

# Genetic Testing in Primary Care

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THE UNIVERSITY OF AUCKLAND  
NEW ZEALAND

## Genetic testing in primary care

- Haemochromatosis (HFE 282 mutation)
- Factor V Leiden (Arg 506 Gln)

Not are recommended for population screening

Done for work up of clinical events (iron overload or VTE or family history of a VTE)

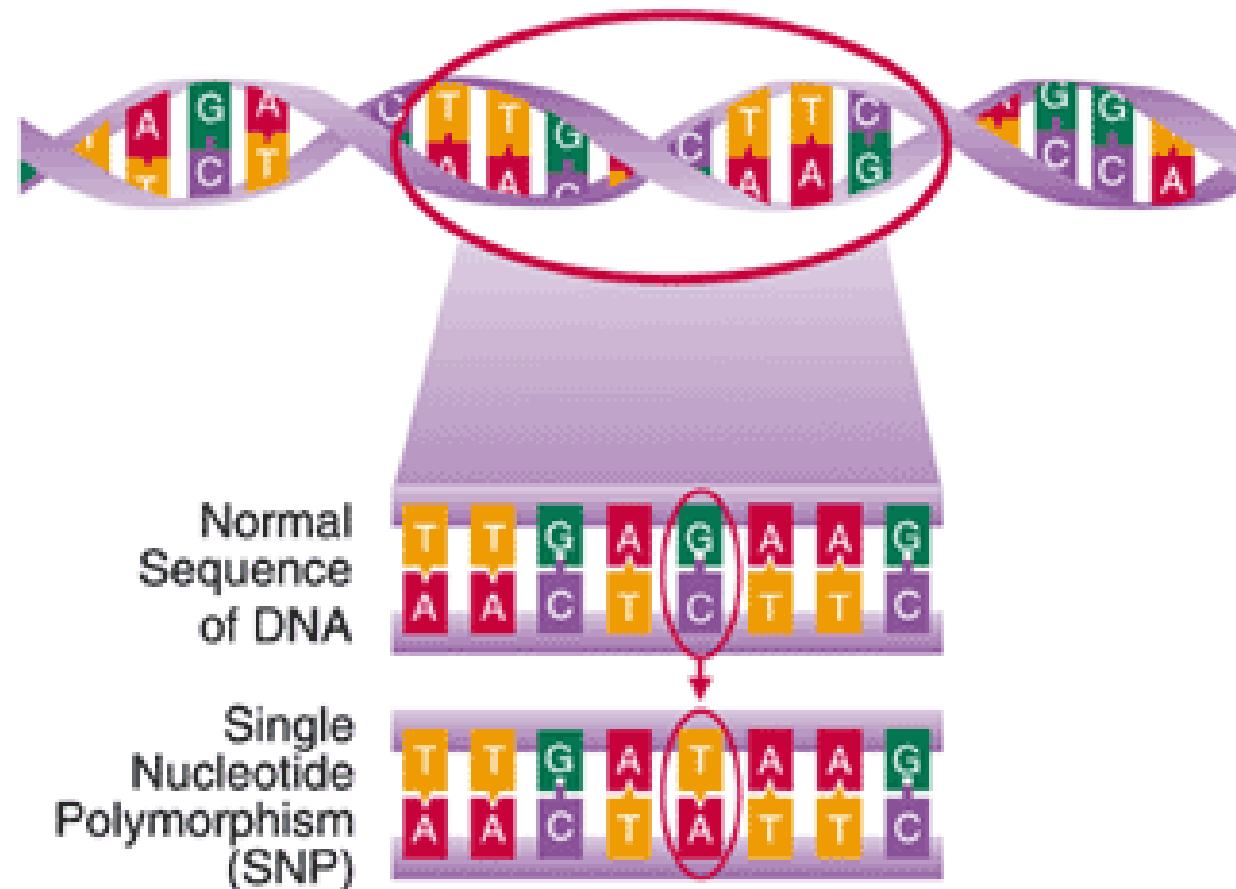
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# Basis of genetic variation: SNP/polymorphism



Naturally occurring genetic variants

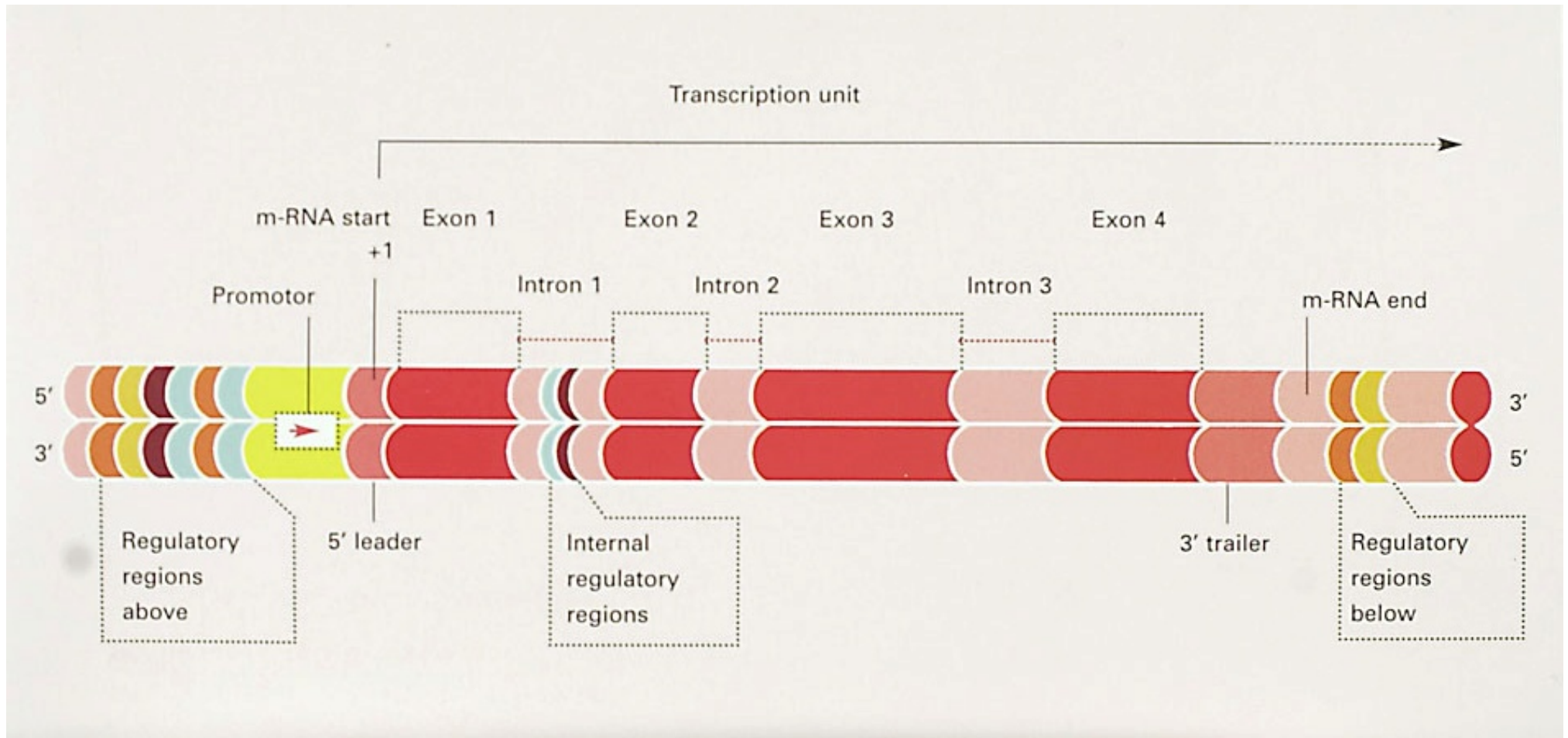
Prevalence 1-90%

Easily identified by high throughput technology

Many have functional effects on protein amount or function

SNP variant may confer protection (higher in controls) or susceptibility (higher in cases)

# Structure of a gene



# Genetic testing in primary care

## Haemochromatosis (HFE 282 mutation)

- HFE testing to establish Haemochromatosis diagnosis in iron overload ( $\uparrow$ Fe Satn)
- Poor specificity (25-50% of gene test (+) are affected by iron overload)
- Reduced sensitivity (explains only some patients with idiopathic iron overload)
- Prompts venesection to treat overload

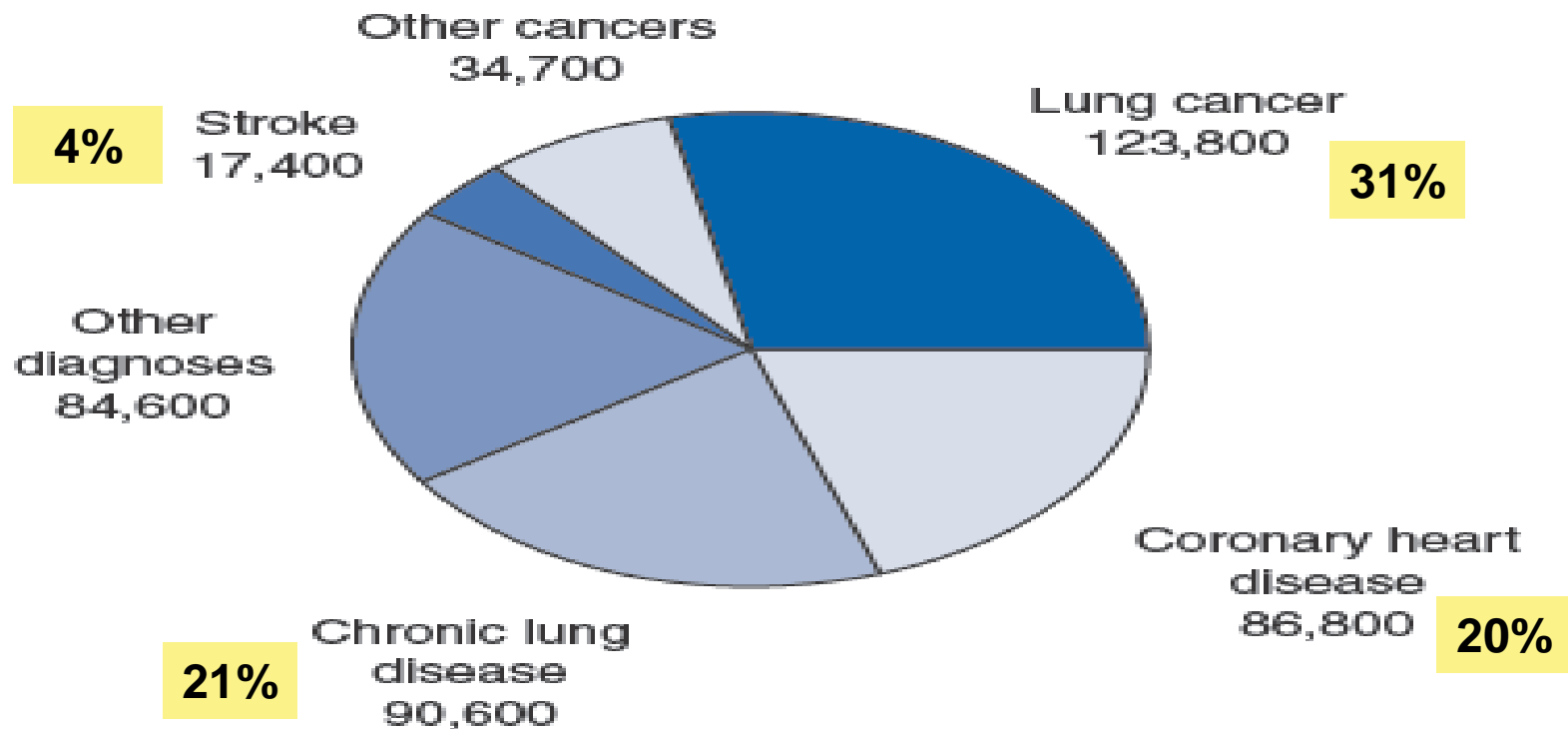
# Genetic testing in primary care

## Factor V Leiden (Arg 506 Gln mutation)

- Part of thrombophilia screen (↑ risk of VTE)
- Mutation occurs in 5% of the general population
- May prompt secondary prevention in those with a history of VTE
- May prompt secondary prevention in those with risk of recurrent fetal loss
- Risk of DVT multiplicative with OCP use

# Lung Cancer & Tobacco Mortality

**About 438,000 U.S. Deaths Attributable Each Year to Cigarette Smoking\***



\* Average annual number of deaths, 1997–2001.  
Source: *MMWR* 2005;54(25):625–8.

