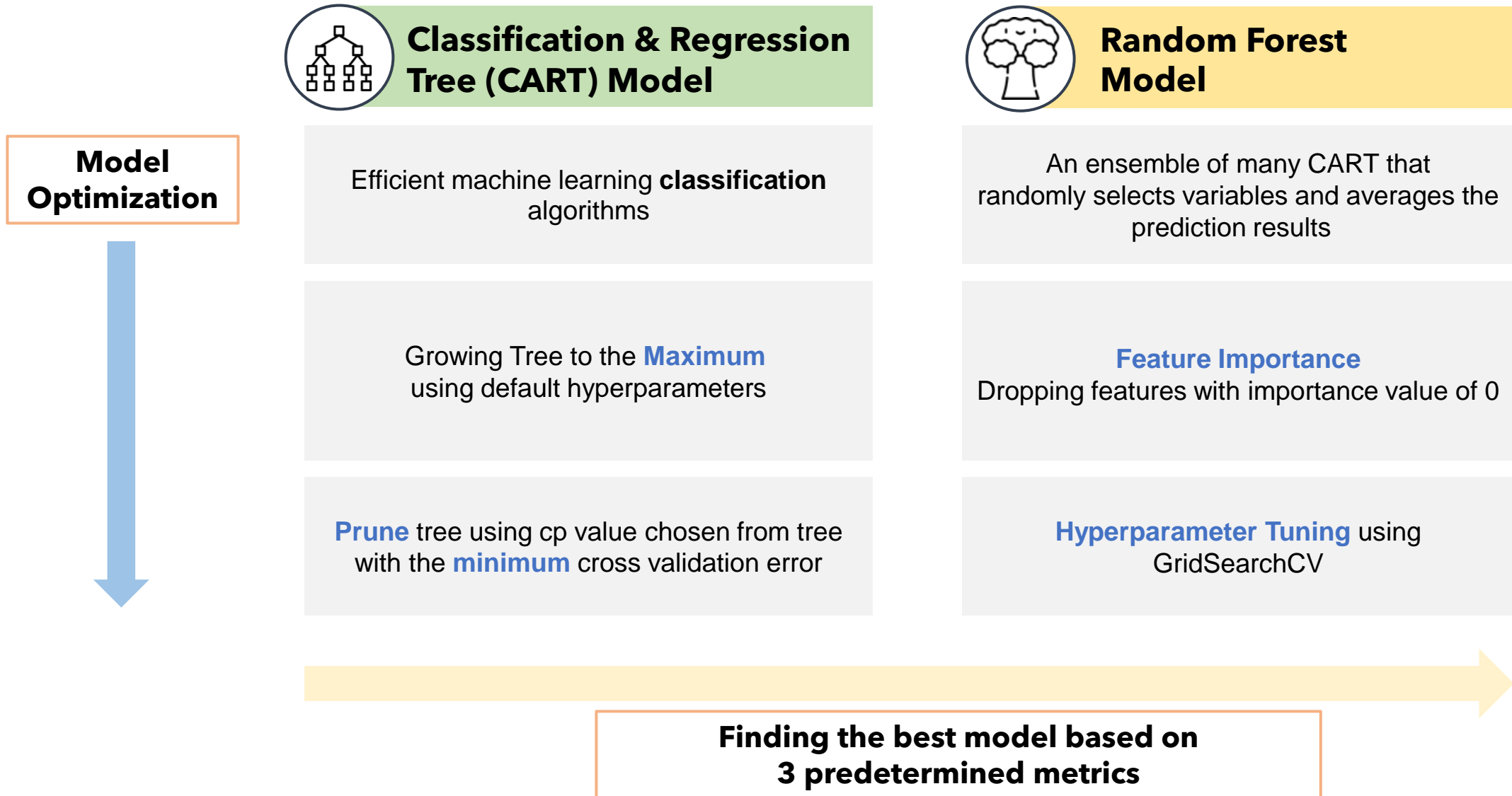
**Classification Accuracy**  
Percentage of correct prediction  
**(>80%)**

**ROC AUC score**  
Evaluate the performance of single model at different thresholds  
**(>70%)**

**False Negative Rate**  
Error of misclassifying high-risk populations as low risk (prediction 0, truth 1)  
**(<=20%)**

## Stage 2: *Primary Care Prediction* - Models

Jing Qiang



## Stage 2: *Primary Care Prediction* - Model Evaluation & Selection

Jing Qiang



### Logistic Regression

Overall Accuracy

74.41%

False Negative  
Rate

30.43%

ROC-AUC Score

0.78



### Random Forest

85.06%

20.93%

0.84

Poor Accuracy  
Undesirable FNR & ROC-AUC Score

Best FNR  
Highest Accuracy & ROC AUC Score



Important Features  
used in  
Random Forest

1. Max Heart Rate
2. Number of major vessels
3. Chest Pain
4. Age
5. Exercise Induced Angina
6. Cholesterol
7. Resting Blood Pressure
8. Sex
9. O2 Saturation
10. Rest ECG
11. Fasting Blood Sugar

How can end-user (doctors)  
**interpret prediction result** -  
high risk / low risk, and  
**proceed** from this result?

