

# Genetics of cancer in EGAT study



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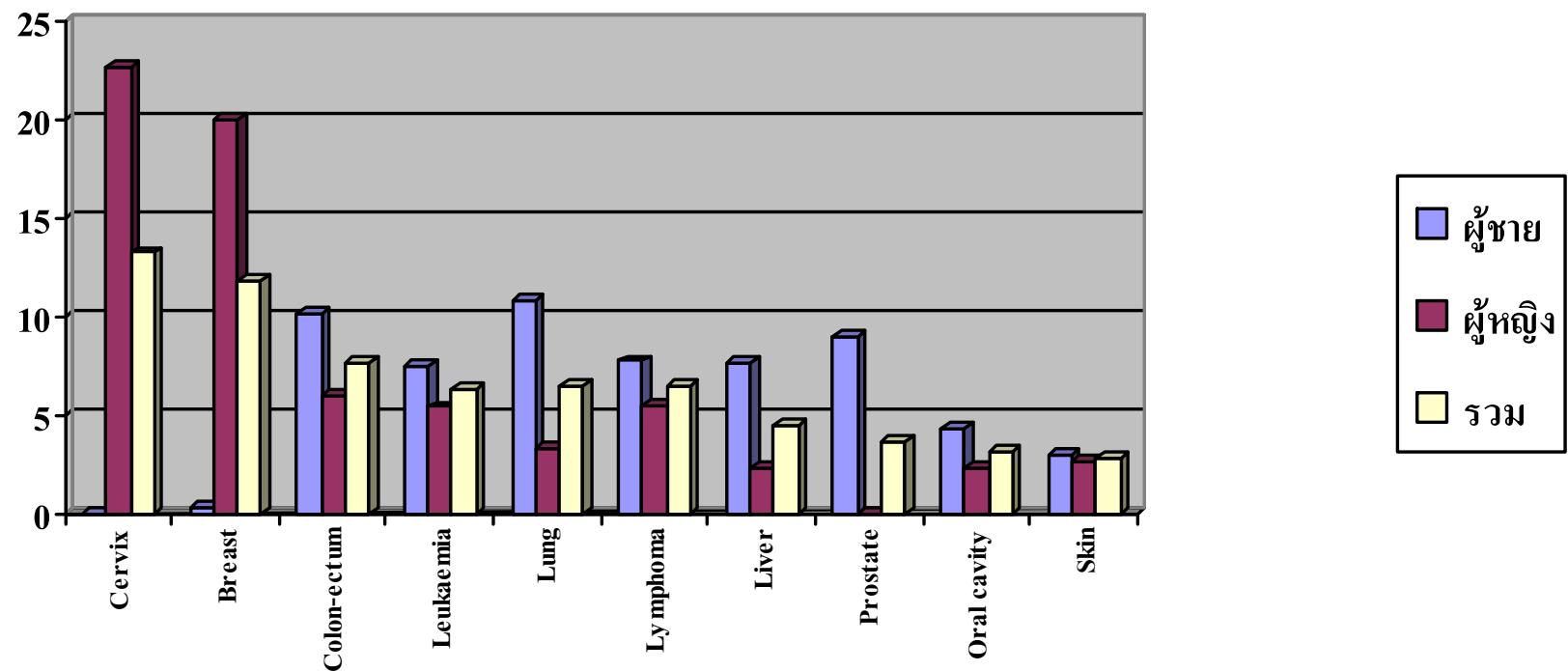
*Bangkok, Thailand*

- **Cancer develops because of a complex mix of environmental and genetic factors.**
- **For some:-**
  - Environmental factors pose the greatest risk
- **For others:-**
  - It is inherited susceptibility
- **For most:-**
  - Combination of all the above.