# Gene test for lung cancer

**NZ scientists develop way to predict smoking risk**

**BY JENNIFER PEARSON**

SCIENTISTS have come up with a genetic test that could predict how long a person will live after they quit smoking.

The scientists, from the University of Otago, have found that some people have a genetic mutation that makes them more likely to die from lung cancer after they quit smoking.

The researchers found that people with this mutation have a higher risk of dying from lung cancer than those without it.

The researchers also found that people with this mutation have a higher risk of dying from lung cancer than those without it.



**They saved my life'**  
 JAMES BROWN (right) and his wife, who has a genetic mutation that makes her more likely to die from lung cancer after she quits smoking, are shown with a scientist (left) who developed a genetic test to predict smoking risk.

**'They saved my life'**

**BY JENNIFER PEARSON**

James Brown, 84, and his wife, who has a genetic mutation that makes her more likely to die from lung cancer after she quits smoking, are shown with a scientist (left) who developed a genetic test to predict smoking risk.

Brown, who has a genetic mutation that makes him more likely to die from lung cancer after he quits smoking, is shown with a scientist (left) who developed a genetic test to predict smoking risk.

## Couple win big: \$250,000 plus a baby

**BY JENNIFER PEARSON**

A MARRIED COUPLE who were expecting a baby recently received a \$250,000 windfall when they won the grand prize in a lottery.

The couple, who were expecting a baby, were shown the winning numbers on the lottery ball and they were the lucky ones.

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## Slain girl's dad on sex charges

**BY JENNIFER PEARSON**

The father of a slain girl is accused of sexual offenses in a case that has shocked the community.

The father, who is accused of sexual offenses, is shown in a courtroom setting.

The father, who is accused of sexual offenses, is shown in a courtroom setting.

### INSIDE



#### Hard labour for reporters

Reporters face tough conditions in the field, often working long hours and in difficult environments.



#### Transport to rick

Transportation issues are becoming a major concern for many people, especially in urban areas.



#### Roger wins over Paris

Roger Federer has won a significant victory in a tennis match in Paris, defeating a top opponent.



#### Birth of a giant

A giant baby was born in a Canadian hospital, weighing in at a record-breaking weight.

WEATHER: A6 | BUSINESS: B1 | SPORTS: B2 | ENTERTAINMENT: B3 | TRAVEL: A6-30 | WORLD BY: 31 | AS: 32

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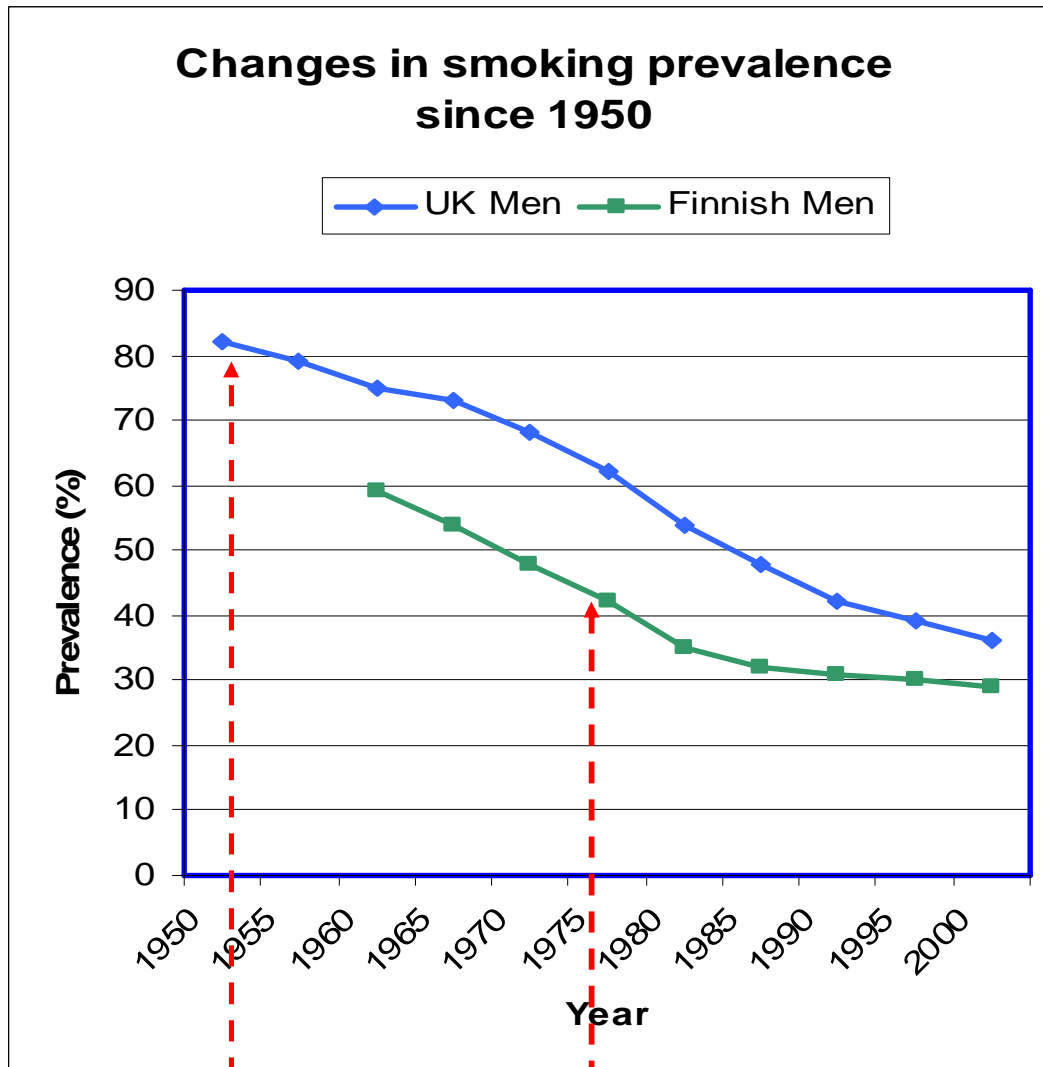
FOR FREE INFORMATION VISIT [www.snorex.co.nz](http://www.snorex.co.nz)  
 OR CALL 0800 333 333

# Genetic susceptibility to lung cancer (COPD)

- Environmental factor known and measurable
- Preventable with smoking cessation
- Lifestyle intervention (quitting) has many benefits (health, financial, social)
- Smoking cessation is very cost effective
- Risk assessment has been shown to both trigger and improve smoking cessation rates
- Many available treatments to assist with quitting
- Potential benefits of statins in reducing COPD complications and risk of lung cancer (Booth 60A)

## Smokers attitudes to smoking: literature review

- Smokers want to know their risk for smoking related complications (>80%)
- Smokers generally under-estimate their personal risk for lung cancer (>50% of smokers with lung cancer did not think they were at risk)
- Smokers state fear of lung cancer as their greatest concern and that fear of future poor health motivates them to quit (older smokers)
- Recognition that risk information has inherent value to patients above that of what doctors might act on



## Smoking prevalence

The link between smoking and lung cancer was made public in the 1950s and 1960s

Public health initiatives continued to reduce smoking rates

Smoking prevalence has levelled out over the last 20 years

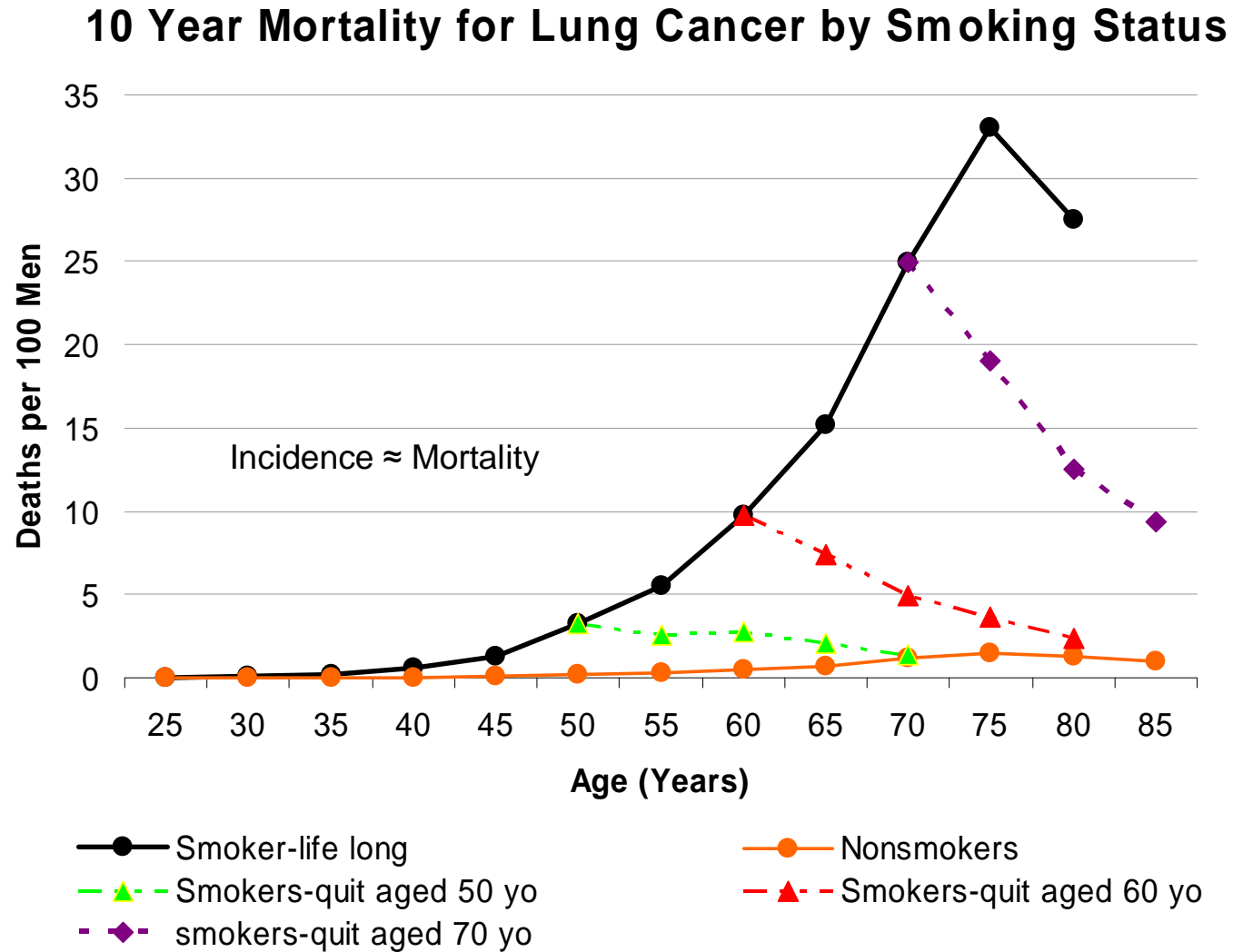
Link made between smoking and lung cancer