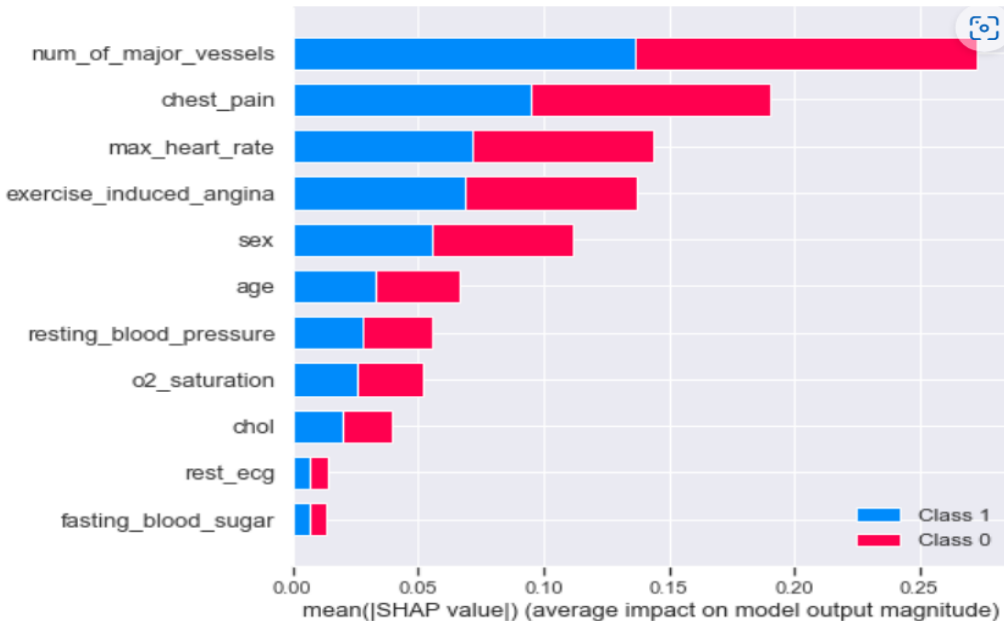
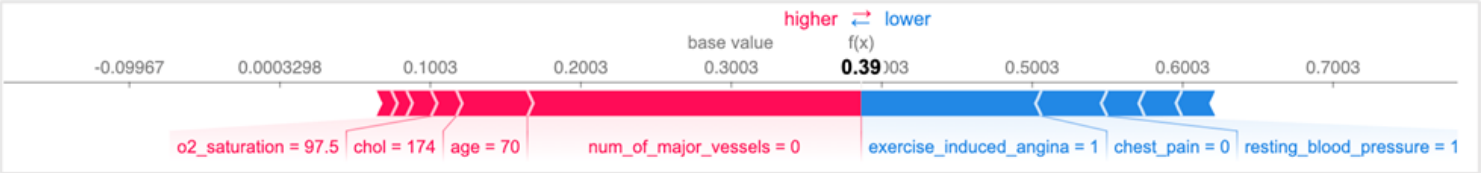


# Stage 2: *Primary Care Prediction* - Model Explainer

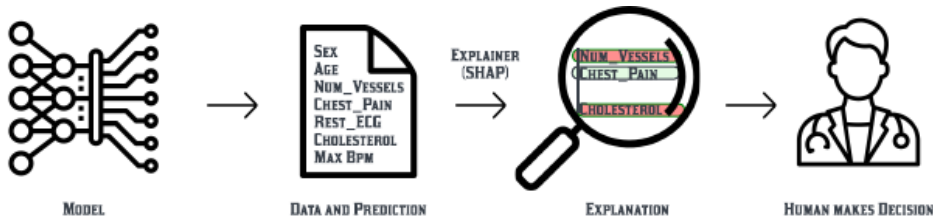
Jing Qiang

## Sample Analytic Report about a Patient for A Doctor

Danger! The patient is at **high-risk** for heart disease. The following factors (in blue) **contribute** to the patient's high risk heart health. Conduct a more **detailed medical test / administer treatments** in those areas.



## SHapley Additive exPlanations (SHAP)



### Enables Global Interpretability

The collective SHAP values can show **how much** each predictor contributes, either **positively** or **negatively**, to the target variable.