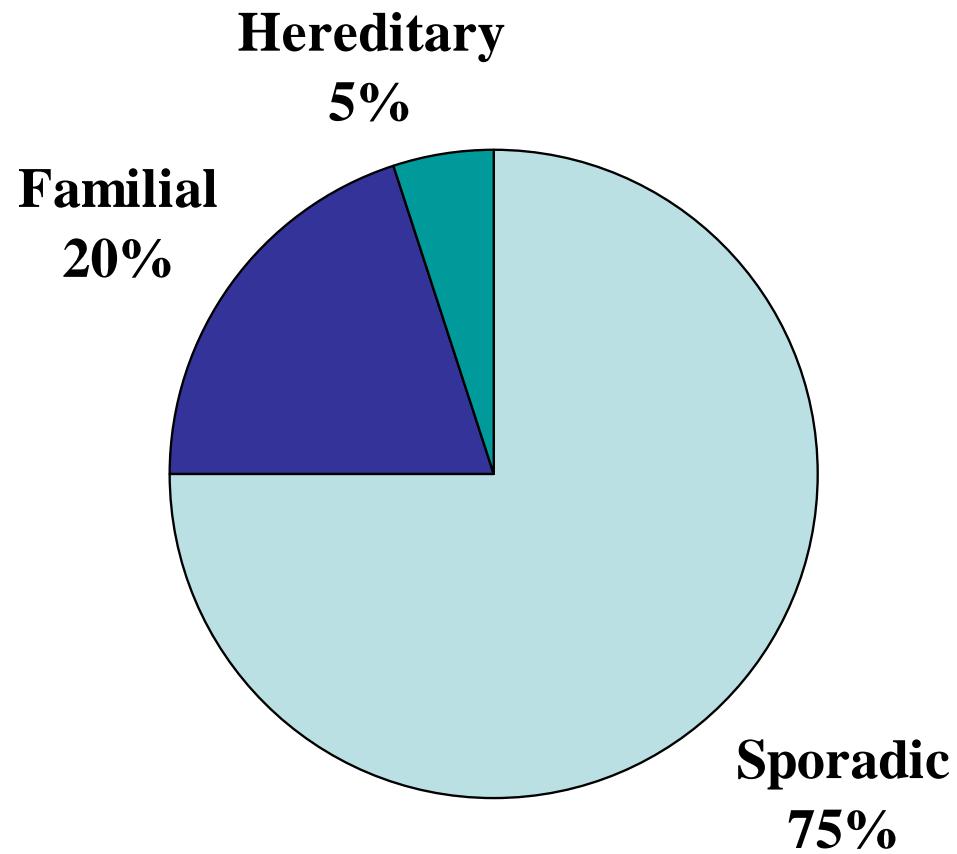


# The leading sites of cancer in Thailand

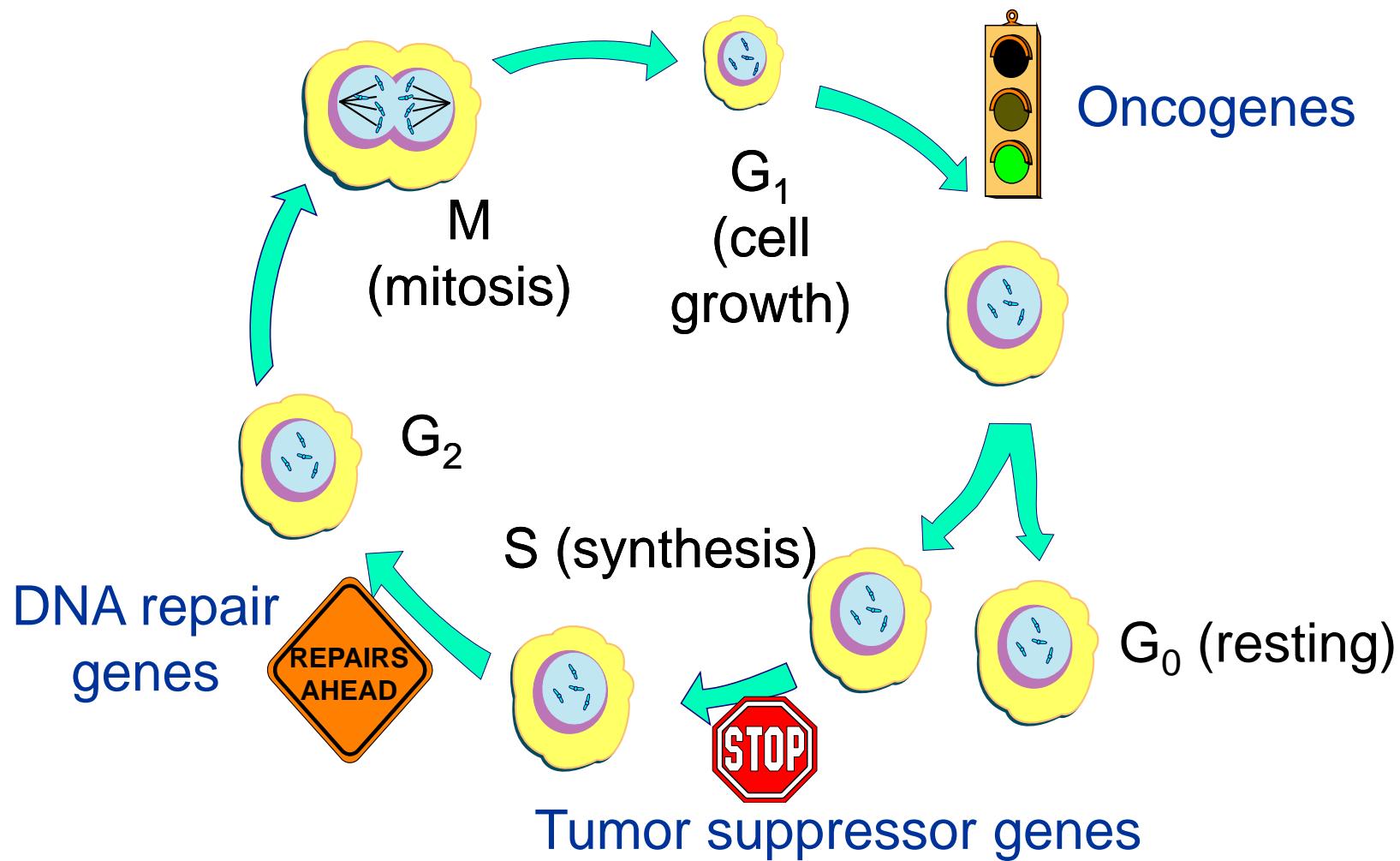
Ministry of Health 2005



# Etiology of Cancers

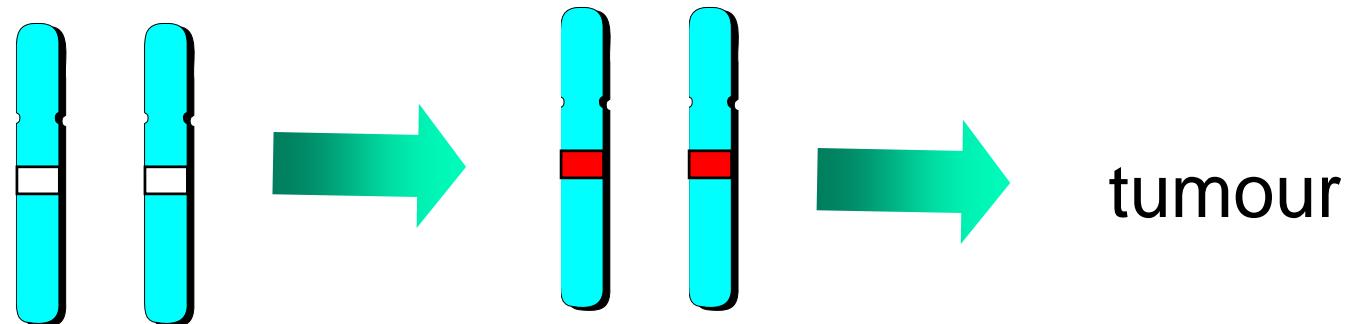


# The Cell Cycle



# Cancers Arise From Gene Mutations

in genes protecting **against** cancer



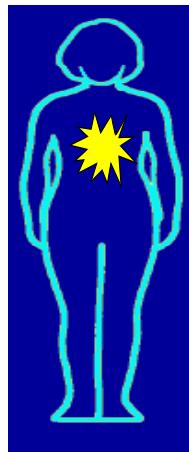
All cancer is genetic

BUT

not all cancer is inherited!

# Most Cancers Arise From Somatic Mutations

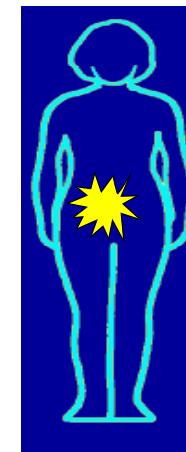
- Somatic mutation
  - Localised to a specific tissue



breast

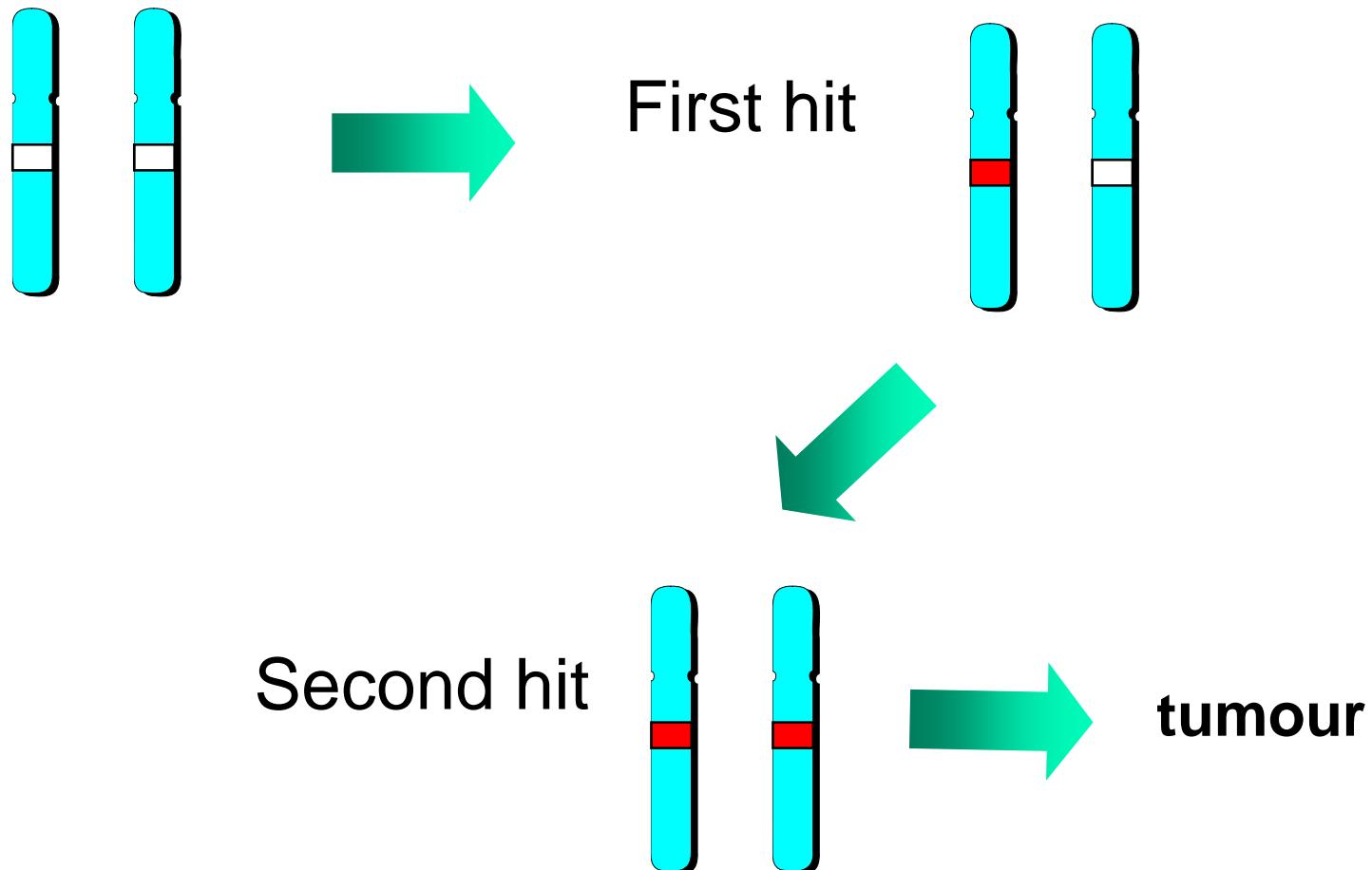
or

bowel



- Not in germline tissues
- Not inherited

# Knudson's 'Two-Hit Hypothesis' (Somatic Mutation)

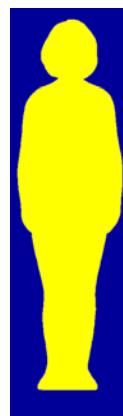


# 5-10% of Cancers Arise From Germline Mutations

Parent



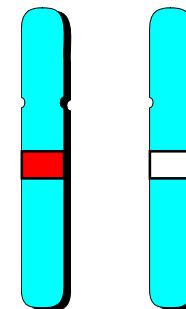
Child



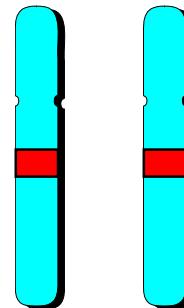
- Germline mutation
  - In egg or sperm
  - May be passed on (inherited)
  - All cells in offspring carry the mutation