Introduction of public health measures eg taxes, advertising bans and health warnings


# Epidemiology of lung cancer

- Smoking (90%)
  - Duration over 30 years or over 30 pk years
- Age (over 50 yo)
- Other factors
  - Asbestos, radon, radiation, cooking fuels
  - Low consumption of fruit and vegetables (antioxidants)
  - Lower risk in atopics
- Lung function
- Family history

# Lung Cancer Risk climbs steeply with age



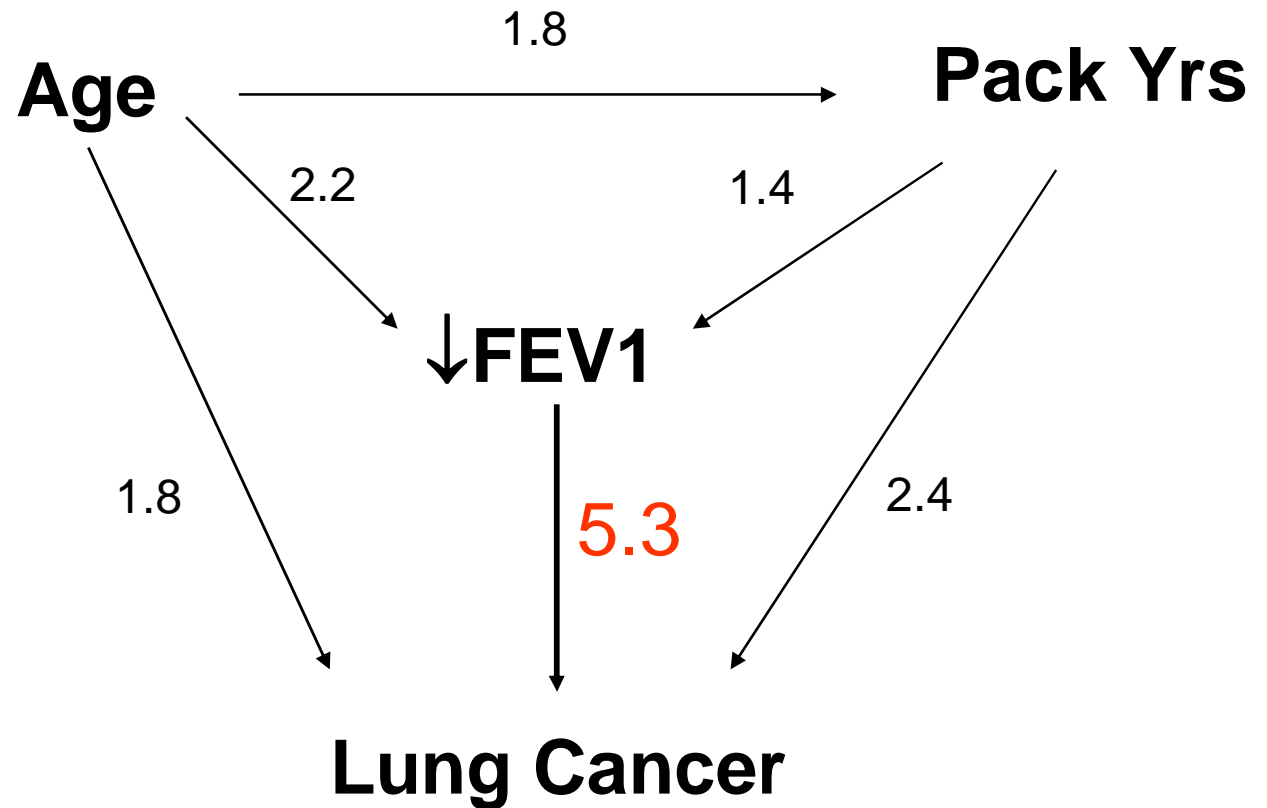
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- 
- Genetic factors**

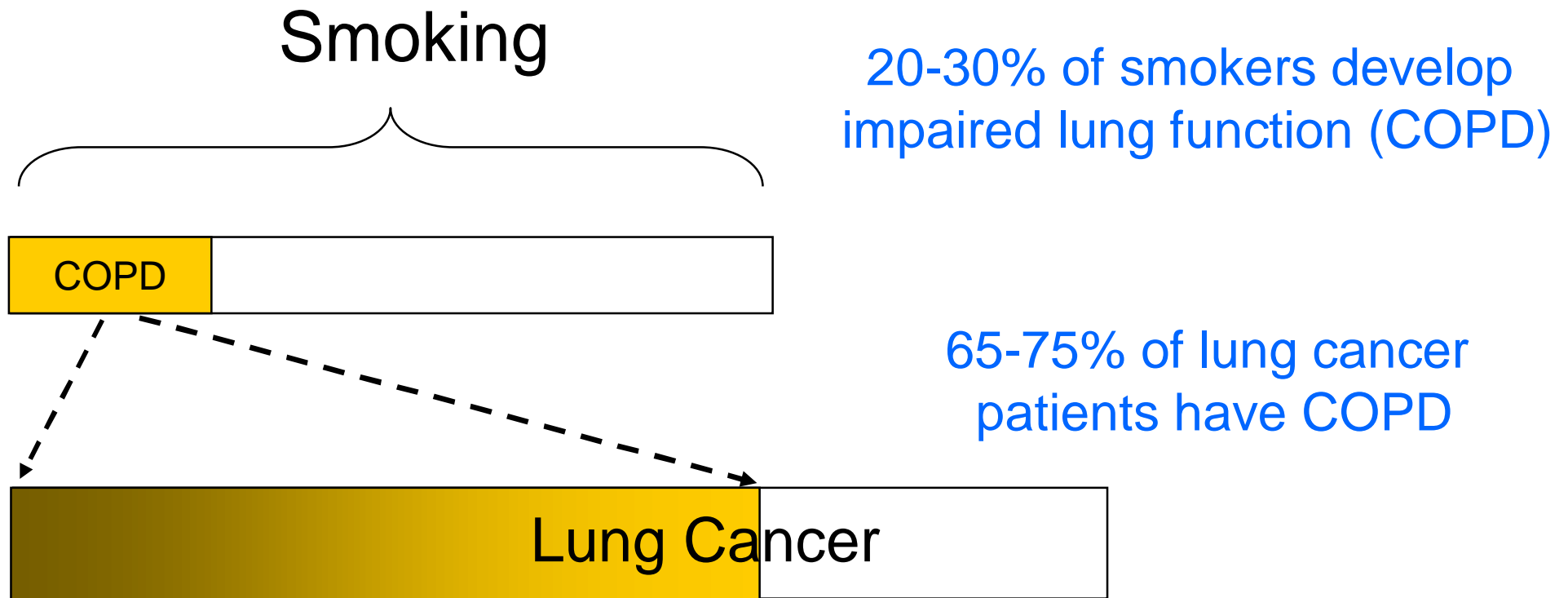
# Lung Function and Lung Cancer

Consistently reported risk of 3-6x for lung cancer in smokers with impaired lung function