### Enables Local Interpretability

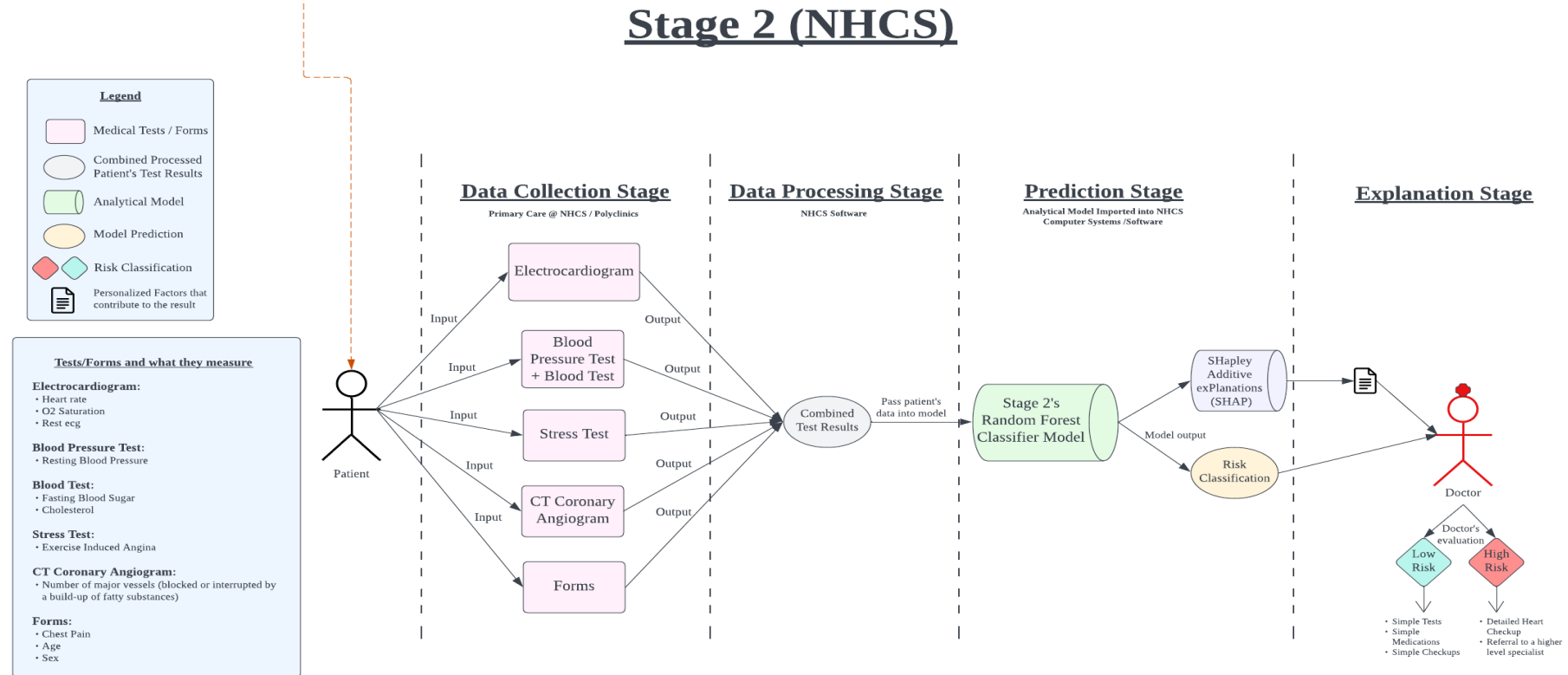
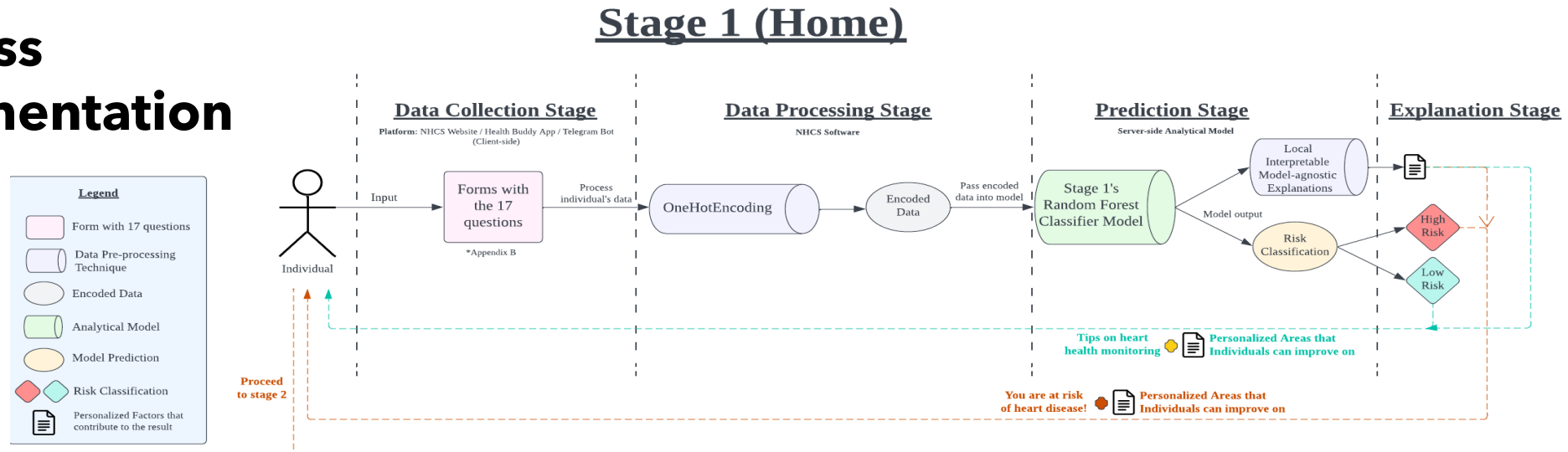
Each prediction has its own set of SHAP values, increasing transparency as it enables doctors to **pinpoint** and **contrast** the impacts of different features on the prediction