# Knudson's 'Two-Hit Hypothesis' (Germline Mutation)

First hit is in  
germline



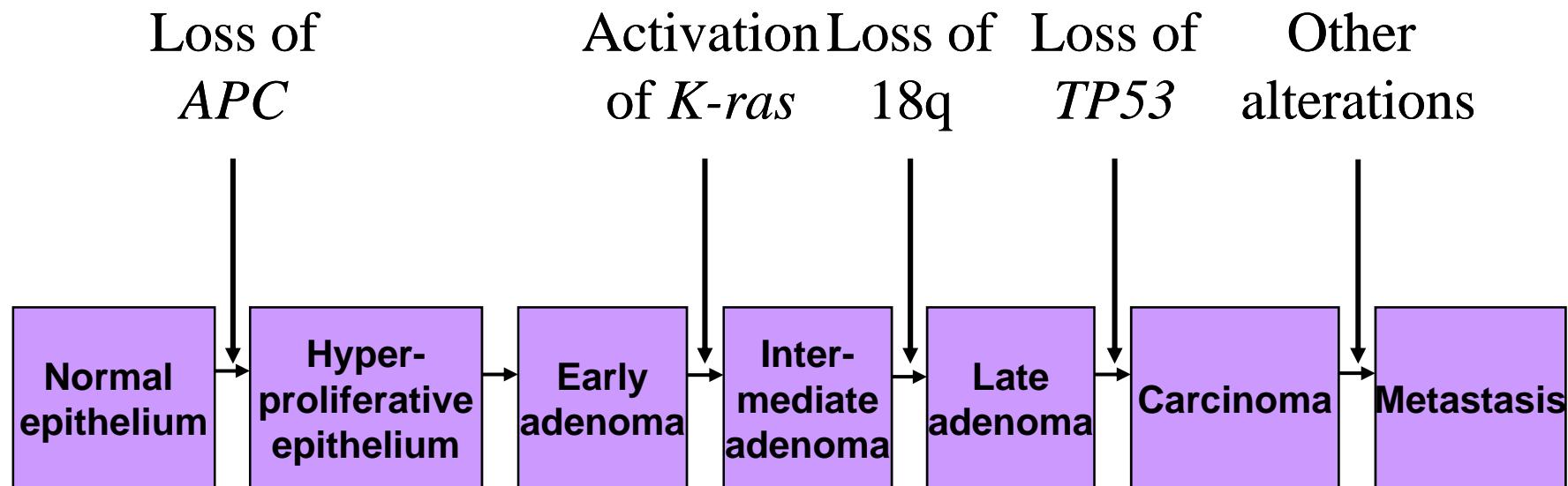
Second  
hit is  
somatic



tumour

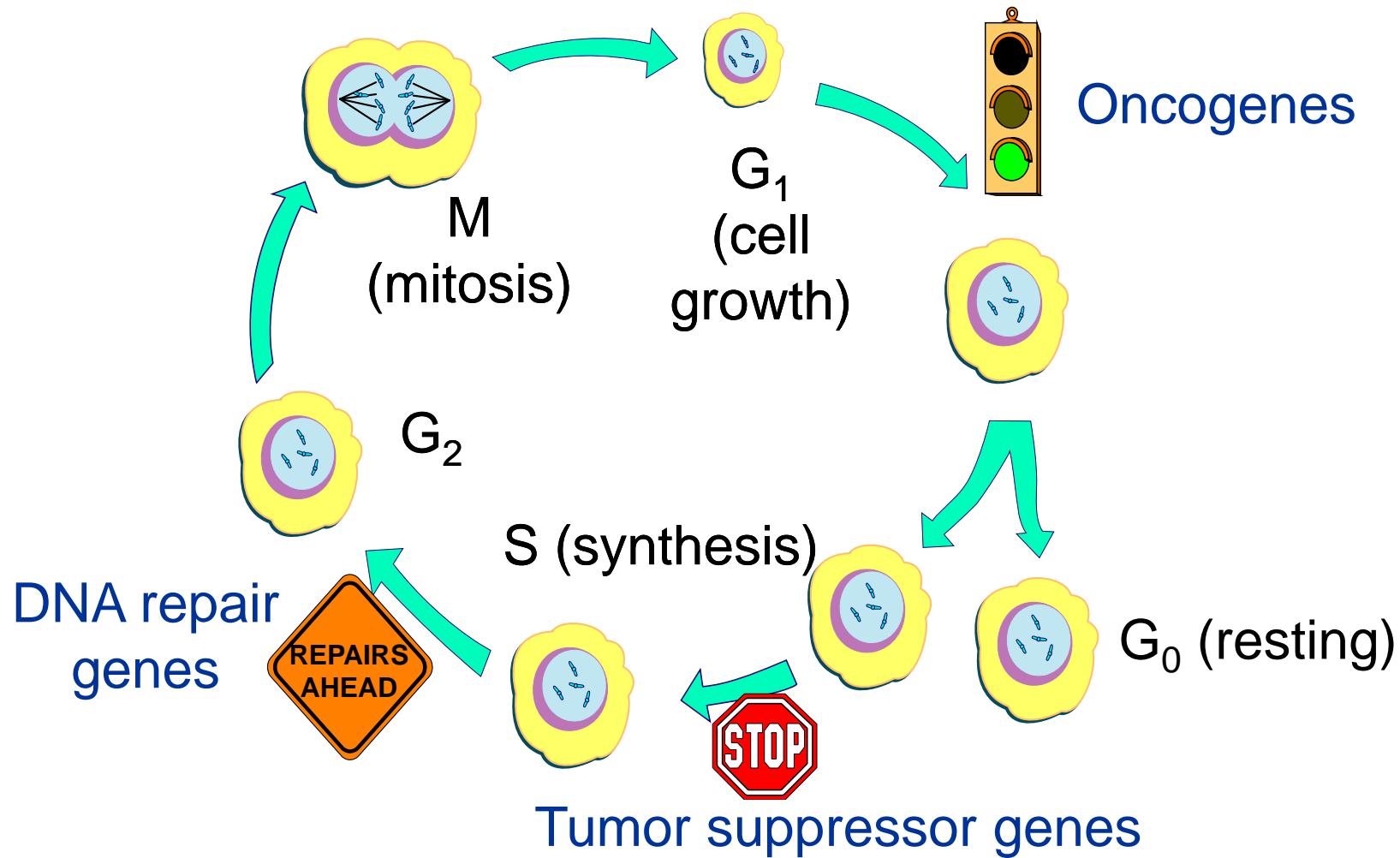
# Multi-Step Carcinogenesis (eg, Colon Cancer)

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Adapted from Fearon ER. *Cell* 61:759, 1990

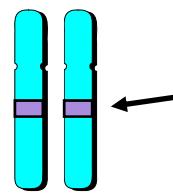
# The Cell Cycle



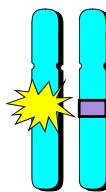
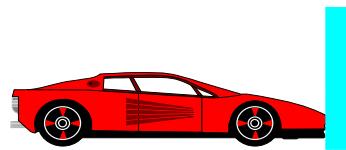
# Genes Associated With Cancer

## 1. Tumor suppressor genes:

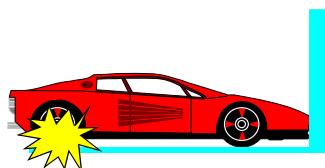
the cell's brakes for tumor growth



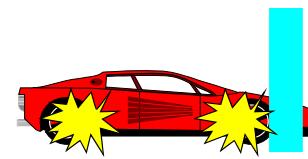
Normal genes  
(prevent cancer)



1st mutation  
(susceptible carrier)

