Biomedical Informatics

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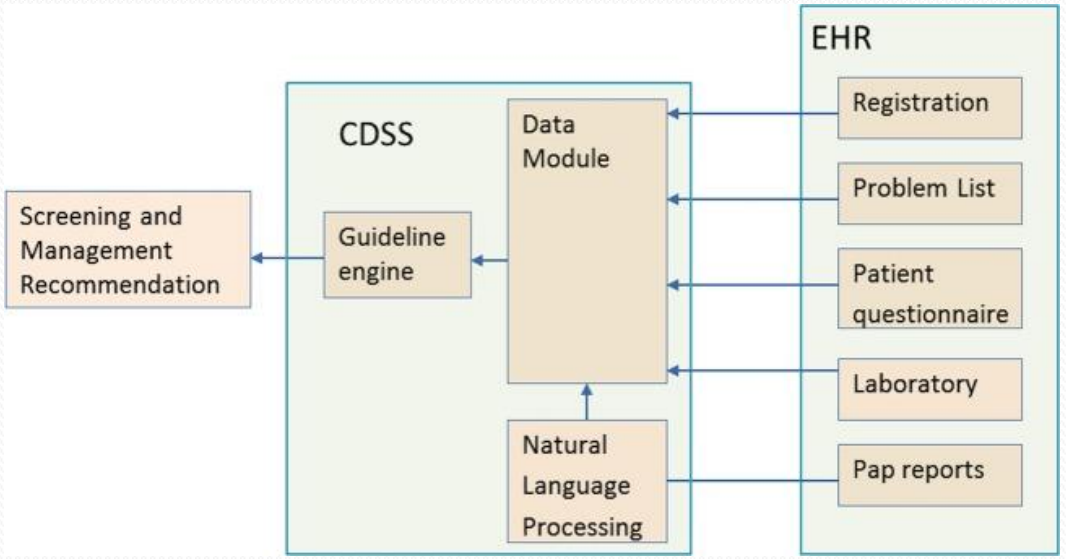
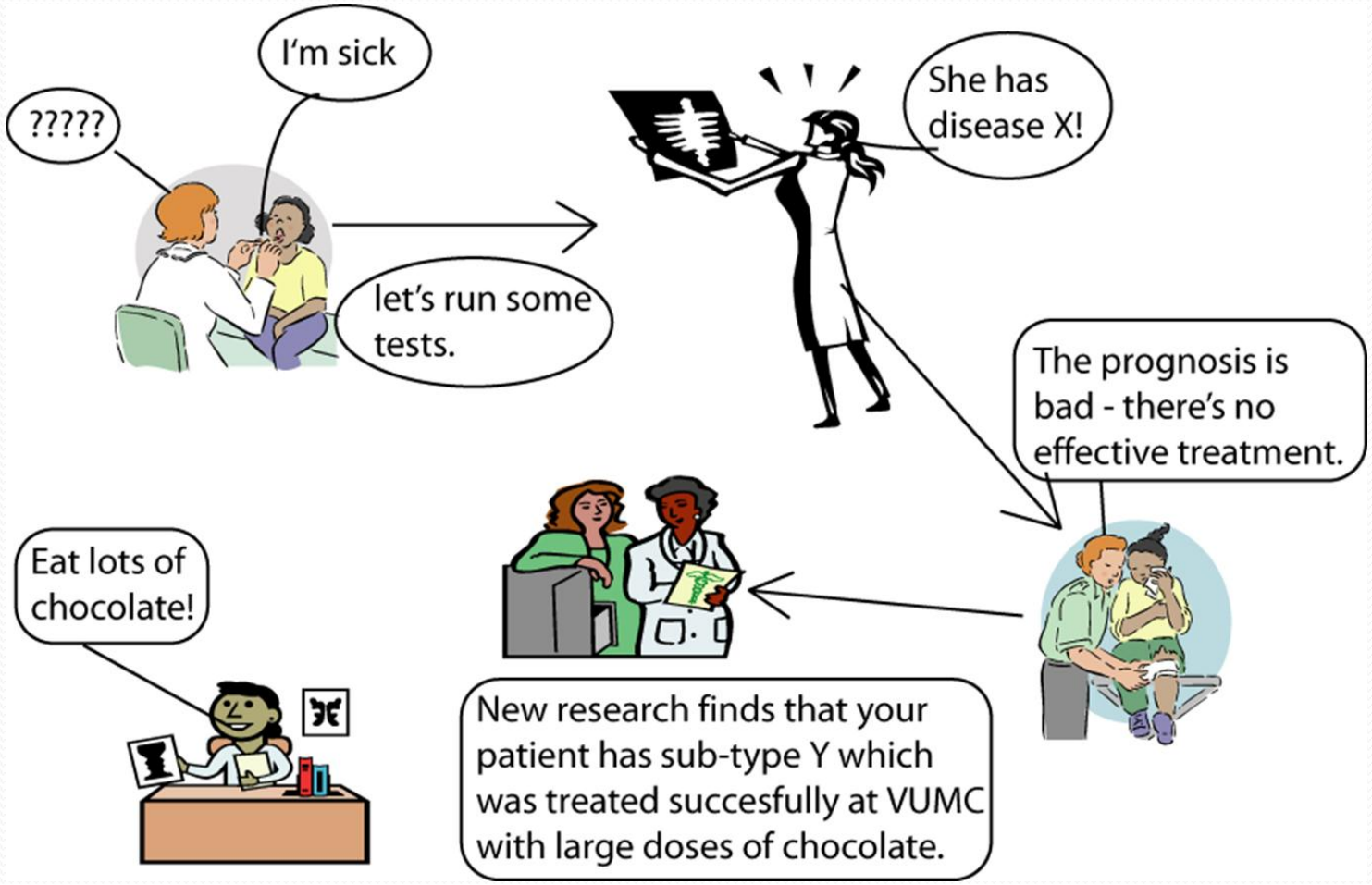
Clinical research and risk scores

Introduction to Clinical Research

Clinical research aims to improve patient outcomes using data, statistics, and technology.