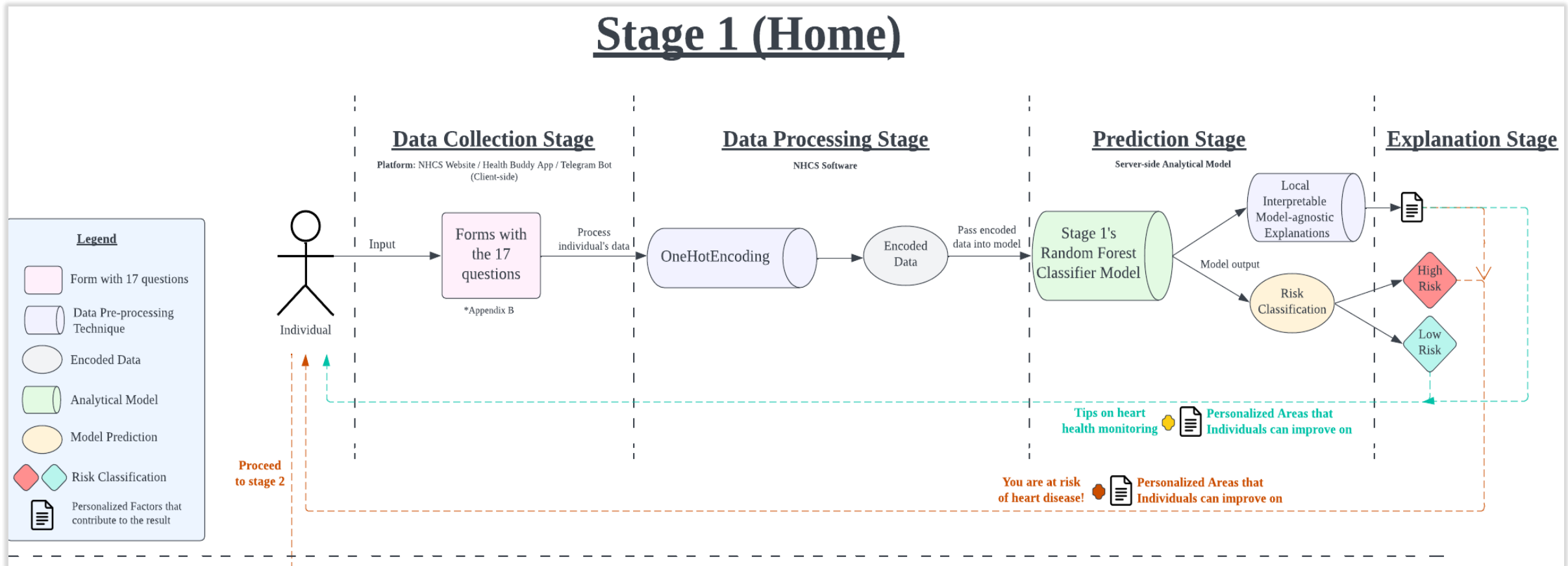
### Trust in Heart Predictions

Use positive & negative drivers (variables) to explain prediction results and gain doctors and patients' **trust**

# Business Implementation

Zainab





## Potential End Users

### General Public

Who is aware of monitoring his/her heart health



**Jolin, 23**  
*NTU Student*

### Visitors of NHCS

Found to have symptoms of heart attack



**Amy, 40**  
*Have chest pain*

### Patients with Relevant Medical History

Diabetes, Stroke, etc.



**Jay, 65**  
*Stroke Patient*

## Accessible Methods

Proactively use prediction tool through online platforms e.g., SingHealth Website, HealthBuddy App, Telegram Bot



An invitation link to online risk prediction will be sent to their phones periodically as a reminder for regular heart health monitoring

Work with Active Ageing Hub / Eldercare Centre to provide manual data collection and automated risk prediction for seniors who have difficulty accessing the Internet



# Business Implementation: *Stage 1* - User Journey Map

Zainab



Jay, 65  
Stroke Patient

1

## Answer Simple Questionnaire

17 non-medical indicators will be used as inputs for the questionnaire



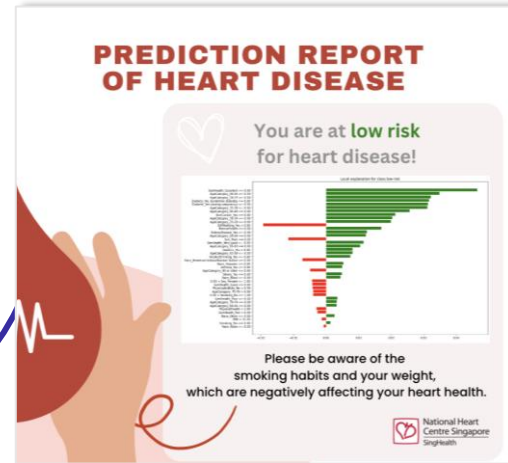
National Heart  
Centre Singapore  
SingHealth