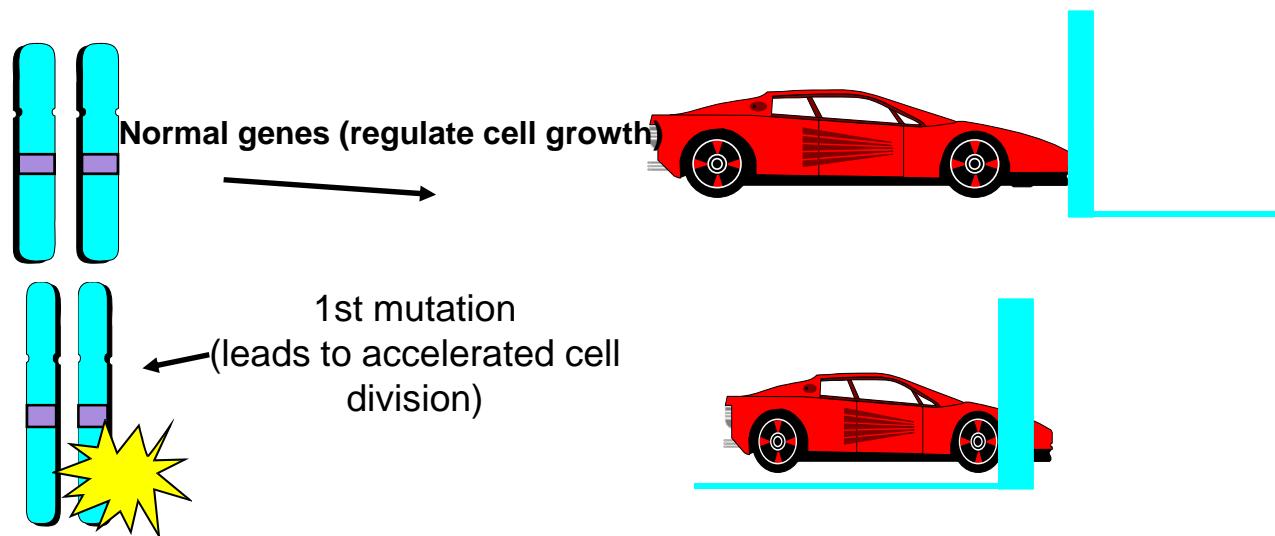


2nd mutation or loss  
(leads to cancer)



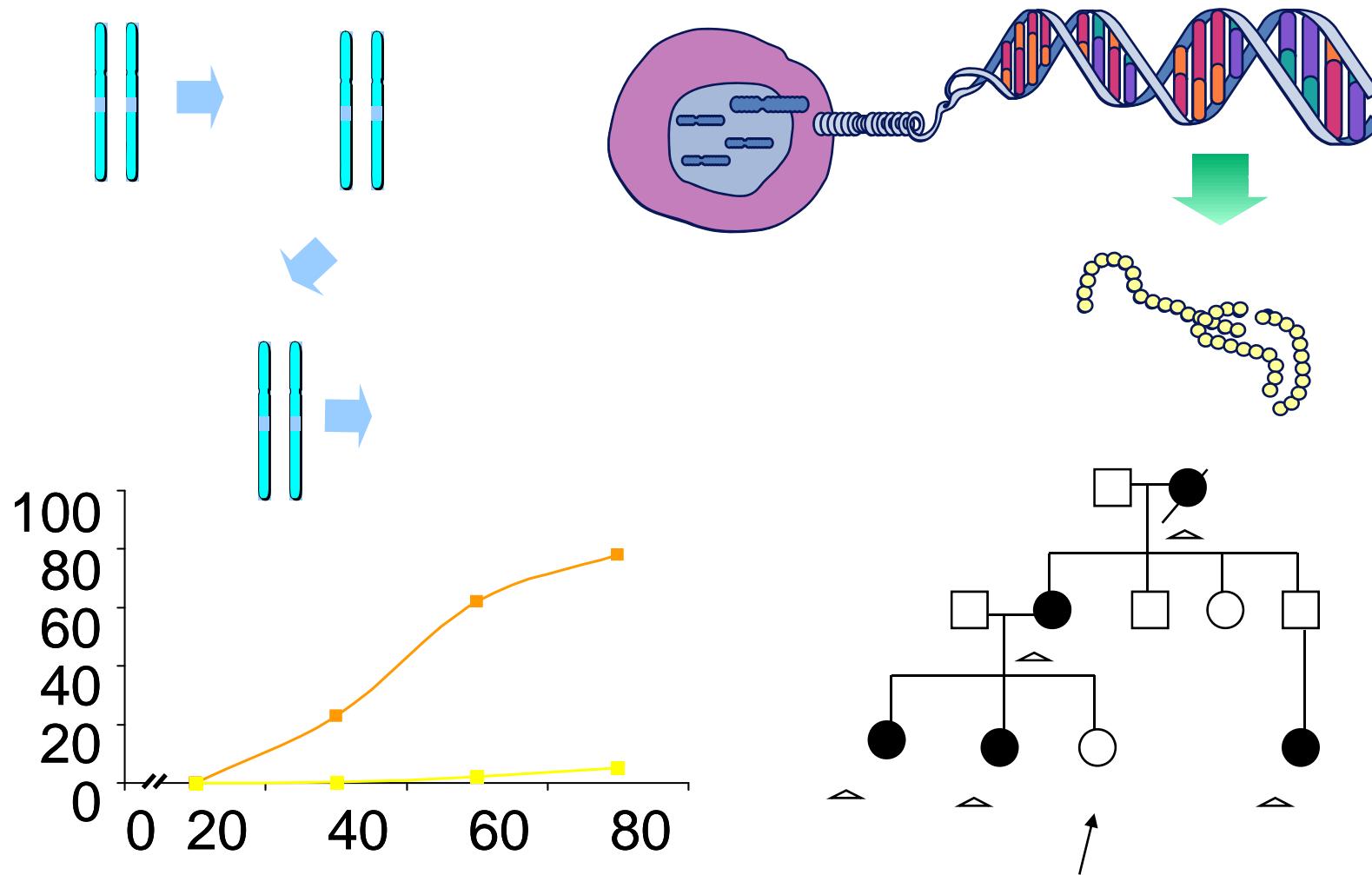
# Genes Associated With Cancer

## 2. Oncogenes: accelerate cell division



1 mutation sufficient for role in cancer development

# In summary...



# Examples of hereditary cancer genes

1p35	SDHA/B/C	Phaeochromocytoma/Paraganglioma
2p16	MSH2	HNPPCC
2p16	MSH6	HNPPCC
3p21	MLH1	HNPPCC
3p25	VHL	von Hippel-Lindau
5q21	APC	Colon polyposis
7p22	PMS2	HNPPCC
9p21	P16 (CDKN2)	Melanoma/pancreatic
10q22	PTEN	Cowdens syndrome
10q11	RET	MEN2
11q13	MEN1	MEN1
13q12	BRCA2	HBOC
13q14	RB1	Retinoblastoma
16q22.1	CDH1	Gastric cancer
17p13	TP53	Li-Fraumeni
17q21	BRCA1	HBOC

# Pattern of cancer

	Skin	GI tract	Male genital tract	Female genital tract	Endocrine	Nervous system	Musculoskeletal	Urinary tract	Haematological
BRCA1	•			•					
BRCA2	•		•	•					
HNPCC	•	•		•		•		•	•
FAP (APC)	•	•			•	•	•		
PJS		•	•	•	•			•	
Hereditary gastric (ECAD)		•							
LFS	•	•			•	•	•	•	
VHL					•	•		•	
Cowden	•	•		•	•	•	•	•	
Gorlin	•					•			
RB	•					•	•		
MEN1		•			•	•			
MEN2					•				
NF2	•					•			
Fumarase carrier				•					