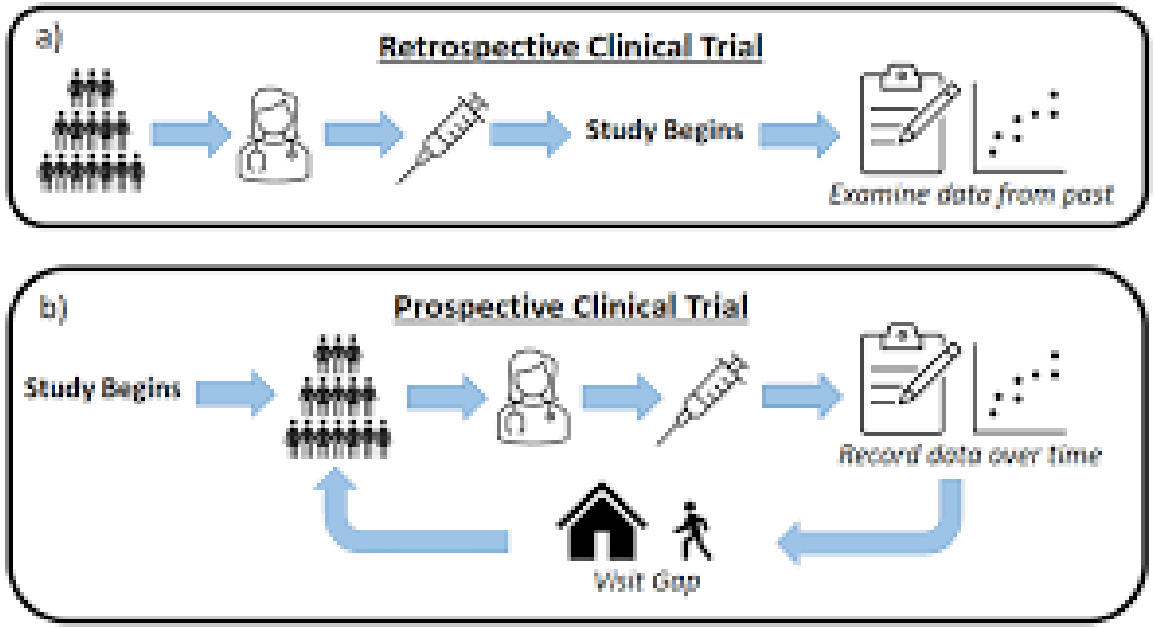
- Key goals:
  - - Improve quality of life
  - - Reduce medical errors
  - - Enable early diagnosis
  - - Reduce healthcare costs




I'm sick
?????
let's run some tests.
She has disease X!
The prognosis is bad - there's no effective treatment.
Eat lots of chocolate!
New research finds that your patient has sub-type Y which was treated succesfully at VUMC with large doses of chocolate.

Types of Clinical Studies

- Retrospective Studies:
  - - Use past data
  - - Faster and cheaper
  - - Limited data quality
- Prospective Studies:
  - - Follow patients over time
  - - More accurate
  - - Expensive and time-consuming



Statistical power of clinical research

Statistical power = probability of correctly detecting a true effect

- Power = 1−**β**

•**Key Components:**

- Effect size (magnitude of difference)
- Sample size (N)
- Significance level (α, typically 0.05)
- Variability (σ) in the data

•**Interpretation:**

- High power (≥ 80%) → high chance of detecting real effects
- Low power → risk of false negatives (missed discoveries)

•**Design Implications:**

- Underpowered studies → unreliable conclusions
- Overpowered studies → unnecessary cost/resources
- Power analysis required **before study starts**

where **β** = Type II error

$\beta = P(\text{fail to reject } H_0 | H_1 \text{ is true})$

- High β → high risk of missing a true treatment effect
- Low β → better ability to detect real differences