### 17 Questions Individuals Can Answer

1. What is your BMI?
2. (Ever told) (you had) a stroke?
3. What is your gender?
4. Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 are you in good physical condition?
5. Now thinking about your mental health, for how many days during the past 30 was your mental health not good?
6. Would you say that in general your health is excellent, very good, good, fair, or poor?
7. Have you smoked at least 100 cigarettes in your entire life? [Note: 5 packs = 100 cigarettes]
8. Have more than 7 drinks per week?
9. (Ever told) (you had) skin cancer?
10. What is your race?
11. (Ever told) (you had) diabetes?
12. (Ever told) (you had) asthma?
13. Do you have serious difficulty walking or climbing stairs?
14. Which of the fourteen-level age category do you fall into?
15. Would you say that in general your health is good?
16. On average, how many hours of sleep do you get in a 24-hour period?
17. Not including kidney stones, bladder infection or incontinence, were you ever told you had kidney disease?

2

## Receive Risk Prediction Result & Analytics Report

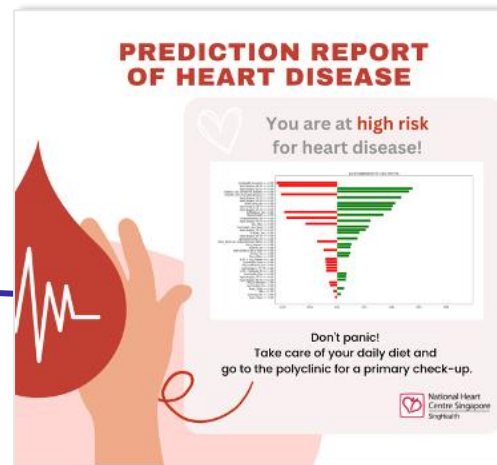


**Low Risk**

instructed to maintain heart health

3

## Decision Making



**High Risk**

guide users to primary care @ NHCS for primary heart checkup



National Heart  
Centre Singapore  
SingHealth

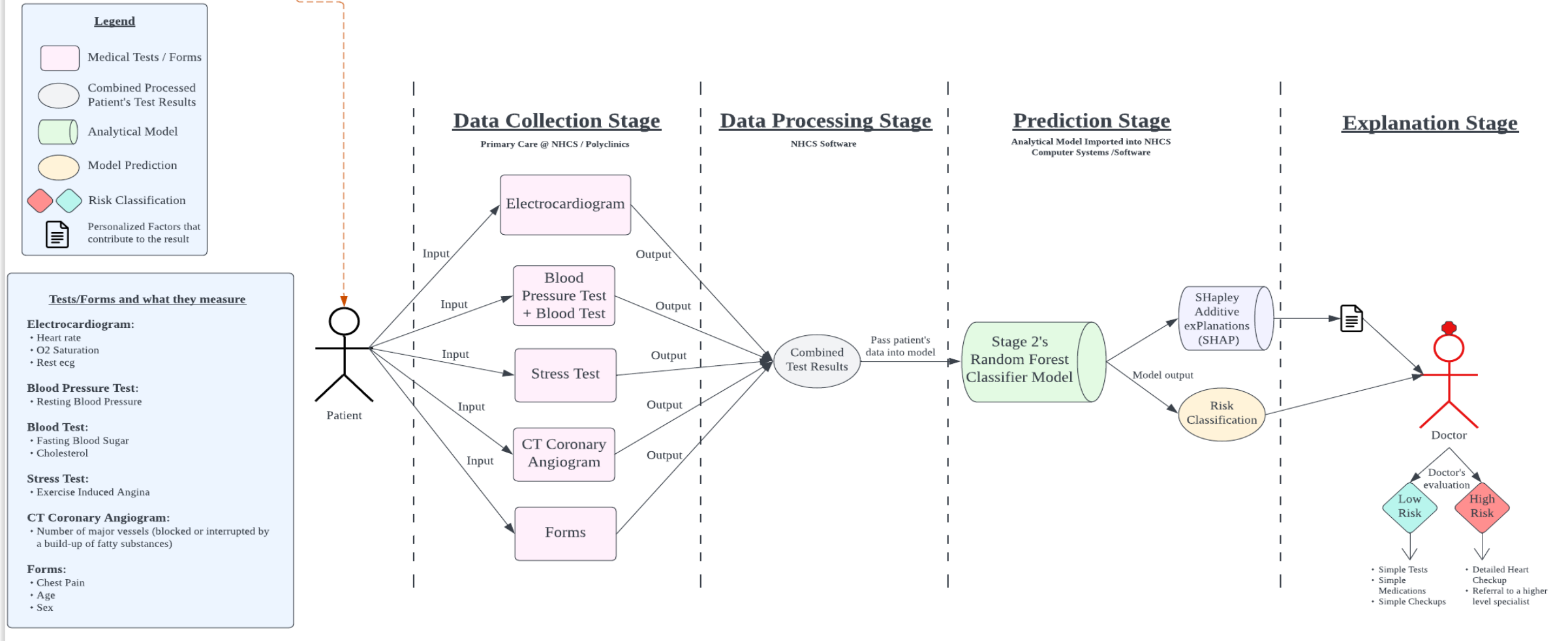
**Stage 2** →

Prediction of Heart Disease Risk using medical attributes

# Business Implementation: *Stage 2* - Technical Flowchart

Zainab

## Stage 2 (NHCS)







# Business Implementation: *Stage 2* - User Journey Map

Zainab



Amy, 40  
Self-checked  
High-risk Patient

1

## Primary Tests

5 basic tests conducted at primary care



ECG



Blood Test



Blood Pressure



Stress Test



CT Coronary  
Angiography

2

## Received Risk Prediction Result

With analytics report