<u>Lung cancer</u>	
Age	RR 2.8
↓FEV1	RR 6.4
Pk yrs	RR 3.1

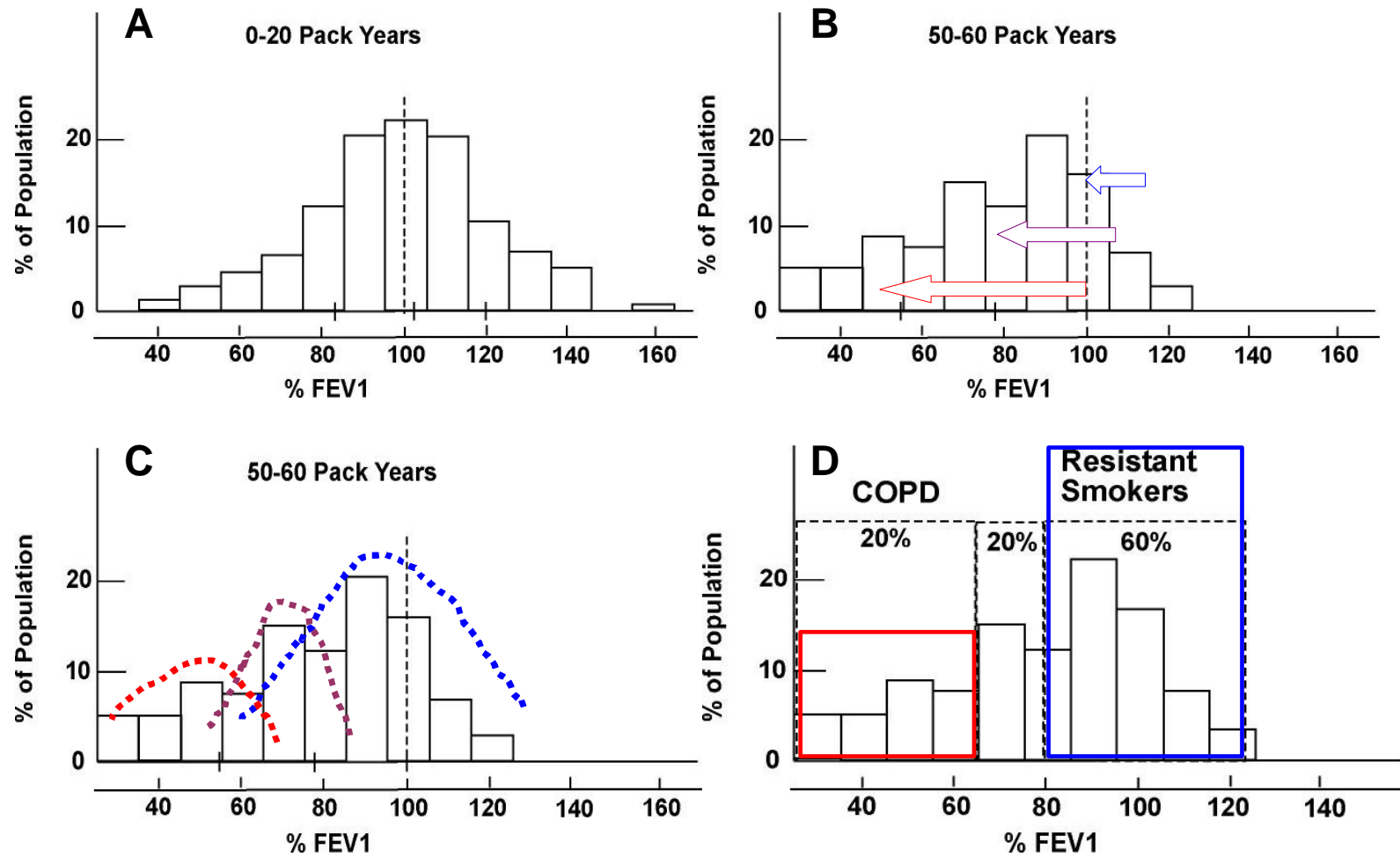


# Smoking, lung function and lung cancer

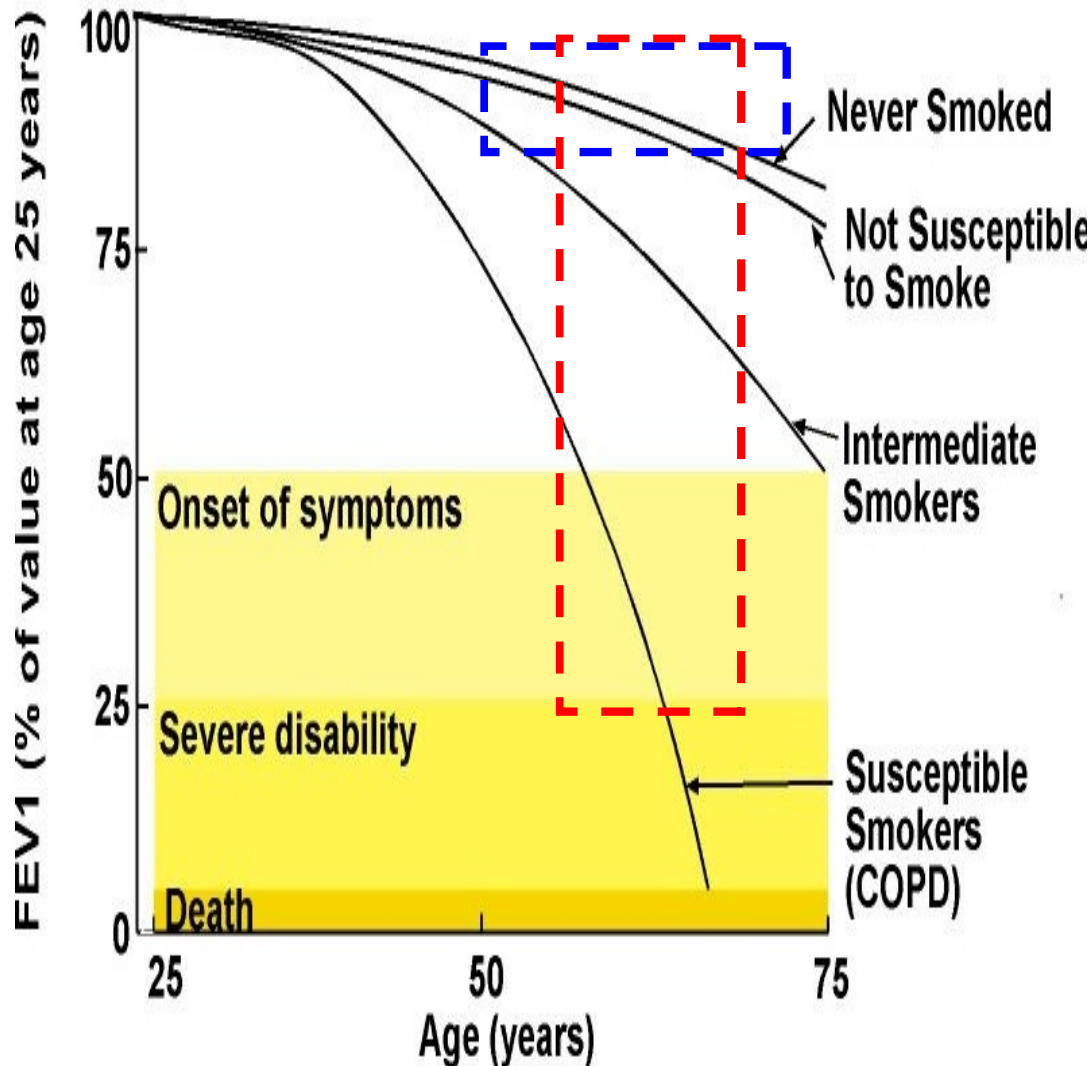


Parallel:  
Obesity predisposes to diabetes

# Segmentation of Lung Function Decline



# Case association study – novel approach



## *Initial Study*

446 smokers with lung cancer

484 resistant smokers

## *Now screened 160 candidate SNPs from 157 different genes.....*

.... Matrix remodeling

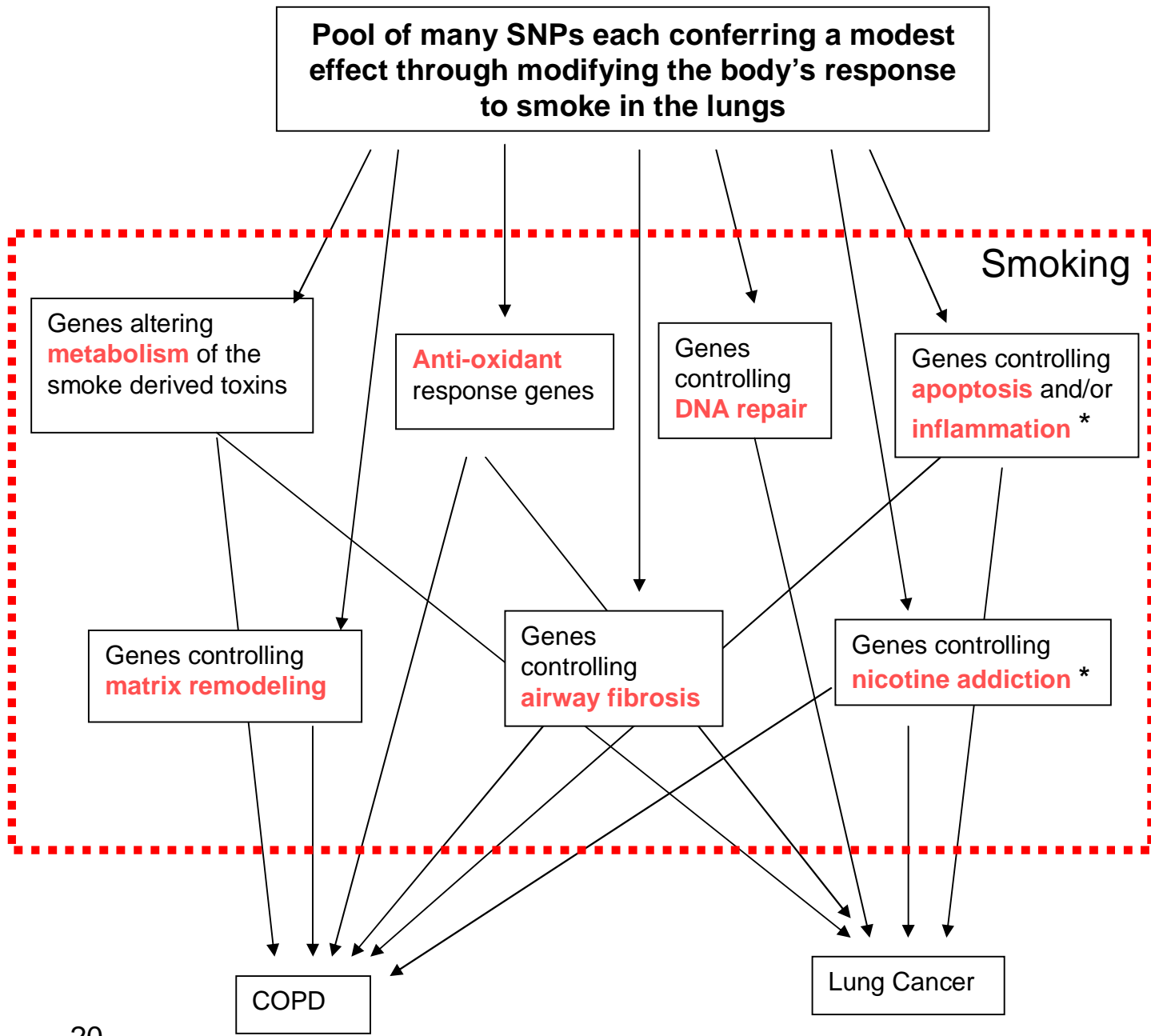
.... Inflammation & innate immunity

.... Anti-oxidant response

.... Apoptosis, DNA repair

**Resistant smokers** = smokers with normal lung function recruited from the community & no history of lung cancer

**Lung cancer** = histologically confirmed lung cancer



Genetic susceptibility to lung cancer

Many genetic variants

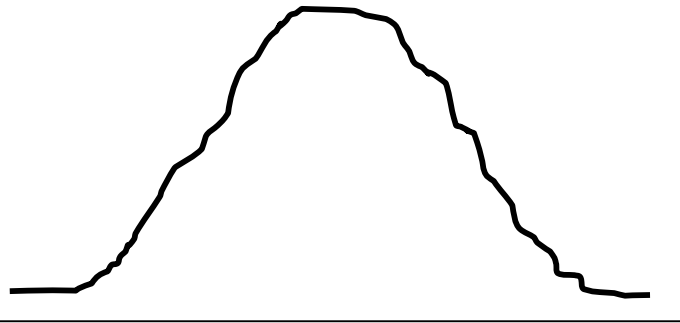
Interaction with smoking

Affect many different pathways

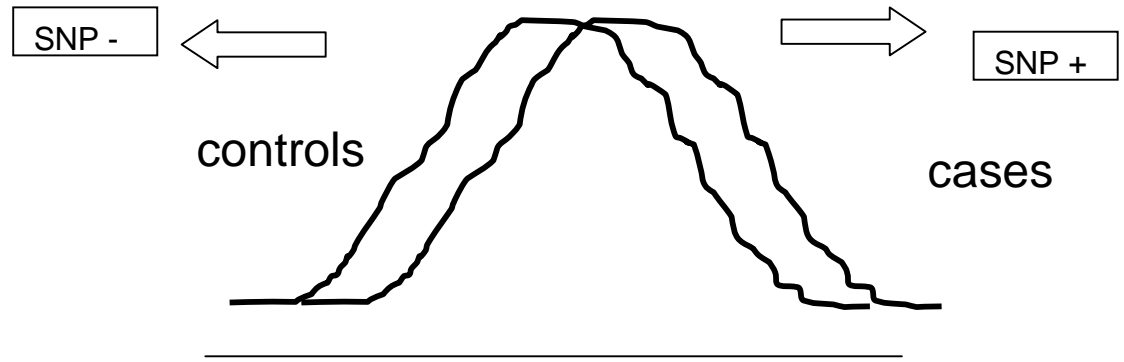
Overlap between genes conferring COPD and lung cancer