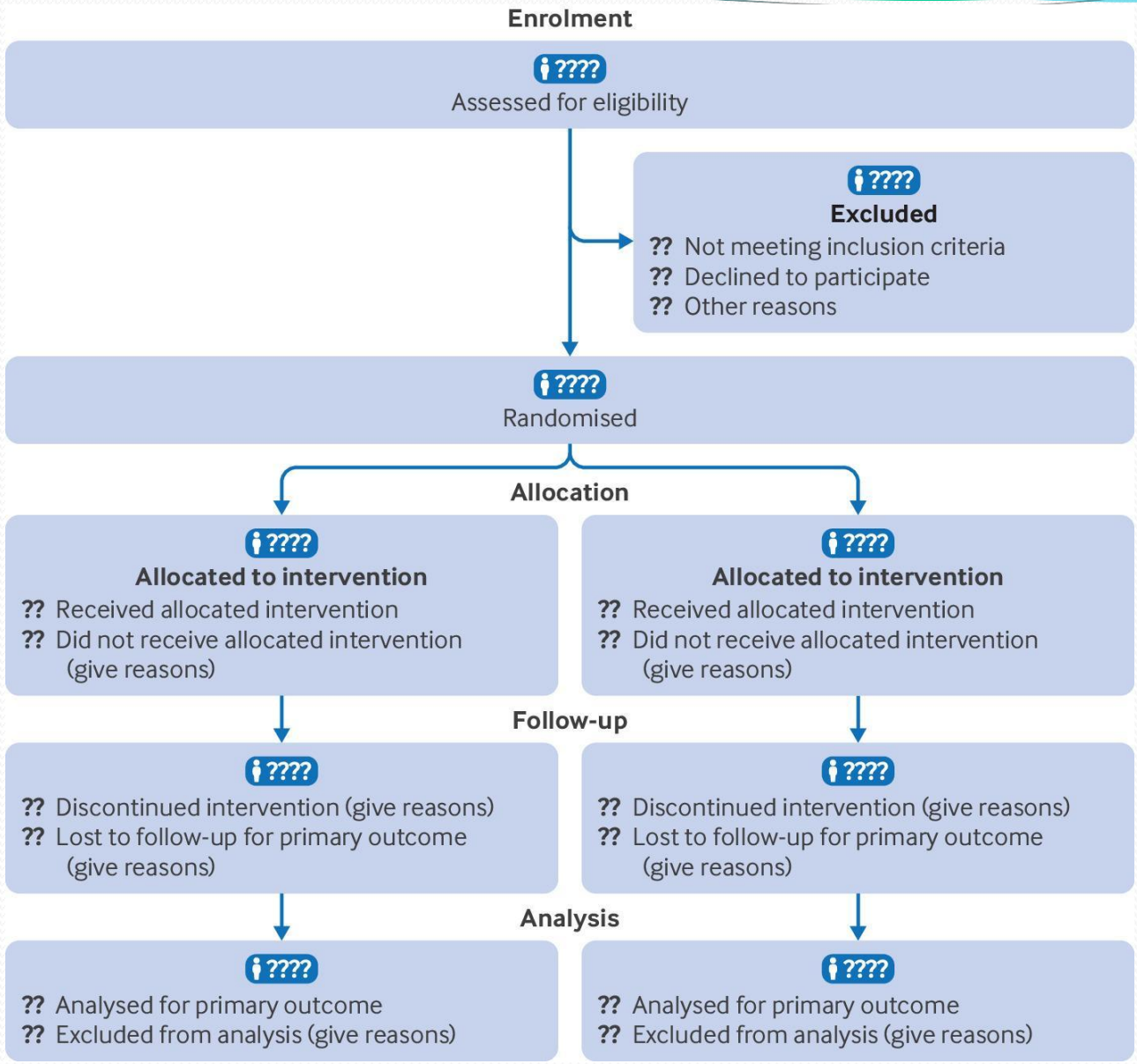
β = 0.20 (Power = 80%) is commonly used

Clinical Trial Phases

Phase 1	Phase 2	Phase 3	Phase 4
			
Focus: Safety. Phase I trials may include a secondary investigation of efficacy or mechanism.	**Focus:** Efficacy becomes a more important factor. Safety still a priority.	**Focus:** Generating enough data to move to regulatory approval of new therapies.	**Focus:** To better understand safety in a broader population or in specific subsets after a therapy is approved.
20-80 participants	100–300	1000–3000	Post-marketing and optimization