**Low Risk**

Analyze reports to understand the patient's heart health and make recommendations accordingly

**High Risk**

Report reveals which factors contribute significantly to the patient's high risk, such as chest pain, and takes the next relevant detailed tests (e.g., screening for coronary artery disease).

3

## Decision Making

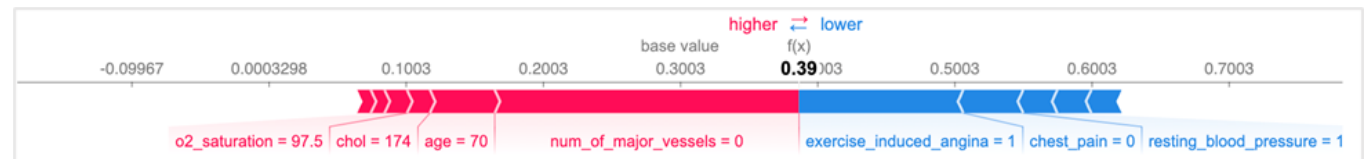
Based on Risk Prediction Level & Analytics Report & Expertise

Given simple testing with **medications** and screening

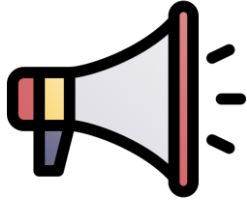
Advised to use stage 1 **self-prediction tool** to monitor heart health closely

Determine the next course of action according to significant contributing factor

e.g., detailed **cardiac examinations** and **referrals to heart center** / specialist consultant







## Raise Public Awareness

By **answering the questions** required for stage 1, **individuals** gain awareness of the risk factors for heart disease



## Provide Timely Alert

From the **prediction result**, individuals can seek timely intervention before the heart disease materialises.



## Optimise Medical Procedures

- **Individuals** would **know** if they need go for a heart check-up
- **Doctors** would be able to **optimise** the next course of action for patient

# Comparison with Latest Solution

Bryan



## PRECISE

### Stage 1

### Stage 2

Purpose

Allow **people** to **self-detect** their risk of having **heart disease**

Allow **doctors** to **detect** the risk of having **heart disease**

Allow **patients/doctors** to **self-detect/detect** the risk of having **coronary artery disease**

Variables

17

11

7

Model Used

Random Forest

Random Forest

Logistic Regression

Explainer Model

LIME

SHAP

-

Output

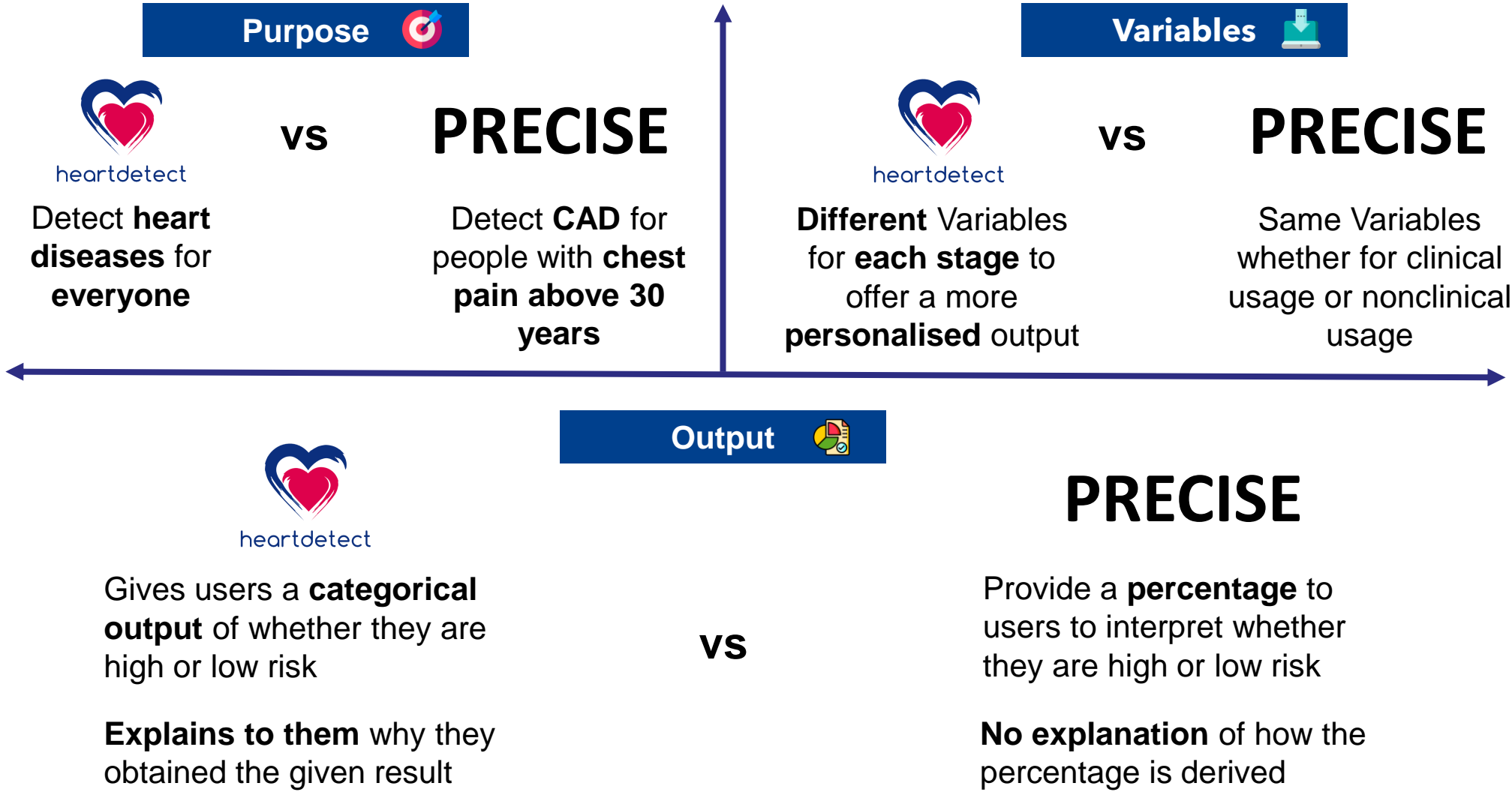
High Risk (1) or Low Risk (0)  
(Categorical) with Explanation of factors