# Population of EGAT study

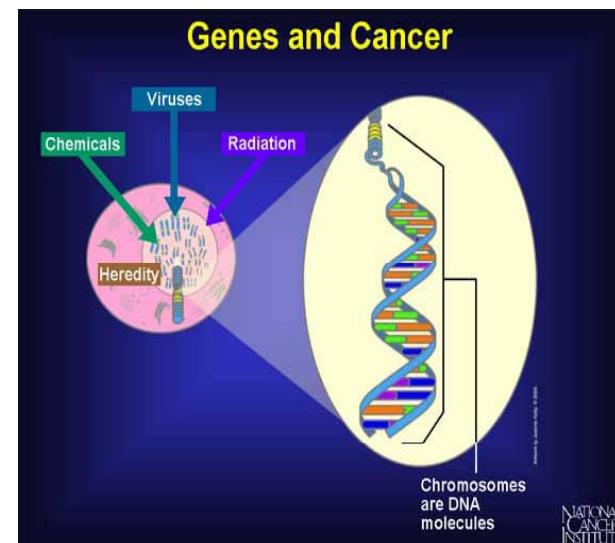


- EGAT 1 ~ 2,800
- EGAT 2 ~ 2,200
- EGAT 3 ~ 2,000

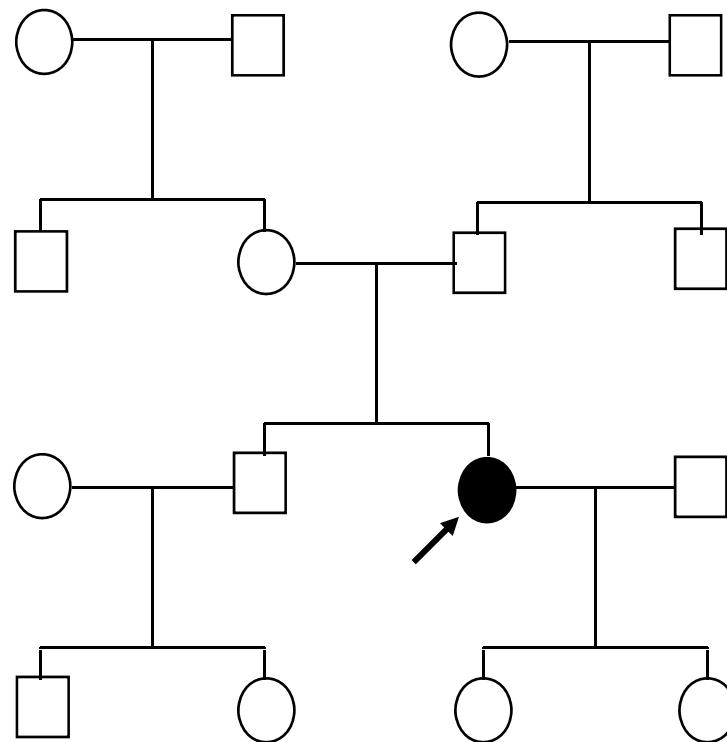


พลิตไฟฟ้าเพื่อความสุขของคนไทย

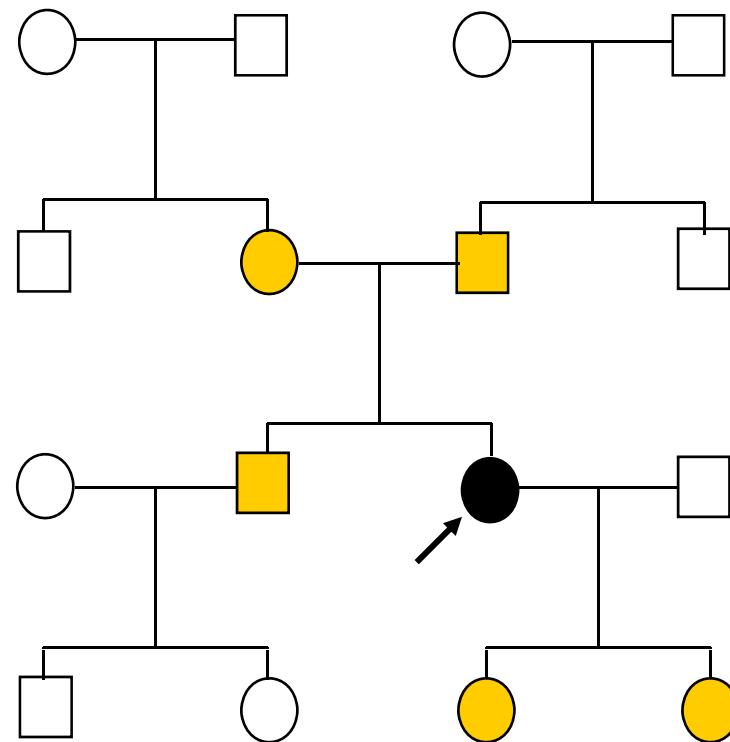
Cancers ~ 480



Half of the population have had a 1st or 2nd degree relative diagnosed with cancer

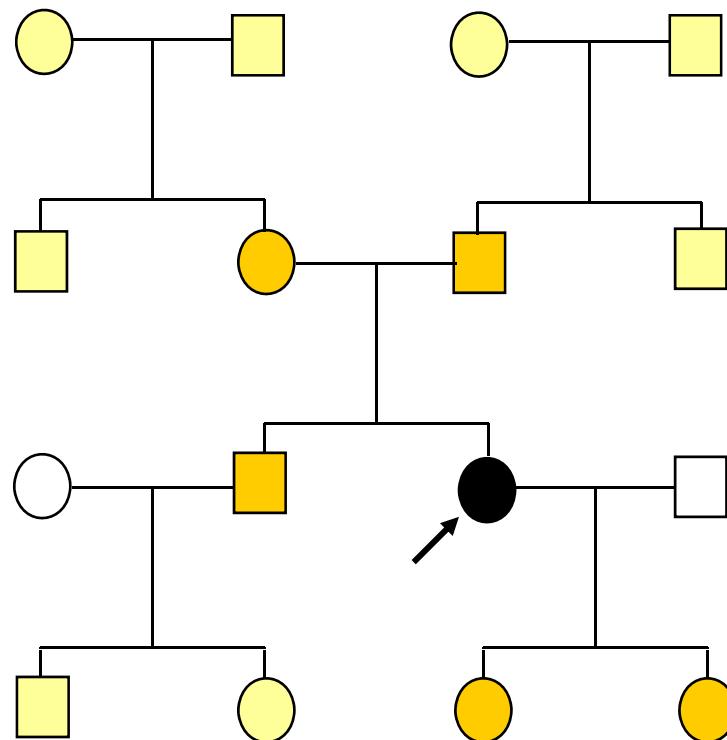


Half of the population have had a 1st or 2nd degree relative diagnosed with cancer



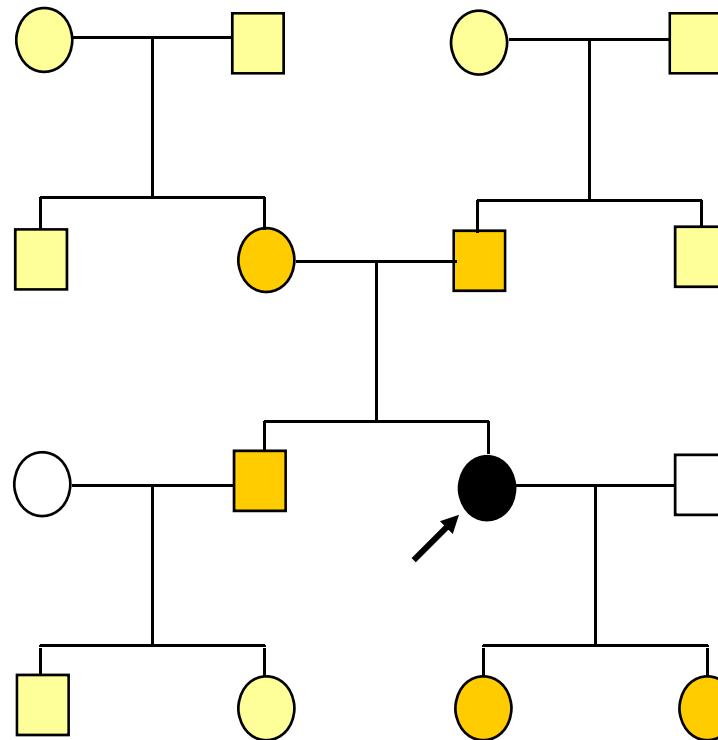
**1st degree  
(parents, siblings,  
children)**

Half of the population have had a 1st or 2nd degree relative diagnosed with cancer



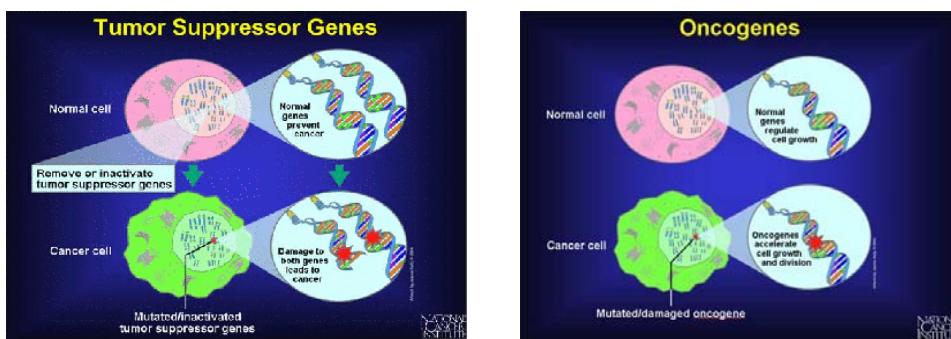
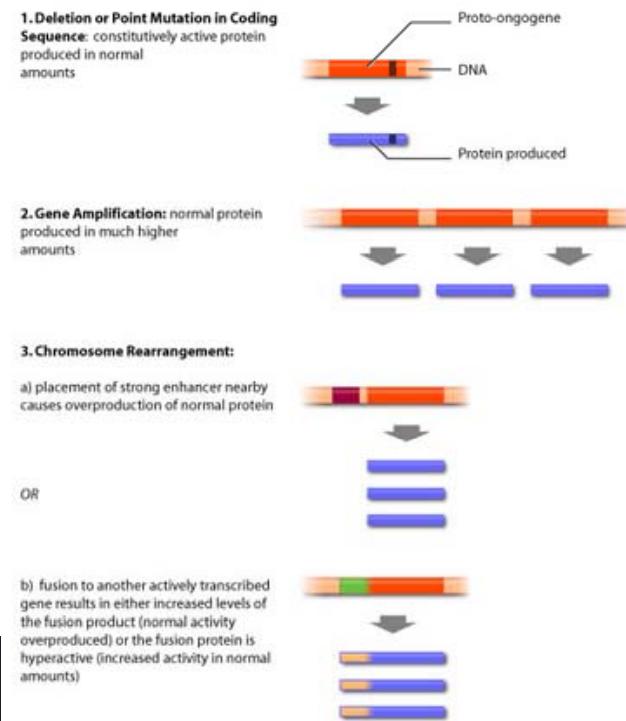
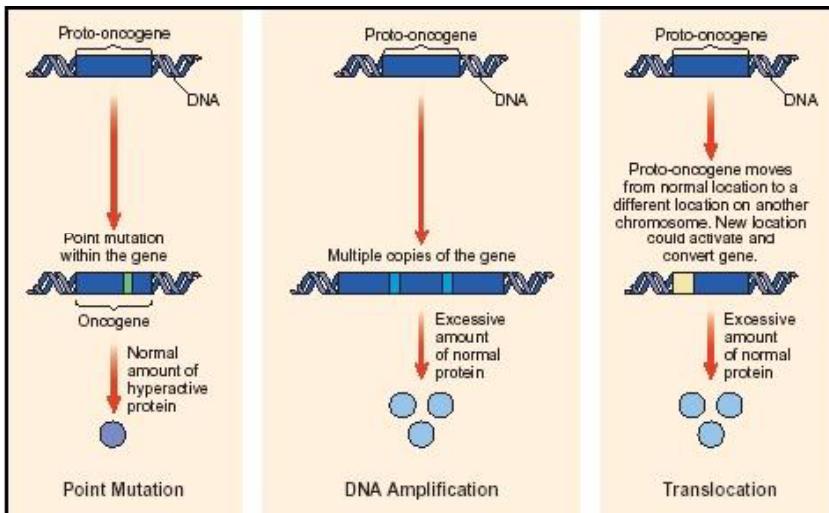
**2nd degree  
(grandparents,  
aunts, uncles,  
nieces, nephews)**