Study Design Process

Protocol Design



Randomization

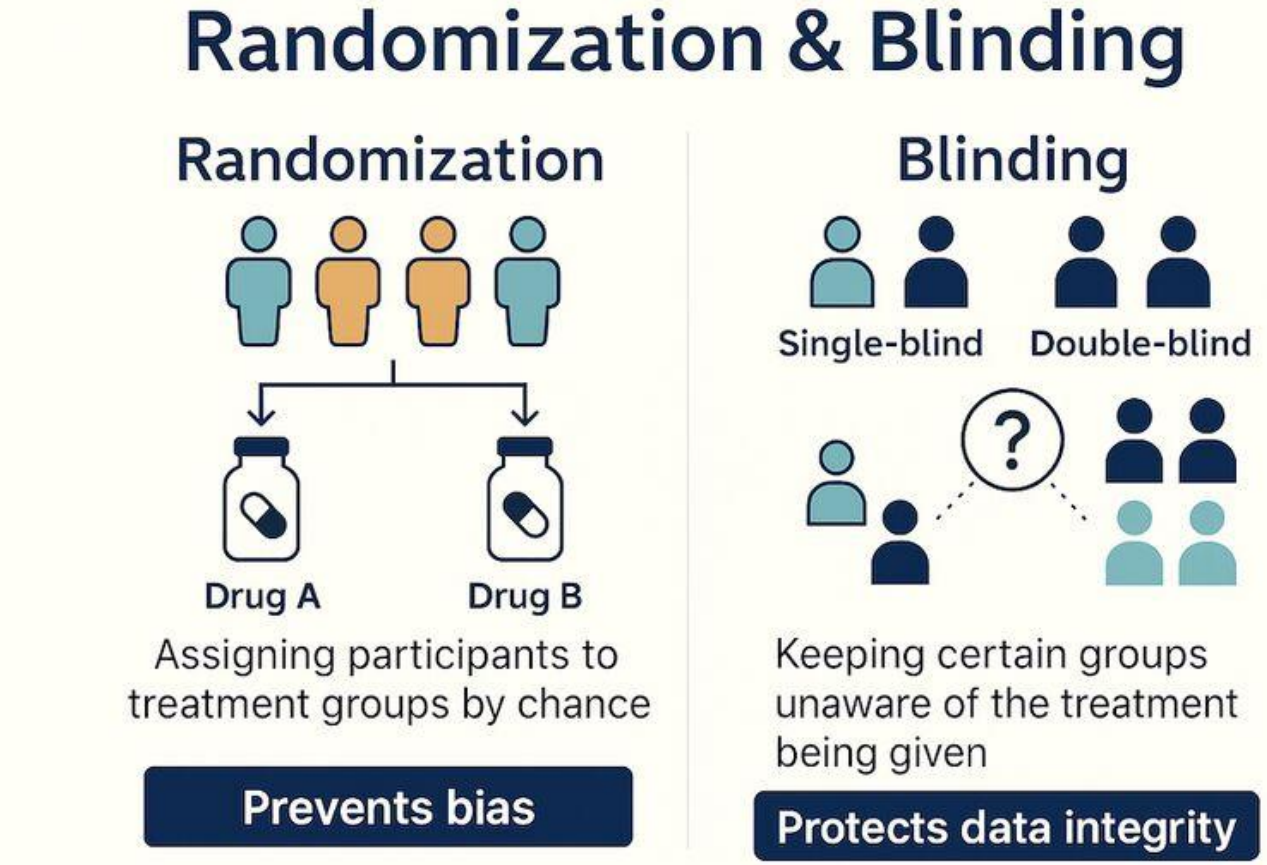
Randomization

Participants are randomly assigned to groups.

- Purpose:
  - Reduce bias
  - Ensure comparable groups
  - Important for valid results

Blinding

- Single-blind: Patient unaware of treatment
- Double-blind: Both patient and researcher unaware
- Prevents placebo effect and bias



Ethics in Clinical Research

- Informed consent is required.
- Participants must know:
  - - Purpose
  - - Duration
  - - Risks
  - - Rights

Ethics committees approve studies

Risk Prediction Models

- Used to estimate probability of disease.
- Based on:
  - - Statistical models
  - - Patient data

- Applications:
  - - Clinical decisions
  - - Screening
  - - Prevention

Medical Risk Calculators

What are risk score/prediction models?

- A “prediction” is a statement or claim that a particular event will occur in the future (current or past event is also sensible).
- Response is often binary (event/non-event) or censored.
- Mathematical equation can be used to model the rate (or probability or likelihood) of event.
- Scoring system (e.g., integer) can be derived to grade the risk, often by simplifying the mathematical model (e.g., regression coefficients).
- Mathematical equation and/or scoring system can be used to stratify subjects (e.g., high vs. low risk)

Importance

- Evidence-based medicine =
  - Science (theory) + Data + Statistics
- Risk score =
  - Statistics + Reality
- One of real practical solutions to reduce the burden/incidence of some diseases.
- People use it in real world (esp., lay and underserved people)
- used in clinical setting, community setting, or self-use for pre-screening, screening or risk assessment/prediction.

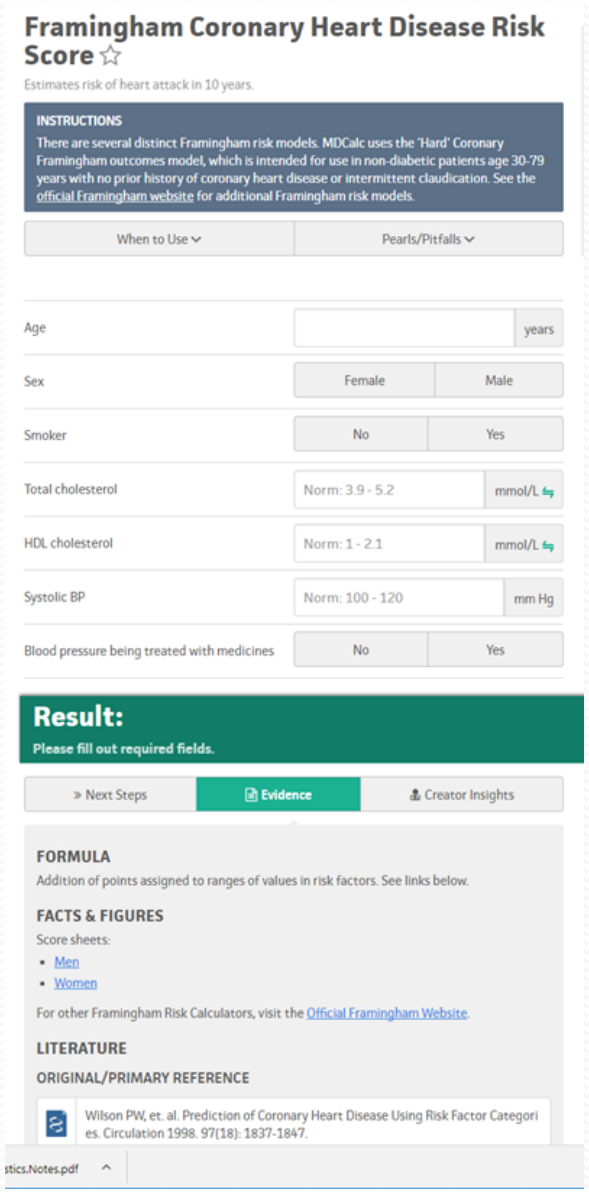
Some risk scores on internet

- Cancer: http://riskfactor.cancer.gov/cancer_risk_prediction/
  http://www.mskcc.org/mskcc/html/5794.cfm
  http://www4.utsouthwestern.edu/breasthealth/cagene/
- APACHE: http://www.sfar.org/scores2/apache22.html
  http://www.apache-web.com/public/pub_main.html
- Charlson comorbity index: http://www.medalreg.com/qhc/medal/ch1/1_13/01-13-01-ver9.php3
- Framingham score: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof
  & http://www.nhlbi.nih.gov/about/framingham/riskabs.htm
- UK CVD score: http://www.riskscore.org.uk/
- PROCAM score: http://www.chd-taskforce.de/
- Reynolds score: http://www.reynoldsriskscore.org/
- Herman et al.'s diabetes risk score: http://www.diabetes.org/risk-test.jsp
- German diabetes risk score: http://www.dife.de/
- Angina score: http://www.anginarisk.org/
- Pneumonia score: http://www.ahrq.gov/clinic/pneuclin.htm#head1
- SCORED: http://kidneydiseases.about.com/od/diagnostictests/a/scored.htm
- Depression: http://www.psycom.net/depression.central.screening.html
- Medical calculator: http://medcalc3000.com/ (some are commercial)