nAChR gene\* locus associated with lung cancer, COPD and nicotine addiction

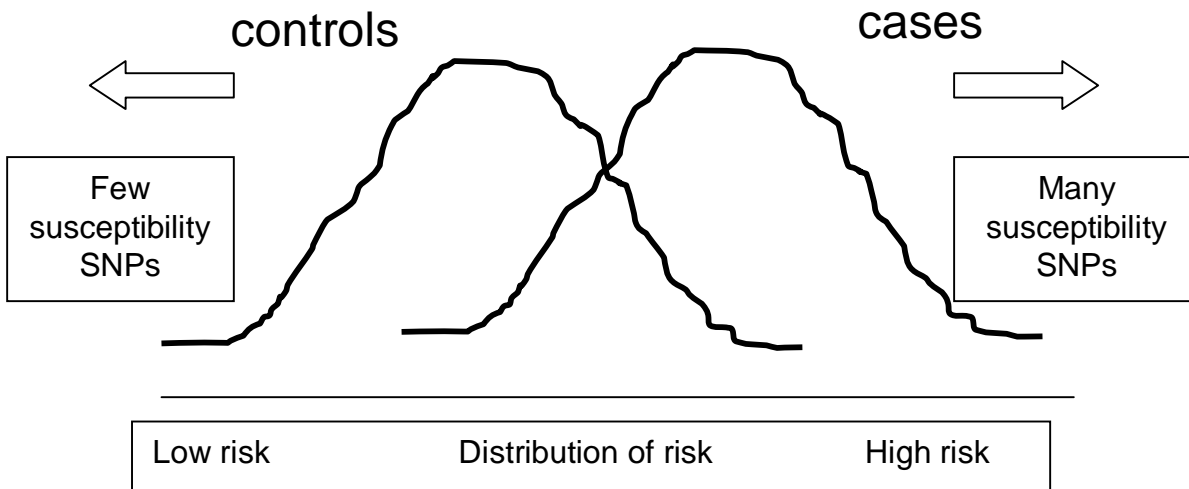
Risk distribution in untested smokers



Risk distribution with 1 SNP tested



Risk distribution with 20 SNPs tested

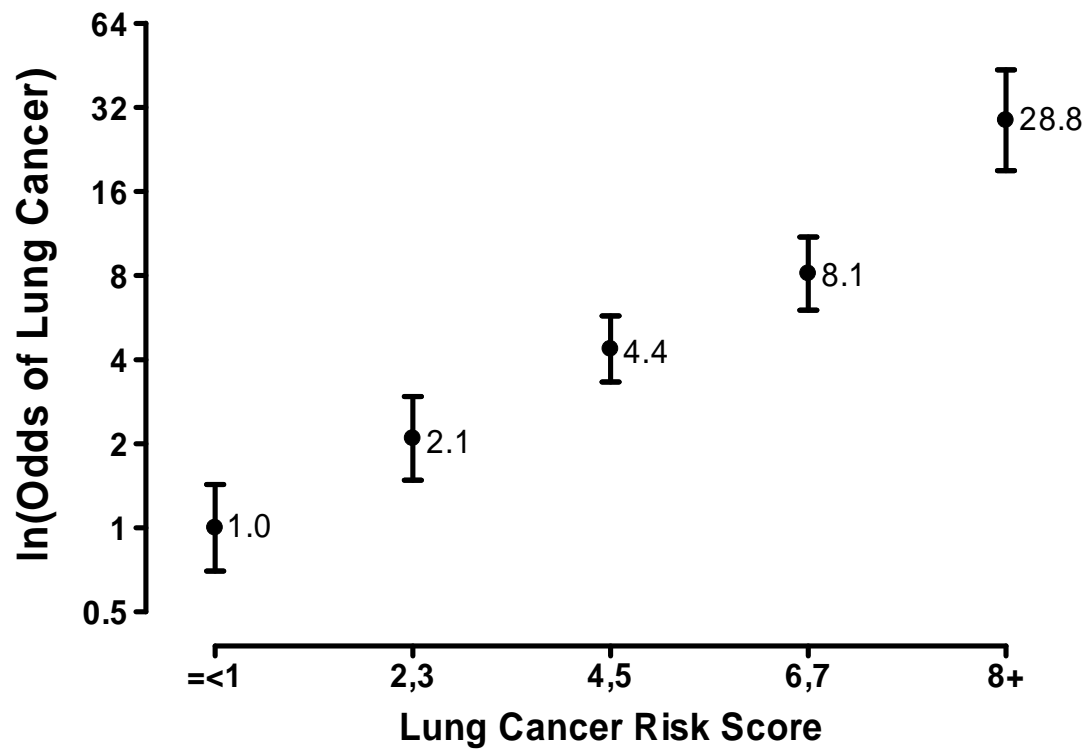


Additive model for lung cancer susceptibility  
Age  
FHx of lung cancer  
PHx of COPD  
SNPs

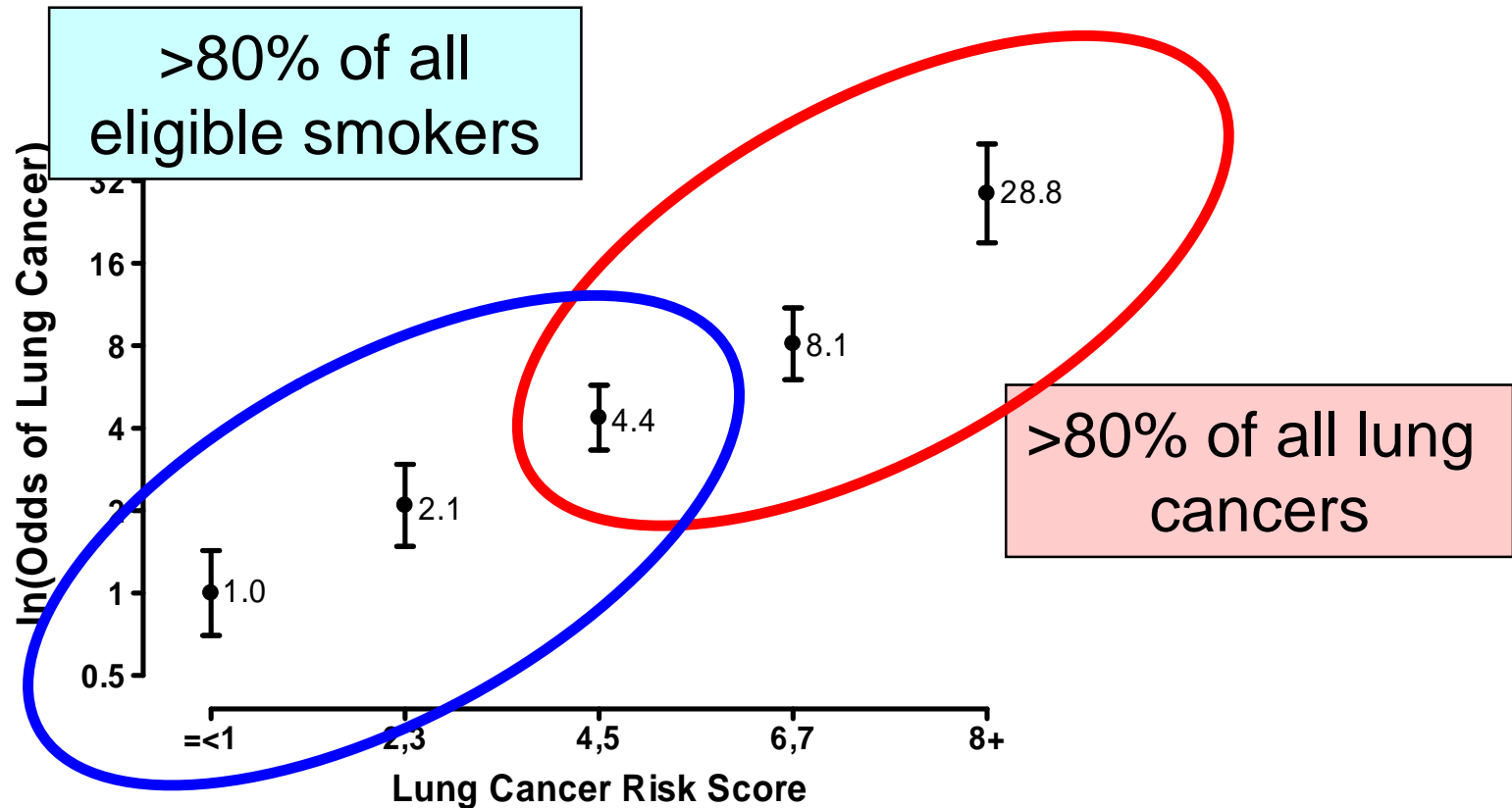
# Lung cancer SNP score

- Based on an algorithm developed in COPD case-controls study
- Combines genotypes from protective and susceptible SNPs
- Makes no assumptions about biological pathways
- Not hierarchical
- Modelled on the Gail score - optimised by age, history of COPD and FHx of lung cancer

# OR according to Lung Cancer risk score



# OR according to Lung Cancer risk score



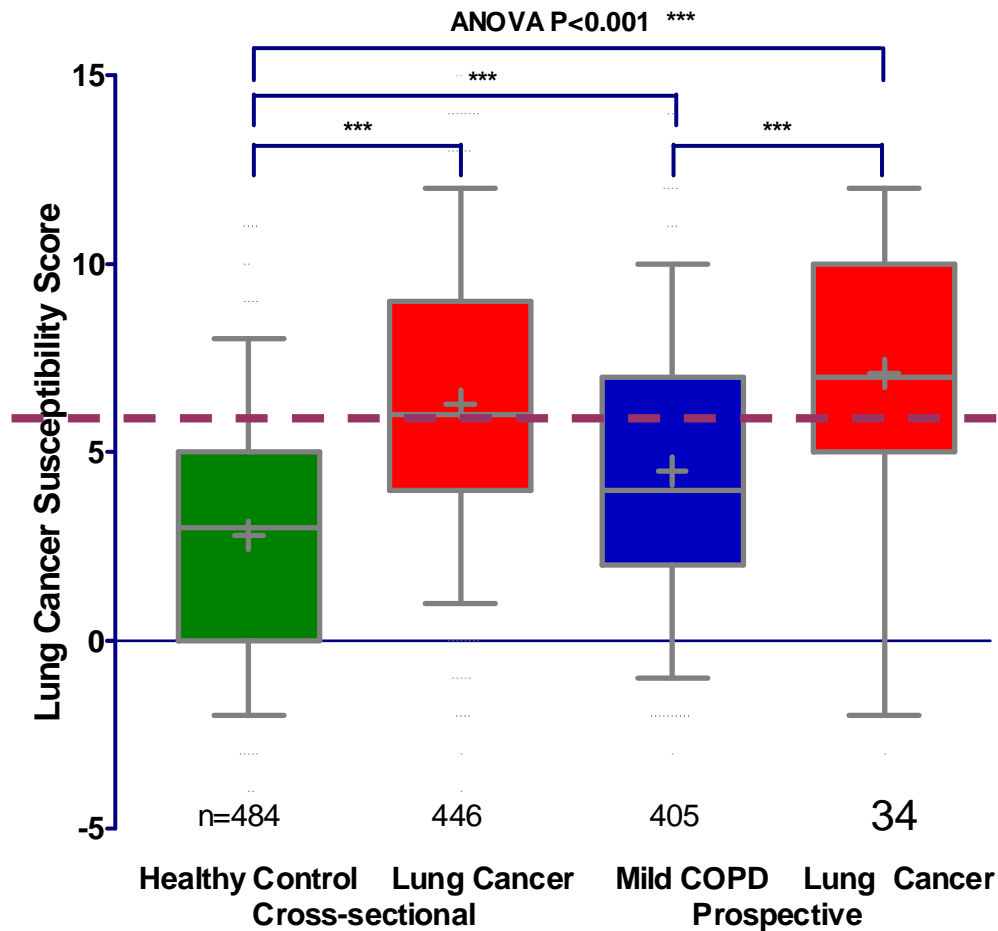
Sensitivity=90%  
Specificity=45%

# Lung Cancer Susceptibility Model Based on Age, Family History and Genetic Variants

Robert P. Young<sup>1\*</sup>, Raewyn J. Hopkins<sup>1</sup>, Bryan A. Hay<sup>1</sup>, Michael J. Epton<sup>3</sup>, Graham D. Mills<sup>4</sup>, Peter N. Black<sup>1</sup>, Heather D. Gardner<sup>1</sup>, Richard Sullivan<sup>2</sup>, Gregory D. Gamble<sup>1</sup>

<sup>1</sup> Department of Medicine, Auckland Hospital, Auckland, New Zealand, <sup>2</sup> Department of Oncology, Auckland Hospital, Auckland, New Zealand, <sup>3</sup> Department of Medicine, University of Otago, Christchurch, Canterbury, New Zealand, <sup>4</sup> Department of Medicine, Waikato Hospital, Hamilton, New Zealand

Box plot of LCSS in the case control study (n=930) and prospective study (n=728)