High Risk (1) or Low Risk (0)  
(Categorical) with Explanation of factors

Probability of having CAD  
(Continuous)

Comparison Analysis: By offering a more personalised approach with clearer explanations for our model, we are better than PRECISE

Bryan



# Limitations, and our strategies to get mitigate them

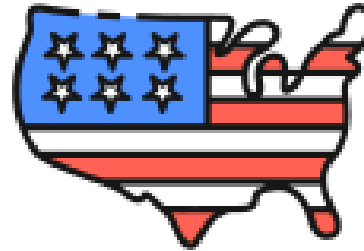
Gerald

## Dataset Limitations

1

### Data Origin

Dataset used is based on **American** individual data, which may **lose accuracy** in local implementation



V/S



# Limitations, and our strategies to get mitigate them

Gerald

## Dataset Limitations

1

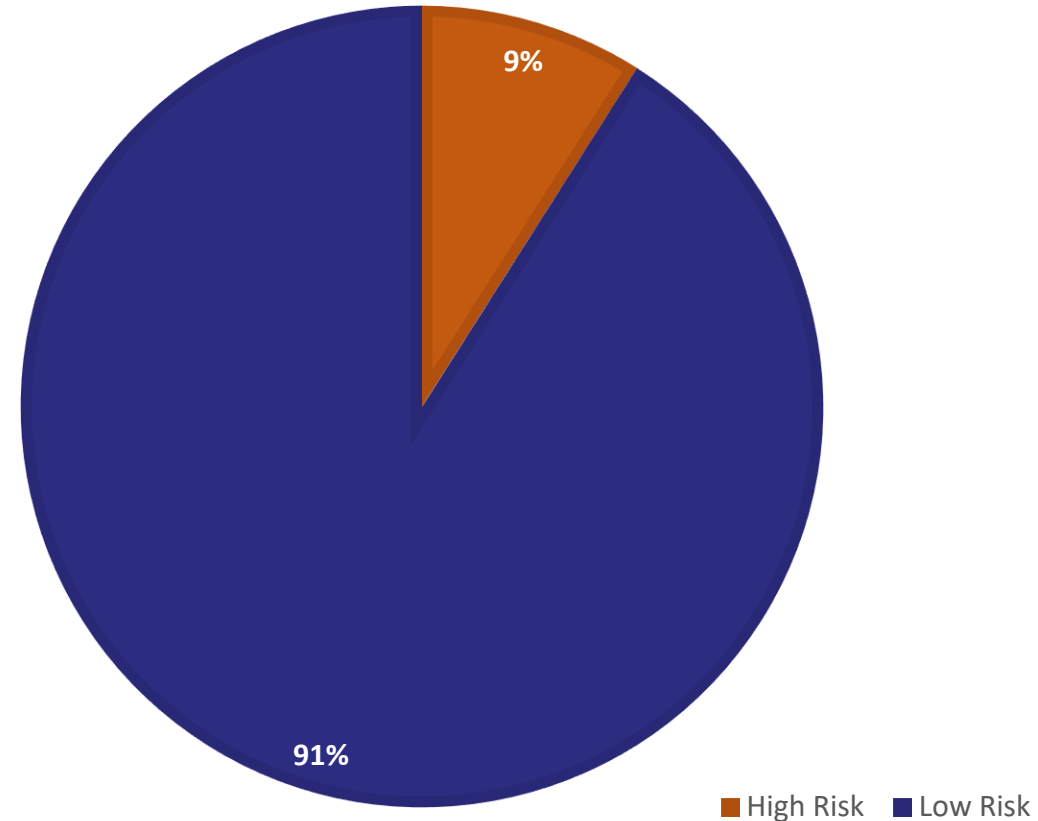
### Data Origin

Dataset used is based on **American** individual data, which may **lose accuracy** in local implementation