MD+CALC

https://www.mdcalc.com

- evidence-based tools and content
- written by physician experts
- support 35+ specialties
- cover 200+ patient conditions
- used by over one million medical professionals globally



http://www.framinghamheartstudy.org/about-fhs

Example – **Framingham Score**

predict and prevent heart disease

- 5,209 patients aged 30-59 enrolled
  - Patients given questionnaire and exam every 2 years
  - Physical characteristics
  - Behavioral characteristics
  - Test results
  - Exams and questions expanded over time

build models using the Framingham data

AGE-SEX DISTRIBUTION AT ENTRY (1948)				
Age	**29-39**	**40-49**	**50-62**	**Totals**
Men	835	779	722	2,336
Women	1,042	962	869	2,873
Totals	1,877	1,741	1,591	5,209

Hypothesized CHD Risk Factors

- Risk factors from first examination
  - *totChol*: Total cholesterol (mg/dL)
  - *sysBP*: Systolic blood pressure
  - *diaBP*: Diastolic blood pressure
  - *BMI*: Body Mass Index, weight (kg)/height (m)2
  - *heartRate*: Heart rate (beats/minute)
  - *glucose*: Blood glucose level (mg/dL)
- Randomly split patients into training and testing sets
- Use logistic regression on training set to predict whether or not a patient experienced CHD within 10 years of first examination
- Evaluate predictive power on test set

Score (for men)

Step 1

Age		
Years	LDL Pts	Chol Pts
30-34	-1	[-1]
35-39	0	[0]
40-44	1	[1]
45-49	2	[2]
50-54	3	[3]
55-59	4	[4]
60-64	5	[5]
65-69	6	[6]
70-74	7	[7]

Step 2

LDL - C		
(mg/dl)	(mmol/L)	LDL Pts
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-190	4.15-4.92	1
≥190	≥4.92	2

Cholesterol		
(mg/dl)	(mmol/L)	Chol Pts
<160	<4.14	[-3]
160-199	4.15-5.17	[0]
200-239	5.18-6.21	[1]
240-279	6.22-7.24	[2]
≥280	≥7.25	[3]

Step 3

HDL - C			
(mg/dl)	(mmol/L)	LDL Pts	Chol Pts
<35	<0.90	2	[2]
35-44	0.91-1.16	1	[1]
45-49	1.17-1.29	0	[0]
50-59	1.30-1.55	0	[0]
≥60	≥1.56	-1	[-2]

Step 4

Blood Pressure					
Systolic (mm Hg)	Diastolic (mm Hg) <80	80-84	85-89	90-99	≥100
<120	0 [0] pts				
120-129		0 [0] pts			
130-139			1 [1] pts		
140-159				2 [2] pts	
≥160					3 [3] pts

Step 5

Diabetes		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Step 6

Smoker		
	LDL Pts	Chol Pts
No	0	[0]
Yes	2	[2]

Key	
Color	Relative Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

* Hard CHD events exclude angina pectoris

** Low risk was calculated for a person the same age, optimal blood pressure, LDL-C 100-129 mg/dL or cholesterol 160-199 mg/dl, HDL-C 45 mg/dL for men or 55 mg/dL for women, non-smoker, no diabetes

Risk estimates were derived from the experience of the Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

(sum from steps 1-6)

Step 7

Adding up the points	
Age	_____
LDL-C or Chol	_____
HDL - C	
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point total	_____

(determine CHD risk from point total)

Step 8

CHD Risk			
LDL Pts Total	10 Yr CHD Risk	Chol Pts Total	10 Yr CHD Risk
<-3	1%		
-2	2%		
-1	2%	[<-1]	[2%]
0	3%	[0]	[3%]
1	4%	[1]	[3%]
2	4%	[2]	[4%]
3	6%	[3]	[5%]
4	7%	[4]	[7%]
5	9%	[5]	[8%]
6	11%	[6]	[10%]
7	14%	[7]	[13%]
8	18%	[8]	[16%]
9	22%	[9]	[20%]
10	27%	[10]	[25%]
11	33%	[11]	[31%]
12	40%	[12]	[37%]
13	47%	[13]	[45%]
≥14	≥56%	[≥14]	[≥53%]

(compare to average person your age)

Step 9

Comparative Risk			
Age (years)	Average 10 Yr CHD Risk	Average 10 Yr Hard* CHD Risk	Low** 10 Yr CHD Risk
30-34	3%	1%	2%
35-39	5%	4%	3%
40-44	7%	4%	4%
45-49	11%	8%	4%
50-54	14%	10%	6%
55-59	16%	13%	7%
60-64	21%	20%	9%
65-69	25%	22%	11%
70-74	30%	25%	14%

Framingham Score evolution

- Second generation enrolled in 1971, third in 2002
  - Enables study of family history as a risk factor
  - More diverse cohorts begun in 1994 and 2003
  - Social network analysis of participants
  - Genome-wide association study linking studying genetics as risk factors
  - Many challenges related to funding
  - Funding cuts in 1969 nearly closed study
  - 2013 sequester threatening to close study