LCSS score  $\geq 6$

Specificity of 70-80%  
Sensitivity of 40-50%

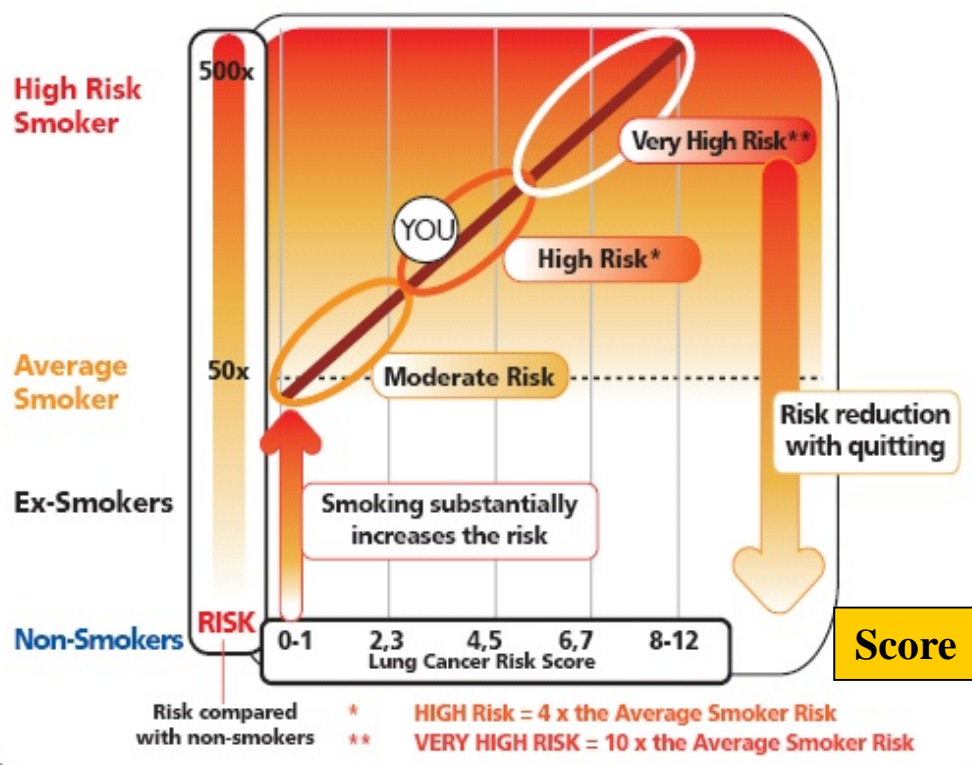
## Lung Cancer Susceptibility Score

Name: \_\_\_\_\_

SCORE

### Risk Level

### Lung Cancer Risk Score (Range 0-12)



No one is lower than average risk for lung cancer

## Lung cancer susceptibility score

- Educational tool to personalise risk and raise awareness of lung cancer

- Refines existing risk derived from smoking exposure

- Based on age, FHx of lung cancer, COPD and SNP markers

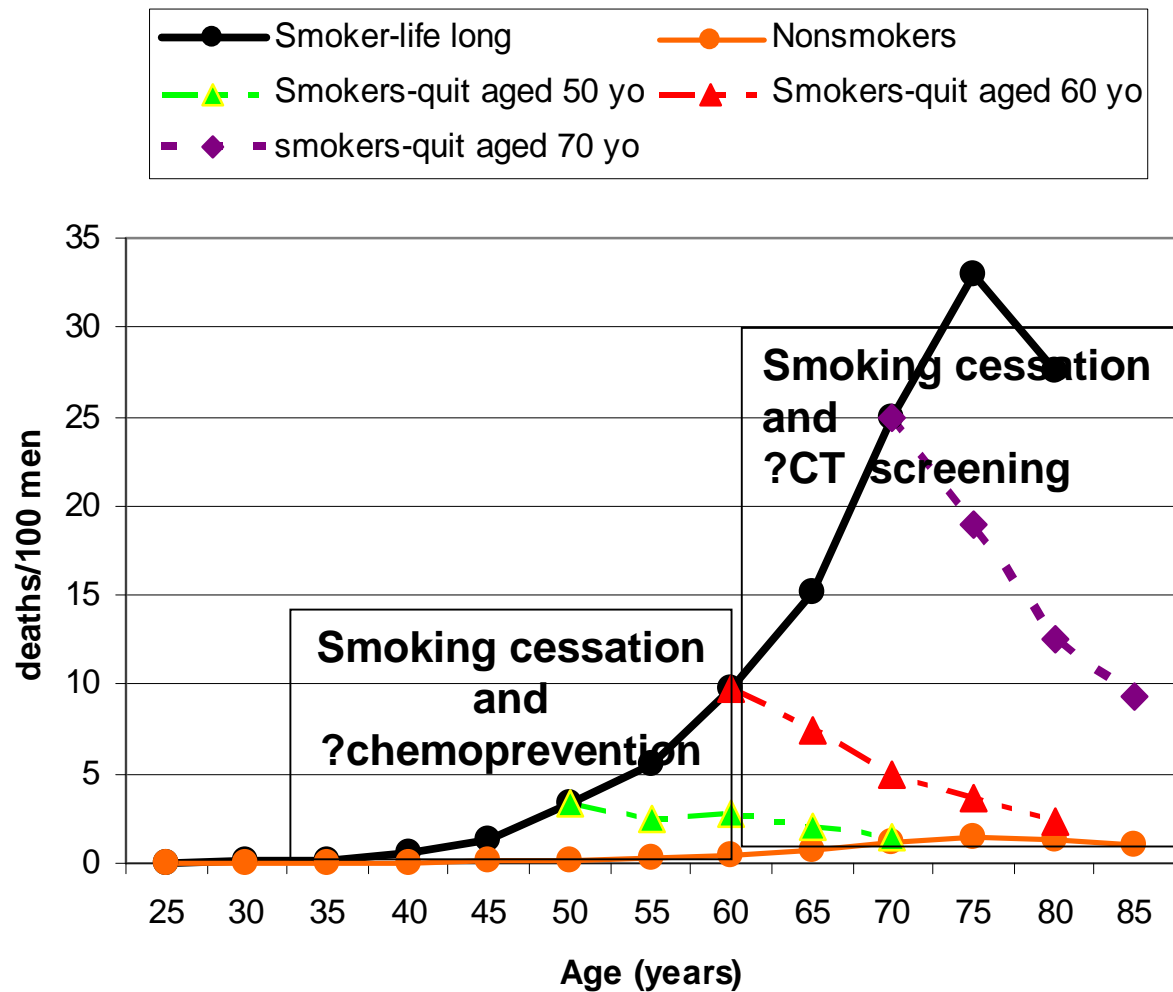
- Target 40+ yr old who are smokers and ex-smokers (last 10 years)

- Aim to motivate smoker to quit or ex-smoker to avoid relapse

- Referenced against the “average” smoker’s risk

- Shows risk reduction with quitting

## 10 year mortality for lung cancer by smoking status



## Lung cancer risk and clinical utility

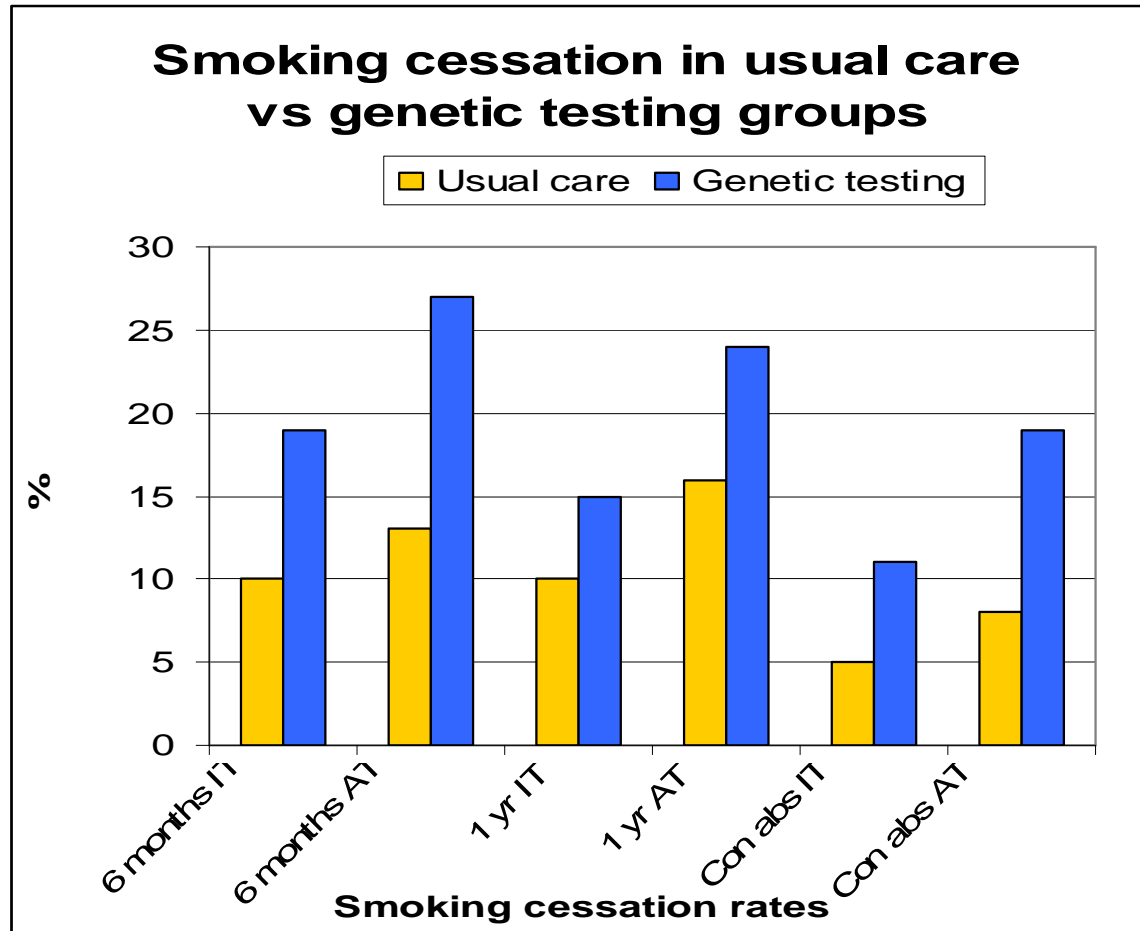
**Smoking cessation**

**?CT screening**

**?Chemoprevention**

**Targeted by genetic testing**

# Genetic risk of lung cancer and quitting

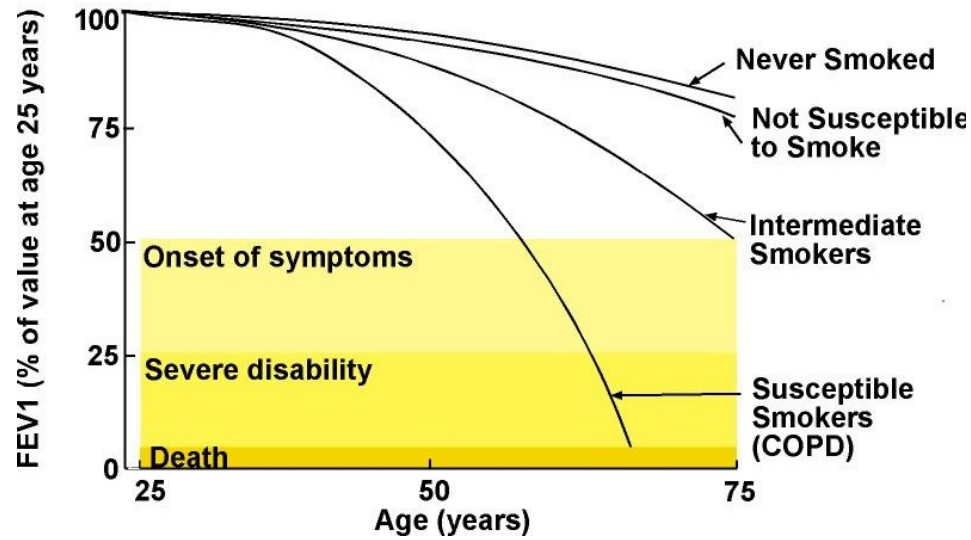


Genetic testing for risk of lung cancer helps to personalize the risk from continued smoking