Half of the population have had a 1st or 2nd degree relative diagnosed with cancer

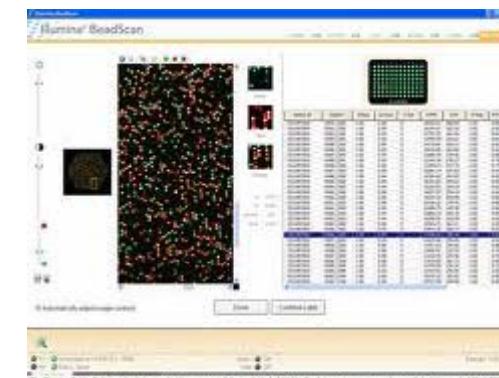
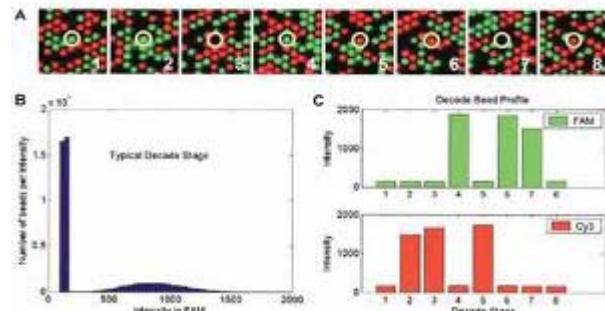
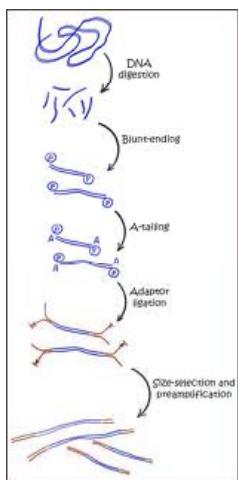
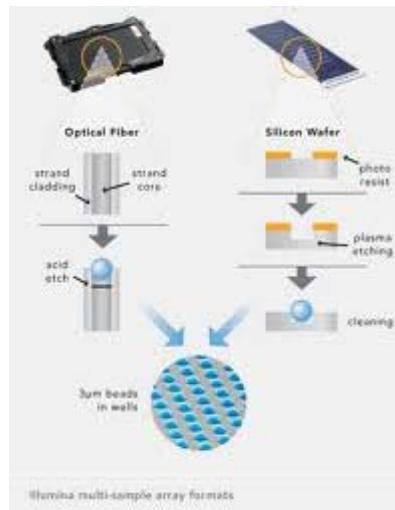
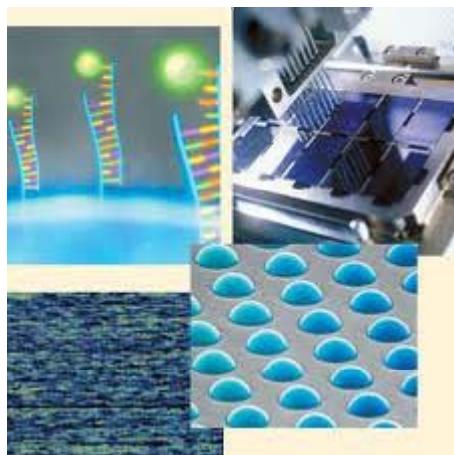