AGE-SEX DISTRIBUTION AT ENTRY (1948)

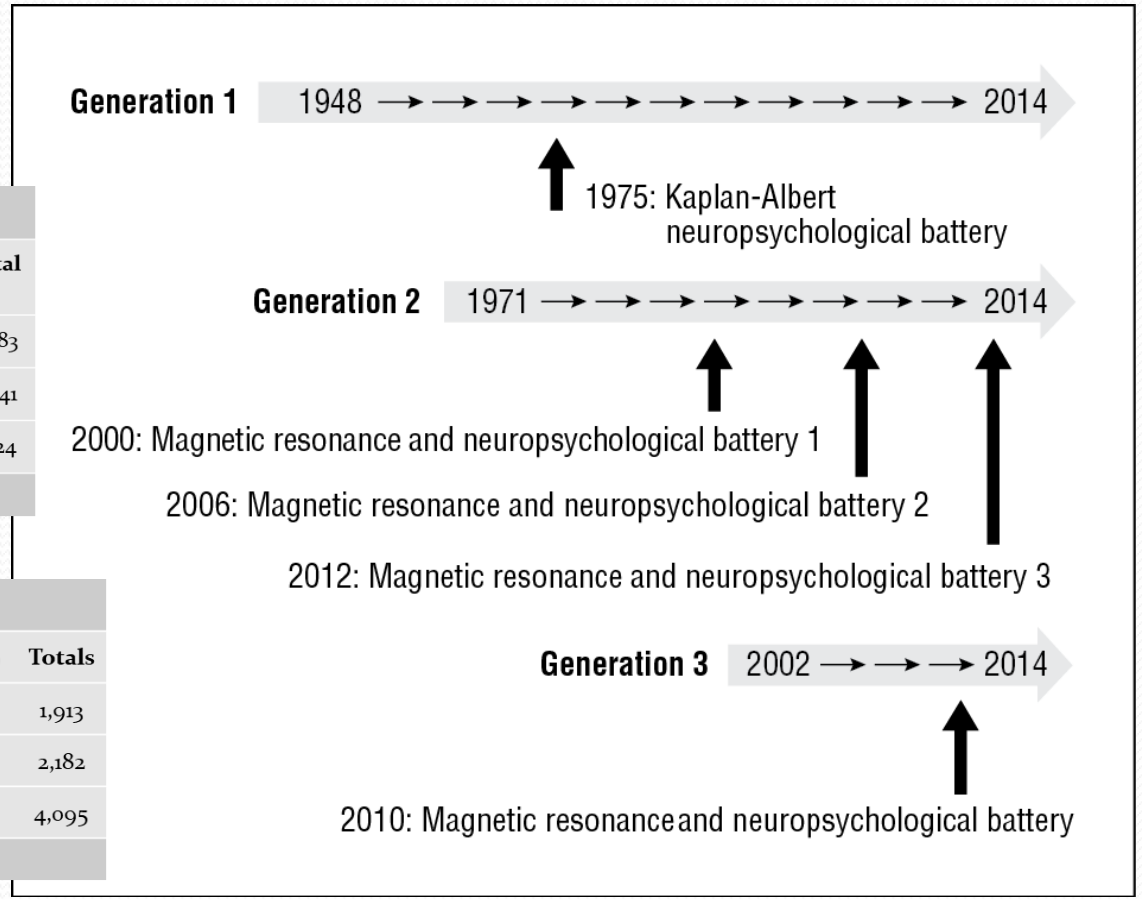
Age	29-39	40-49	50-62	Totals
Men	835	779	722	2,336
Women	1,042	962	869	2,873
Totals	1,877	1,741	1,591	5,209

AGE-SEX DISTRIBUTION AT ENTRY (1971)

Age	<10	10-19	20-29	30-39	40-49	50-59	60-70	Totals
Men	0	126	543	789	694	293	38	2,483
Women	6	113	692	835	740	242	13	2,641
Totals	6	239	1,235	1,624	1,434	535	51	5,124

GEN3: AGE-SEX DISTRIBUTION AT ENTRY (THROUGH 2005)

Age	19	20-29	30-39	40-49	50-59	60-69	70-79	Totals
Men	4	220	656	737	276	19	1	1,913
Women	3	262	759	848	293	16	1	2,182
Totals	7	482	1,415	1,585	569	35	2	4,095