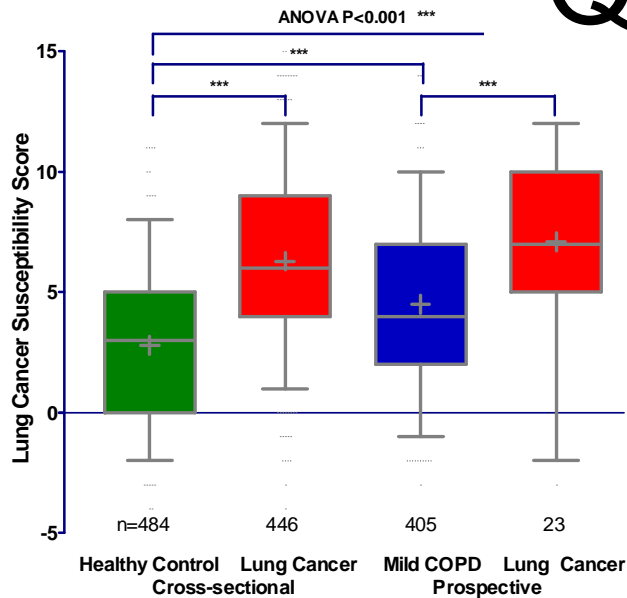
Smokers who underwent genetic testing (blue bars) in a randomized trial had higher quit rates than those in a smoking cessation programme alone (yellow bars)

Personalising the risks of smoking helps people choose healthier lifestyle options (eg quitting smoking and preventing relapse)

McBride, C.M., et al: Incorporating genetic susceptibility feedback into a smoking cessation program for African-American smokers with low income. *Cancer Epidemiol Biomarkers*



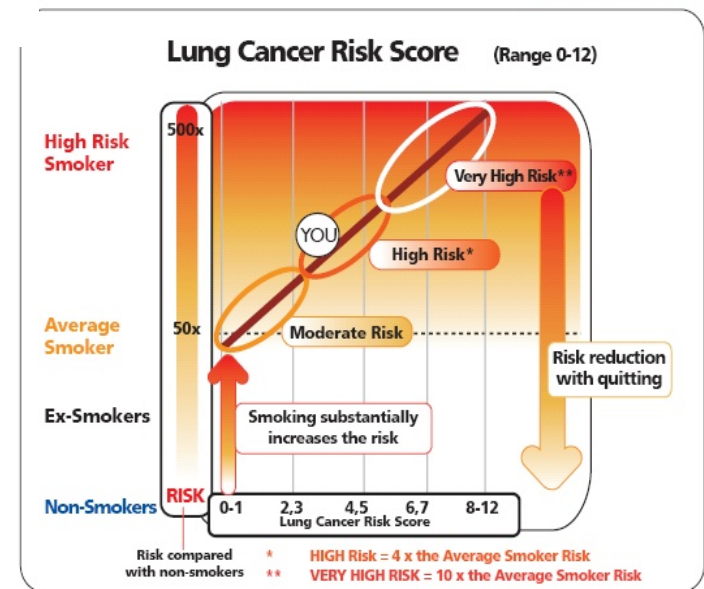
# Questions?



## Lung Cancer Susceptibility Score

SCORE

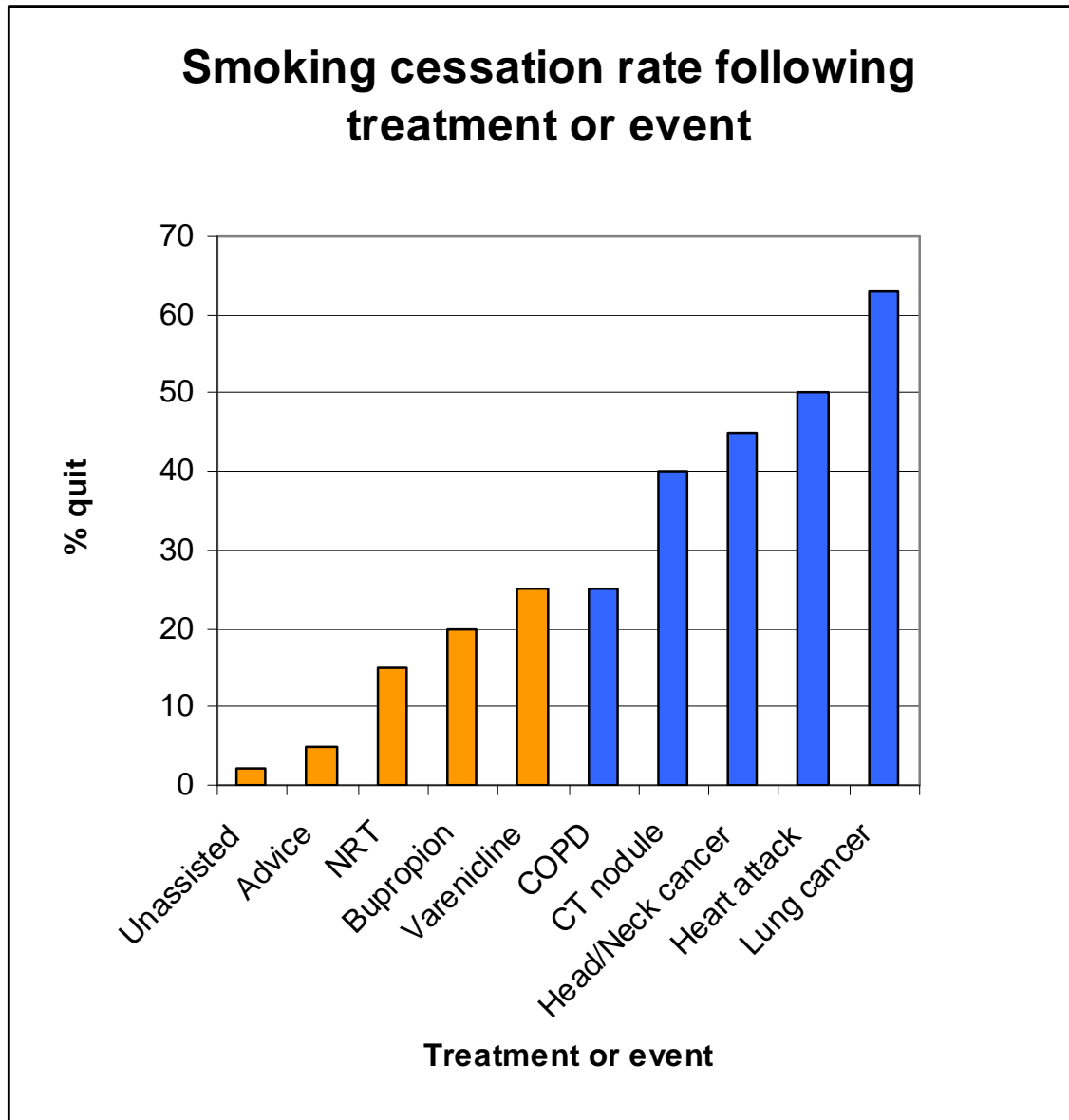
Name: \_\_\_\_\_



Test results



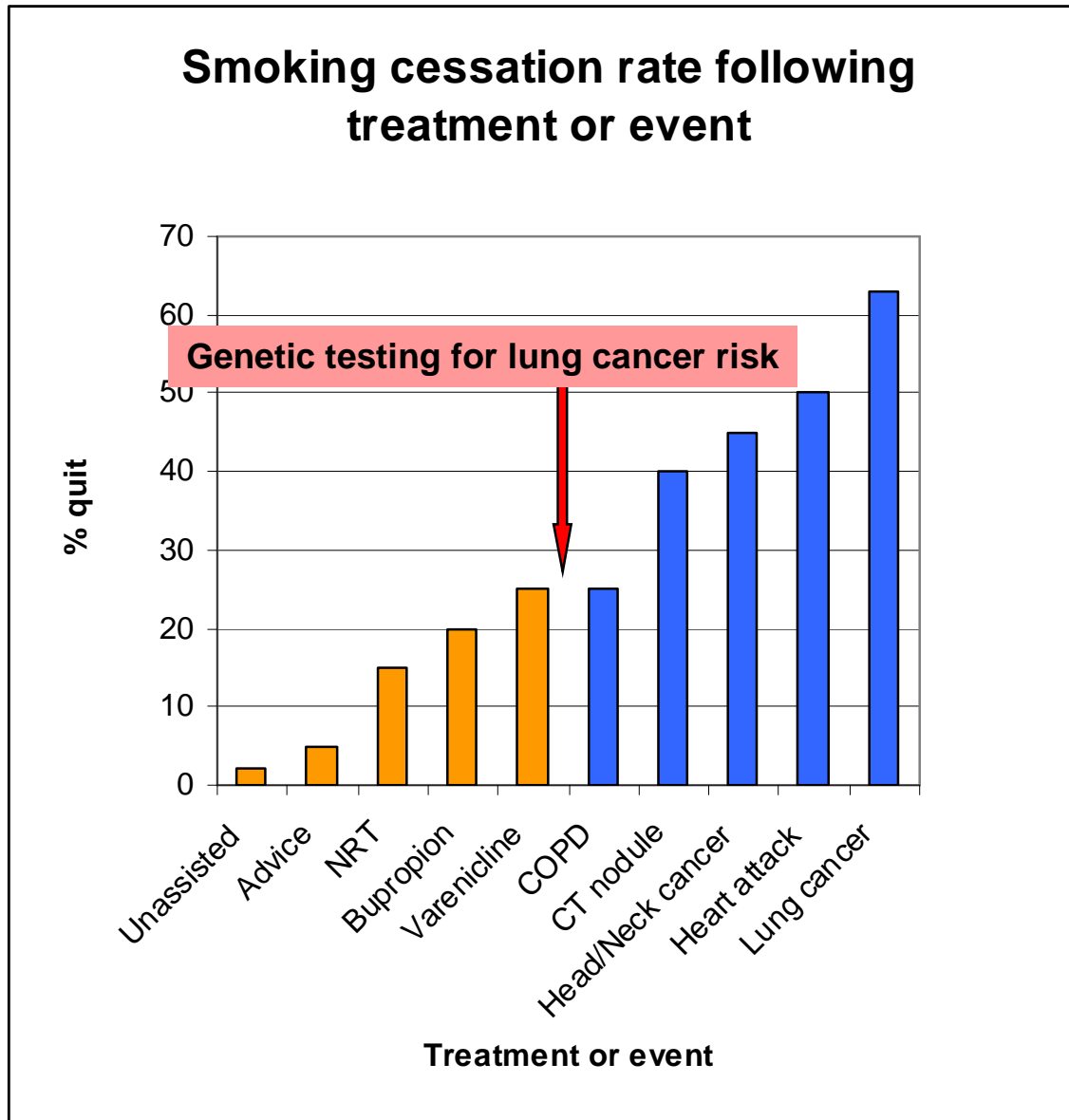
## Smoking cessation



3 Nothing Treatment Events

- Most smokers quit using cold turkey
- For older smokers, future poor health is the most cited reason for quitting
- Developing lung cancer and COPD are the most feared complications
- Most smokers continue to smoke on the basis the benefits outweigh the harms
- Most smokers overestimate the general risk of lung cancer but underestimate their own risk (below average risk = optimistic bias)
- Smokers quit when the motivational tension favour quitting (trigger)