2

### Data Imbalance

Dataset used is **imbalanced** in terms of individuals with low and high risk of heart disease



# Limitations, and our strategies to get mitigate them

Gerald

## Dataset Limitations

1

### Data Origin

Dataset used is based on **American** individual data, which may **lose accuracy** in local implementation

2

### Data Imbalance

Dataset used is **imbalanced** in terms of individuals with low and high risk of heart disease

	2021	2020	2019
Total No. of Deaths	24,292	22,054	21,446
Ischaemic Heart Diseases	20.1%	20.5%	18.8%
Cerebrovascular Diseases (including stroke)	6.1%	6.0%	5.8%
Hypertensive Diseases (including hypertensive heart disease)	3.4%	2.9%	2.6%
Other Heart Diseases	2.3%	2.1%	2.0%
Atherosclerosis	0.2%	0.2%	0.1%
Total % of Deaths from Cardiovascular Disease	32.0%	31.7%	29.3%
Total No. of Deaths from Cardiovascular Disease	7,762	6,990	6,291

# Limitations, and our strategies to get mitigate them

Gerald

## Dataset Limitations

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### Data Origin

Dataset used is based on **American** individual data, which may **lose accuracy** in local implementation

2

### Data Imbalance

Dataset used is **imbalanced** in terms of individuals with low and high risk of heart disease

3

### Other factors

Other risk factors such as **genetics**, were not considered though research has shown its role in risk prediction



High Blood Pressure



High Cholesterol



History of Heart Disease

# Limitations, and our strategies to get mitigate them

Gerald

## Dataset Limitations

1

### Data Origin

Dataset used is based on **American** individual data, which may **lose accuracy** in local implementation

2

### Data Imbalance

Dataset used is **imbalanced** in terms of individuals with low and high risk of heart disease

3

### Other factors

Other risk factors such as **genetics**, were not considered though research has shown its role in risk prediction

## Mitigating Strategies

1

2

Collecting more cardiovascular disease data from **Singaporeans**

3

**Research or consult experts** to determine which genetic indicators are valuable



## Stages

1

### Stage 1

#### Individual Empowerment

Convenient self-predicting & monitoring tool

2

### Stage 2

#### Prediction @ Primary Care

A decision support tool for physicians to make decisions based on analytics result



Increase involvement of individuals and primary care sector



Reduce life-threatening impacts of Heart Disease through early detection, timely intervention and optimal treatment



Shift the focus from post-diagnosis treatment to prevention

# Conclusion



# THANKS!

If you have any question, feel free to contact us at:

- Email: [Jlei002@e.ntu.edu.sg](mailto:Jlei002@e.ntu.edu.sg)
- GitHub: <https://github.com/xJQx/bc2406-project>



## References

- Carauna, C. (2018 , December 14). SciDev.Net. Retrieved from Lifestyle diseases swamp Asia's healthcare systems : <https://www.scidev.net/asia-pacific/news/lifestyle-diseases-swamp-asia-s-healthcare-systems/>
- Perret-Guillaume, C., Joly, L., & Benetos, A. (2009). Heart rate as a risk factor for cardiovascular disease . *Prog Cardiovasc Dis.* , 6-10.
- Heart failure - alcohol and smoking. HealthHub. (n.d.). Retrieved October 29, 2022, from <https://www.healthhub.sg/a-z/diseases-and-conditions/716/Heart-Failure-Alcohol-and-Smoking#:~:text=Smoking%20damages%20the%20blood%20vessels,lung%20diseases%20and%20stomach%20ulcers.>
- Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., . . . Løchen, M.-L. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice . *EAS Updates*, 207-274.
- Qian, X., Li, Y., Zhang, X., Guo, H., He, J., & Wang, X. (2022). A Cardiovascular Disease Prediction Model Based on Routine Physical Examination Indicators Using Machine Learning Methods: A Cohort Study . *Front. Cardiovasc. Med.* .
- Singapore Heart Foundation. (2022). Singapore Heart Foundation. Retrieved from Heart Disease Statistics: <https://www.myheart.org.sg/health/heart-disease-statistics/>
- Yates, T., Zaccardi, F., Dhalwani, N. N., Davies, M. J., Bakrania, K., Celis-Morales, C. A., . . . Khunti, K. (2017). Association of walking pace and handgrip strength with all-cause, cardiovascular, and cancer mortality: a UK Biobank observational study . *European Heart Journal*, 3232-3240.