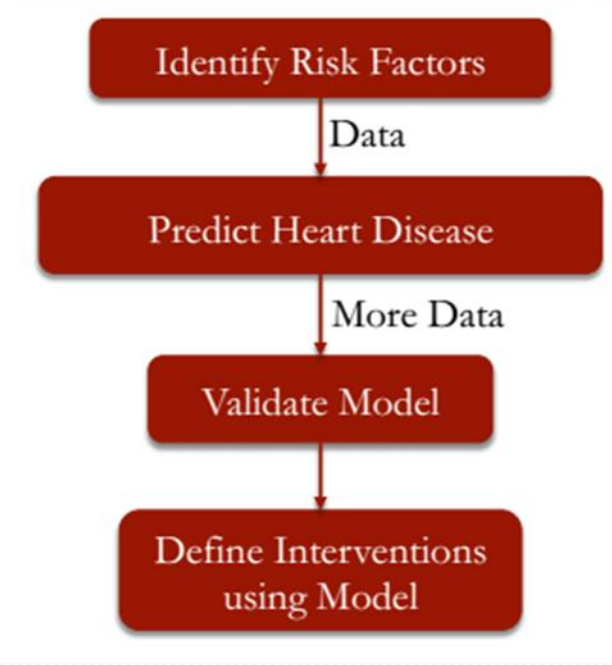


Framingham Risk Model Validation

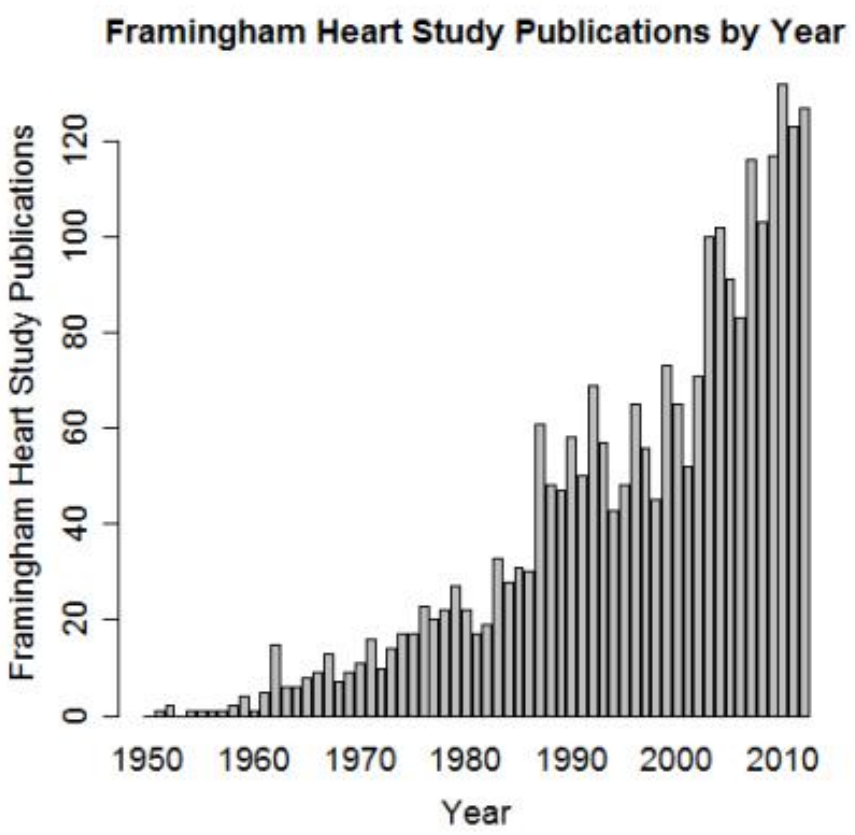
Framingham Risk Model tested on diverse cohorts

Study	Population
Atherosclerosis Risk in Communities (ARIC) Study	White and Black
Honolulu Heart Program (HHP)	Japanese American
Puerto Rico Heart Health Program (PR)	Hispanic
Strong Heart Study (SHS)	Native American

- Cohort studies collecting same risk factors
- Validation Plan
- Predict CHD risk for each patient using FHS model
- Compare to actual outcomes for each risk decile



- More than 2,400 studies use Framingham data
- Many other risk factors evaluated
  - Obesity
  - Exercise
  - Psychosocial issues
  - …
- *Texas Heart Institute Journal*: top 10 cardiology advances of 1900s



Statistics

Understanding Statistics

Excellent health statistics - smokers are less likely to die of age related illnesses.'

- Population
- Description
- Inference
- BIG WORDS
  - *Significant*
  - *Valid*
- No formulas
- Focus on frequentist

Using Statistics in Research

- Statistical methods provide a way for formally accounting for sources of variability in patients' responses to treatment.
- The use of statistics allows the clinical researcher to form reasonable and accurate inferences from collected information, and make sound decisions in the presence of uncertainty.
- Statistics are key to preventing errors and biases in medical research.

Hypothesis Testing

A hypothesis is an assumption, or set of assumptions, that either:

a) asserts something on a provisional basis with a view to guiding scientific investigation; or

b) confirms something as highly probable in light of established facts.

If we have a hypothesis that asserts something, for example, that a new treatment for a disease is better than the existing standard of care treatment, if the new treatment is 'B', and the standard of care treatment is 'A' then the hypothesis states *that 'B' is better than 'A'*.

The ‘NULL’ Hypothesis

- Rather than trying to prove the ‘B’ hypothesis, scientific method assumes that in fact ‘A’ is true – that there is no difference between the standard of care and the new treatment.
- This is known as the ‘Null’ hypothesis.
- Scientists then try to disprove ‘A’. This is also known as proving the Null hypothesis false. If they can prove that hypothesis ‘A’ is false, and that the standard of care is not better than the new treatment – it follows that ‘B’ is true, and that the new treatment ‘B’ is better than the standard treatment ‘A’.