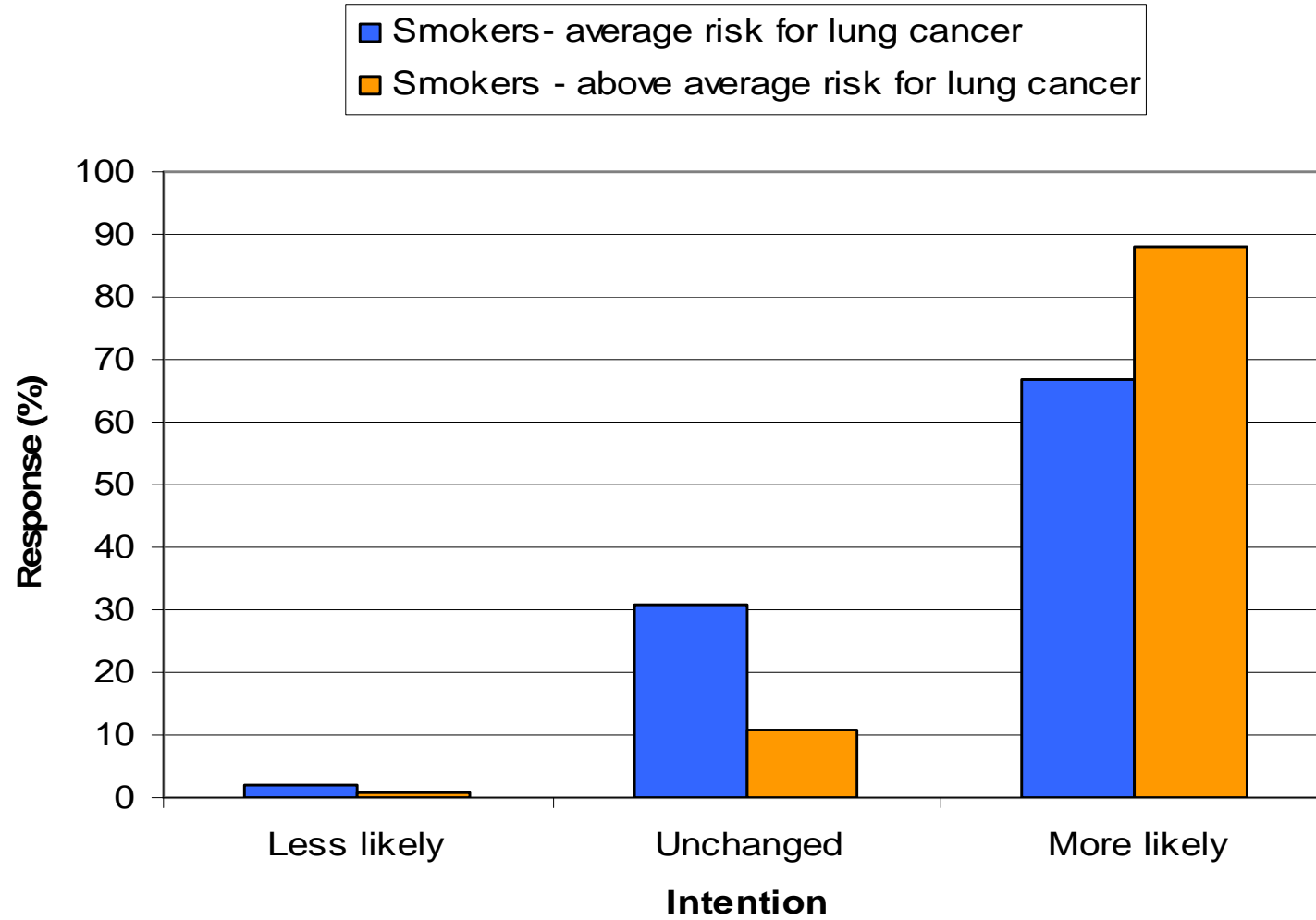
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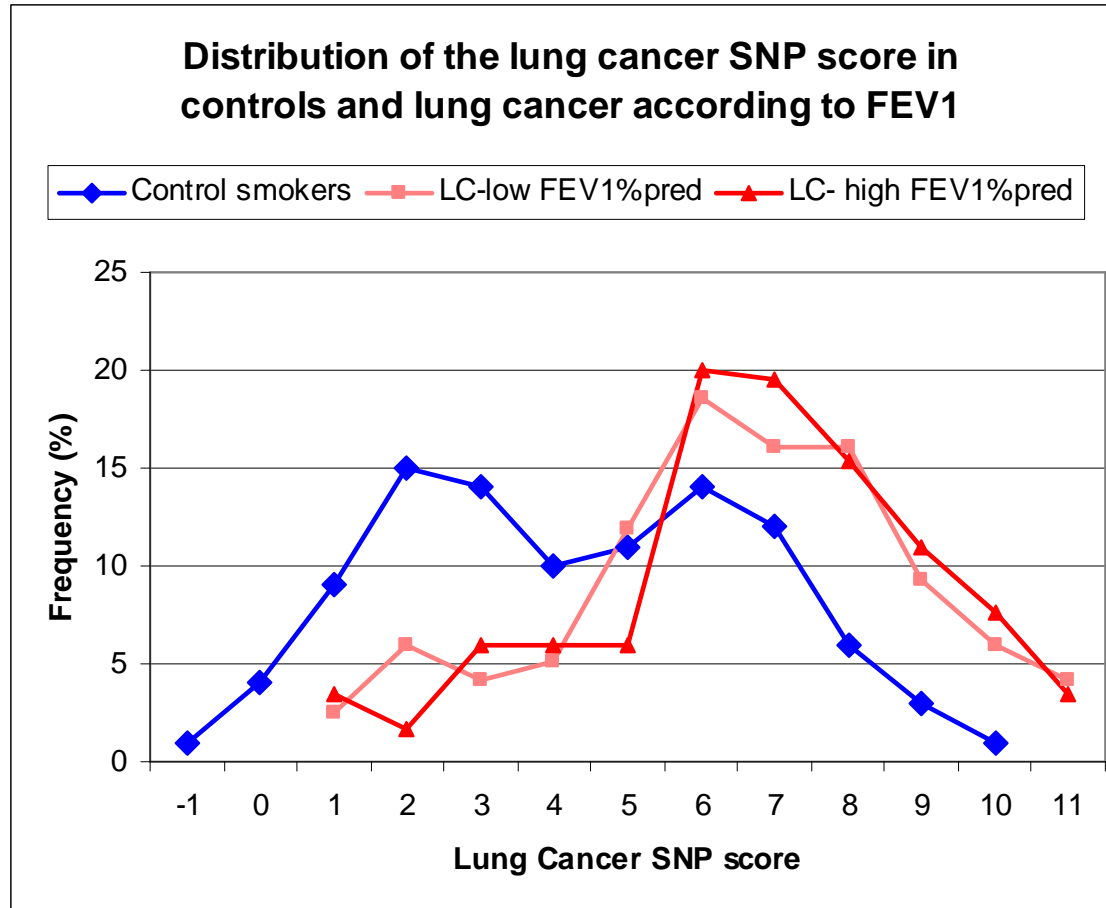
## Intention to quit smoking based on genetic testing for lung cancer risk



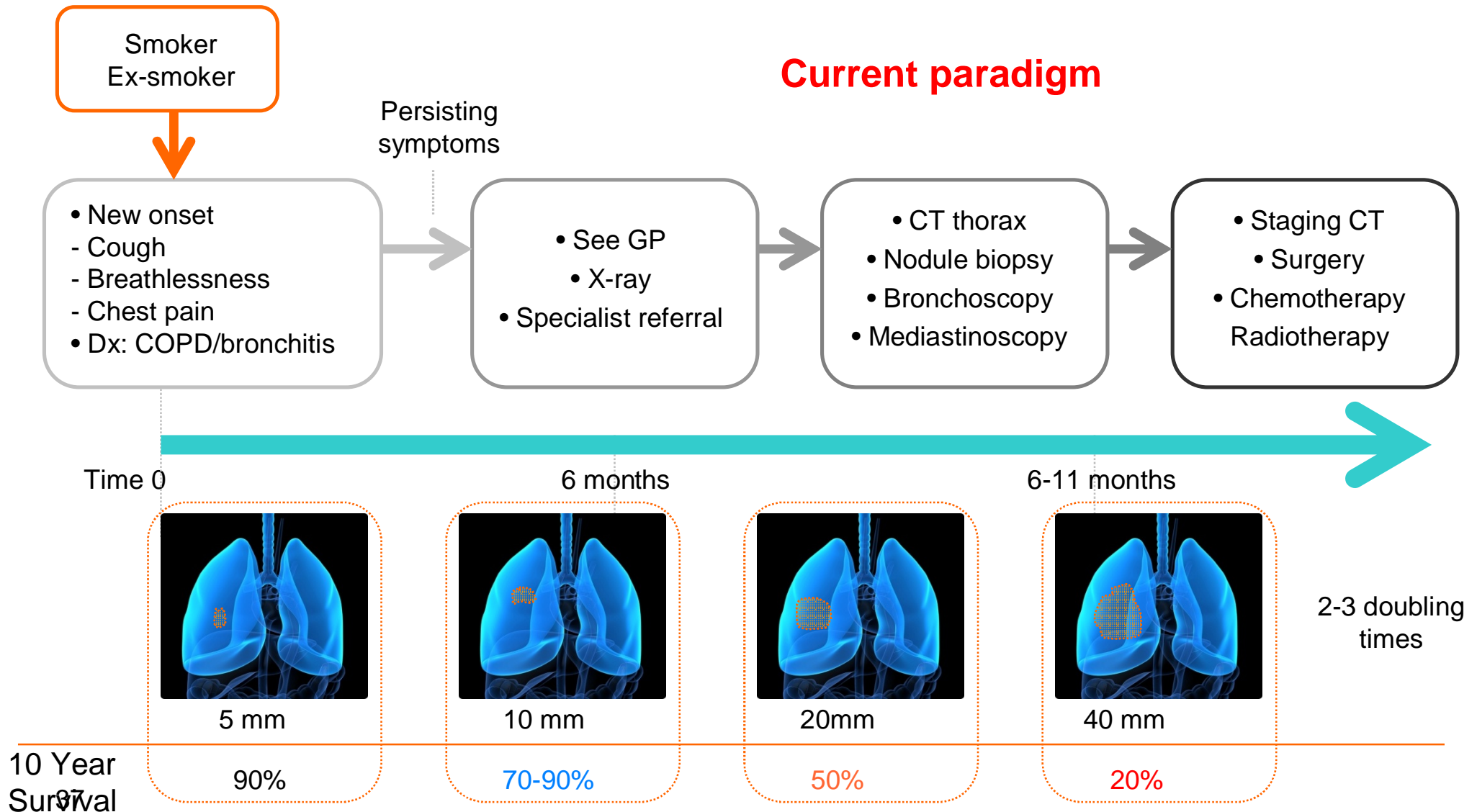
# Lung Cancer SNP score utility

- Personalise risk to smokers/ex-smokers
  - Bach score – age and smoking history
  - SNP score – age, genetic factors and other factors
- Segment the population into high risk and low risk
  - Motivate people to quit smoking or not relapse
  - Prioritise people for screening (?sputum cytology, serum biomarkers, CT screening)
  - Prioritise people for chemoprevention (statins,NSAID)

# Lung cancer SNP score and FEV1



# Poor Prognosis from Late Presentation



# Risk Stratifying with Improved Prognosis from Early CT?