The ‘NULL’ Hypothesis

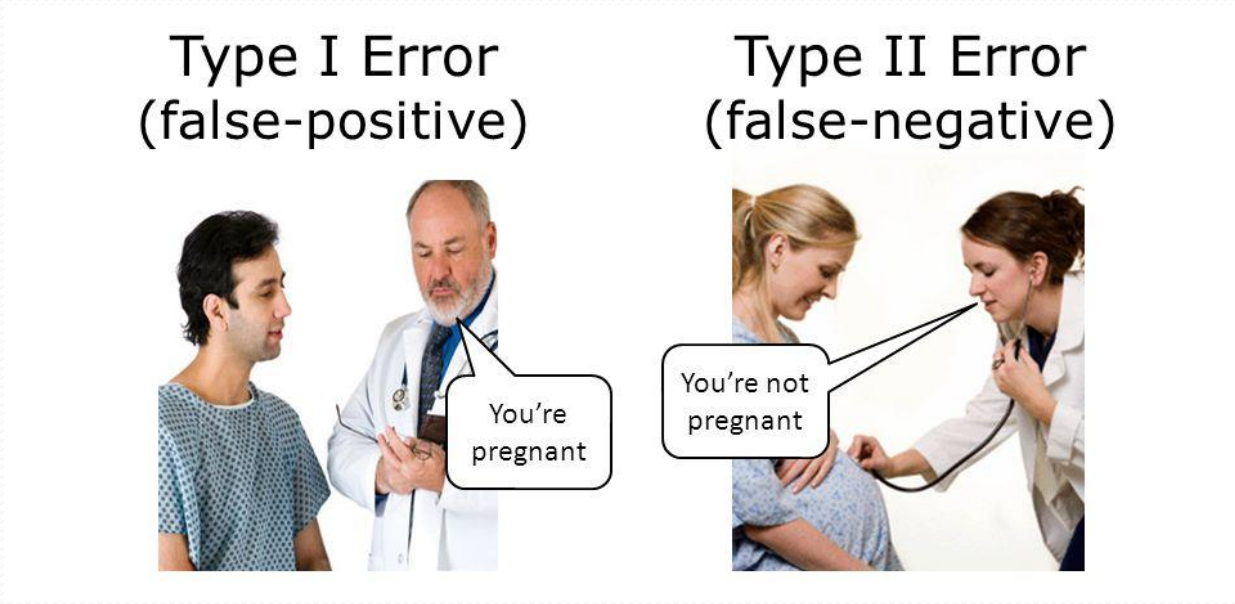
‘***No amount of experimentation can ever prove me right; a single experiment can prove me wrong***.’

A.Einstein

- This seems to suggest that trying to prove the Null hypothesis false or wrong is a more rigorous and achievable objective than trying to prove the alternative hypothesis is right.
- This does not properly explain why science adopts this approach, but perhaps it can help us to comprehend and accept a tricky concept more easily

Type I and Type II Errors

	Null hypothesis is true	Null hypothesis is false
Reject the Null hypothesis	Type I error 'False Positive'	Correct outcome 'True Positive'
Fail to reject the Null hypothesis	Correct outcome 'True negative'	Type II error 'False negative'



Project

My Health App

Develop a multilingual mobile health application in Flutter/Dart for patients. The application must support authentication, retrieval of one motivational message at each login, implementation of a short psychoemotional questionnaire, implementation of the Framingham score and one additional clinical risk score, storage and visualization of user-entered health data, graphical monitoring of scores over time, environmental data retrieval through a free API, management of allergies, medication, and a problem list using ICD terminology, and a calendar view integrating all recorded health events. The app must support English by default and one additional language.

Goal

The goal is to build a mobile application for patients that helps users:

- maintain a simple personal health record,
- monitor selected health indicators over time,
- complete a short psychoemotional questionnaire,
- calculate clinically relevant risk scores,
- visualize score history,
- receive a motivational message at each login,
- view environmental information relevant to daily wellbeing,
- access all stored information through a calendar-oriented view.

The application must store all user-entered data and allow the user to review previous entries.

App Modules (1/4)

1. **Login**
   - email/username + password login form
   - basic validation
2. **Patient demographics**
   - Create a form where the patient will store the basic demographics age, gender, race, ethnicity, name, birthday, location (city – country).
3. **Motivational message API**
   - At every successful login, the app must call an API and retrieve one motivational message, which is then displayed on the home page as a card. e.g. https://zenquotes.io/api/random
4. **Weather and Pollution**
   - Use the following open APIs to retrieve the temperature and air quality index for Heraklion every time the user logins and display it always in your app

App Modules (2/4)

5. **Psychoemotional questionnaire**
   - The app must implement the short psychoemotional questionnaire WHO-5 Well-Being Index. The app must calculate the final score and store it in the local database.
6. **Framingham score calculator**
   - The app must implement a Framingham cardiovascular risk score calculator and store the score in the local database along with the date of application.
7. **Finnish Diabetes Risk Score calculator**
   - The app must implement the FINDRISC (Finnish Diabetes Risk Score)and store the score in the local database along with the date of application.

App Modules (3/4)

8. **Allergies module**
   - The app must include an Allergies section.Each allergy record should contain: allergen name , reaction description ,severity , onset date, if known
9. **Medication module**
   - The app must include a Medication section.Each medication record should contain: medication name, dosage , frequency , start date , end date or ongoing flag , notes
   - optional reminders as bonus functionality
10. **Problem List using ICD terminology**
    - The app must include a Problem List module using ICD-9 (or ICD-10) terminology.
    - The app must support searchable ICD-9 or ICD-10 list or local lookup

App Modules (4/4)

- **Calendar module**
  - The app must include a calendar where the information from the above modules becomes visible in date-based form. The calendar should display events such as:
  - questionnaire completion
  - risk score calculation
  - medication
  - allergy
  - problem list

- **Multilingual support**
  - The app must be **multilingual**. Mandatory language support:
  - **English** as the default language
  - **one additional language** of the team's choice

Submission

- You should submit:
  - .zip file that includes:
  - All the .dart files you have created
  - The pubspec.yaml file
  - Any folder containing images/assets you used (only if you are using local images)
  - **Do NOT** include the entire project folder.
- Technical report
  - Recommended report length: 8–15 pages
- 10-15 minutes presentation
  - Architecture explanation
  - Example patient workflow and screenshots.