**2nd degree  
(grandparents,  
aunts, uncles,  
nieces, nephews)**

Only 5% - 10% will have an inherited genetic factor

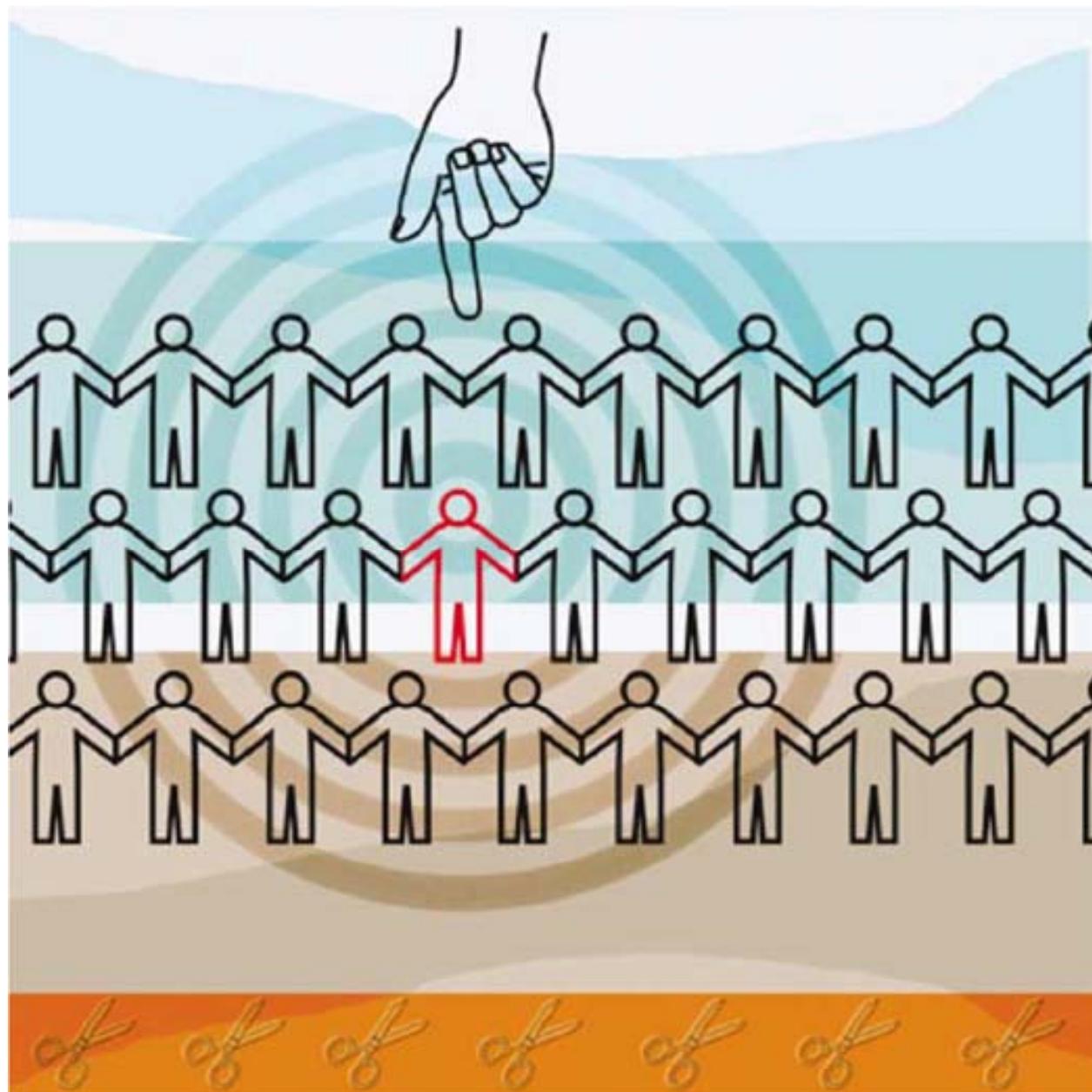


# Illumina technique



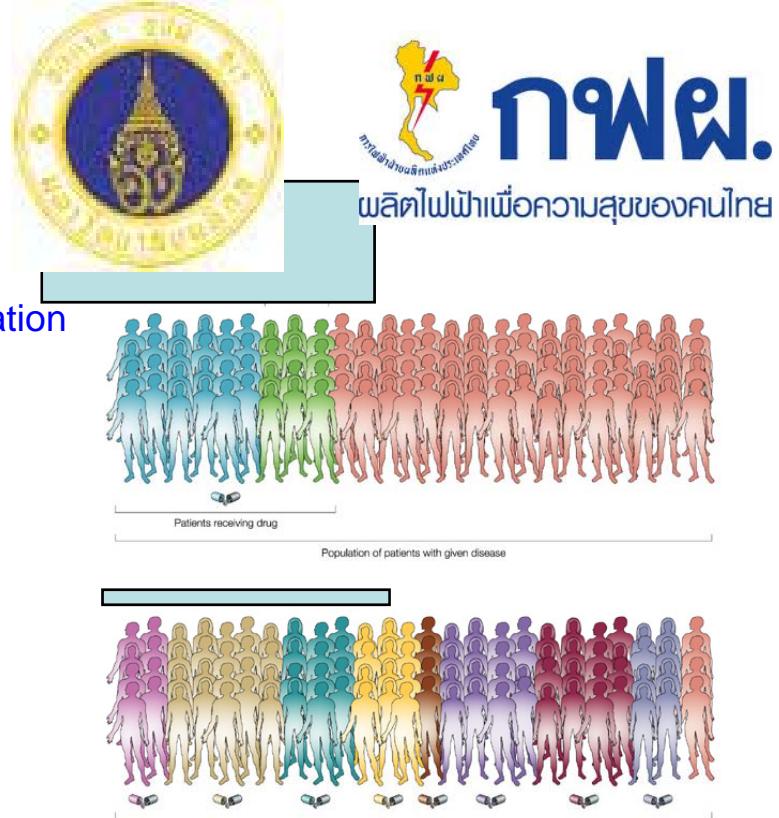
The Genome Sequencer™ sequencing plates have been successfully validated at 2014 by the Joint Genome Institute. An initial pilot project of 2014 2000 samples were sequenced in-house using the recently purchased MiSeq™ sequencer from Illumina. Our experiments aim to identify genome-wide patterns of variation, including novel SNPs, in each of our 10 chicken lines at GATC. These include the Brown Leghorn (BL), White Leghorn (WL), New Hampshire (NH), Leghorn (L), Cornish (C), and a flock of未知 (Unknown), not known, White Leghorn (WL). Our first prioritizing of these lines showed results in a panel of genome-wide SNPs that can be assessed from any combination of several samples or mapping 250x.

ATAAATGTATGAATACTCCATTTCTATTATCCTATGGCCCCAGGTGTAATTGTATAGTATCTCTTT  
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GATTCTCTAGGAATTTCAGTAGCTGGATGGAATGGAGGGCAAAGGTAATTCTCAAAAATGATATTA  
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ATATACTCTATTAAATTGC **TTCTCGGCACTGATATGGACC** TGTGACCAAAACAGGCCT  
TTGAGCTCTATTAAATTGC **TTCTCGGCACTGATATGGACC** TGTGACCAAAACAGGCCT  
TCCAGGTAATTAAATTGC **TTCTCGGCACTGATATGGACC** TGTGACCAAAACAGGCCT  
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CACTGGGAATCACAGGAATTGATGAGGTTGAGCTGCTGGACATGGTGGAAAGTTACCATCTGCTACTTAGAATGTTACAGAAAT  
AAACAACCCATAAGTGCTCTGCTGAAACAAACAAACAAACCCCCCTCAAGTTATCAGTGTAAAAT  
TTTGGCTCCTTACATTCCCTGGGACAATGGTGGAAAGTTACCATCTGCTACTTAGAATGTTACAGAAAT



# Outcome Prediction

1. Identified group of cancer genes in EGAT population
2. Identified individual 's risk for cancer prevention
3. Apply these genetic markers to Thai population
4. Appropriate surveillance screening
5. Compromise health economics





# Gene mutations and inherited cancer

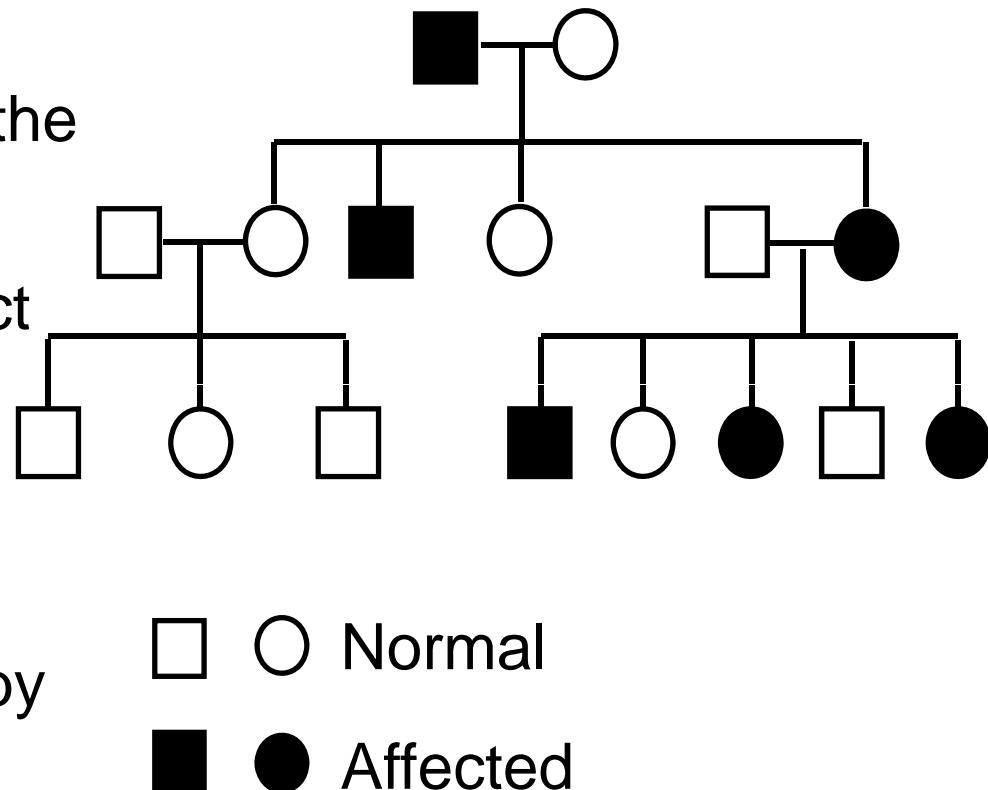
How are cancer  
predispositions inherited?

# Heredity Breast Cancer (high risk)

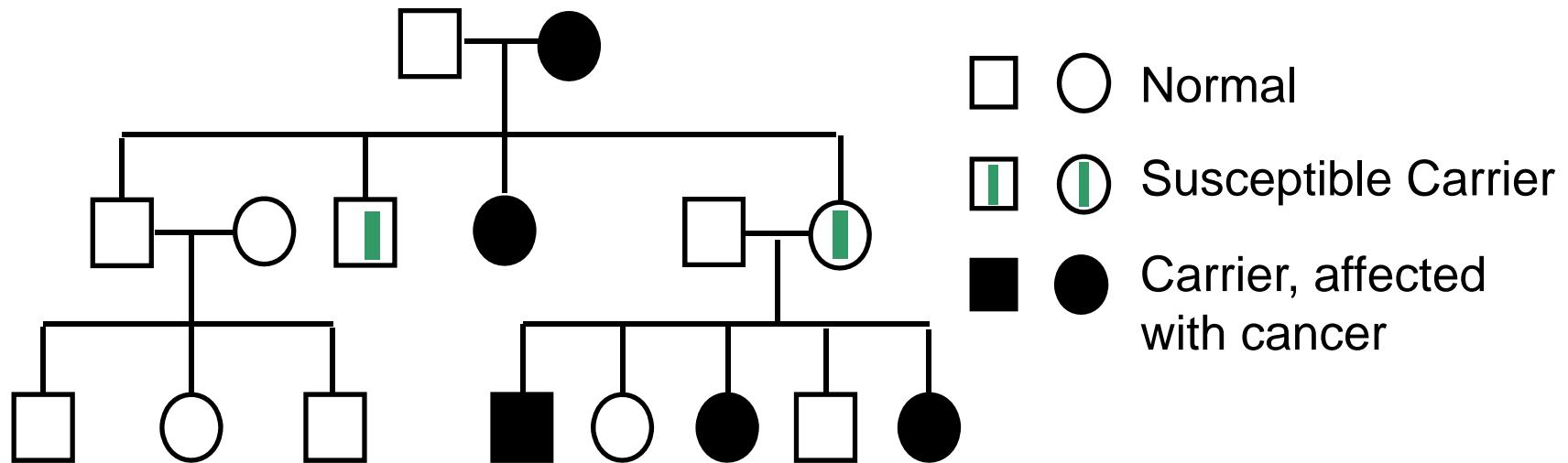
- ~5% of all Breast Cancers
- Monogenetic disorder
- Autosomal dominant inheritance
- High penetrance
- Early onset
- Cancer syndrome (other cancers also)
- BRCA1+2 only known genes of major importance

# Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- Equally likely to affect males and females
- No “skipped generations”
- Equally transmitted by men and women

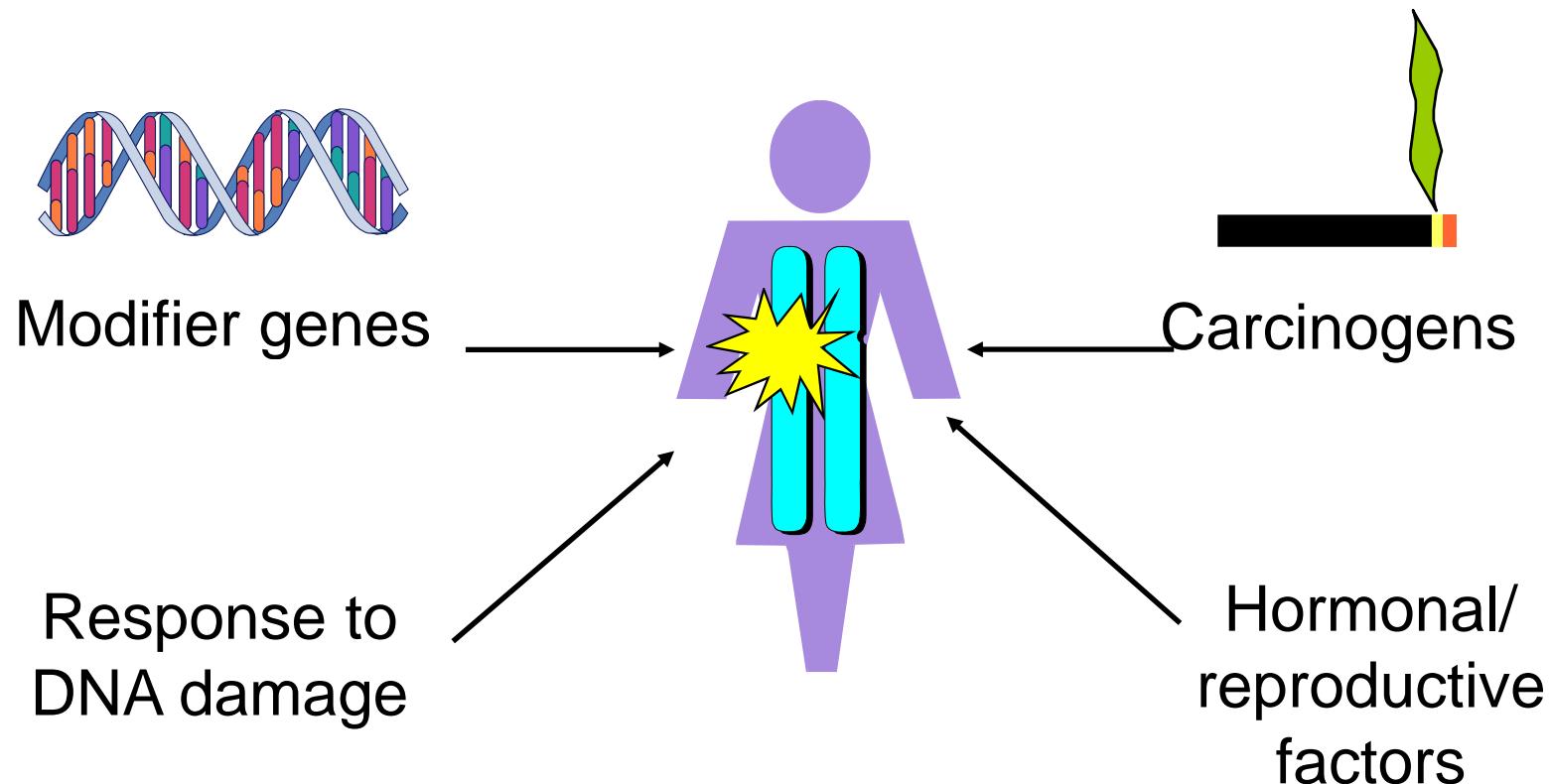


# Penetrance



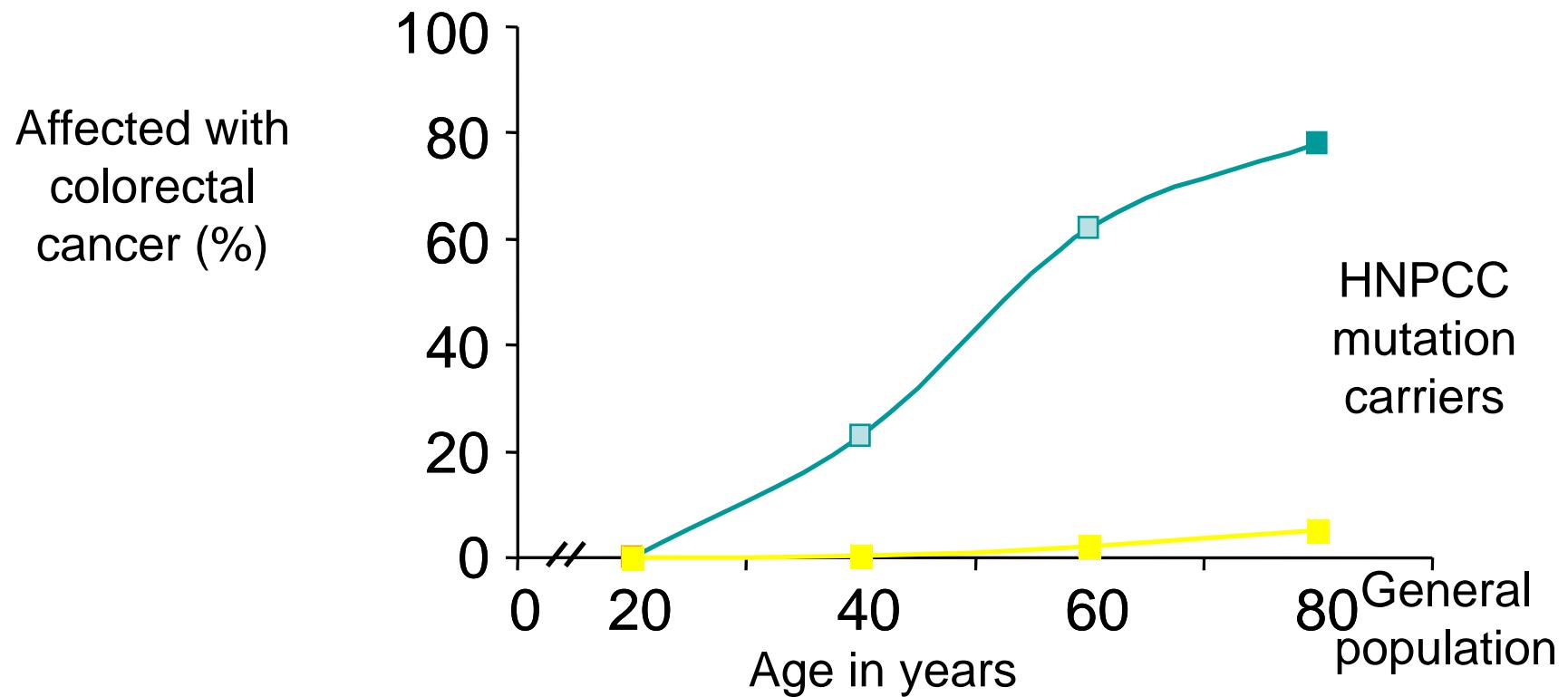
- May appear to “skip” generations
- Individuals inherit altered cancer susceptibility gene - not cancer

# Factors Affecting Penetrance



Not everyone with an altered gene develops cancer

# Age-Specific Penetrance

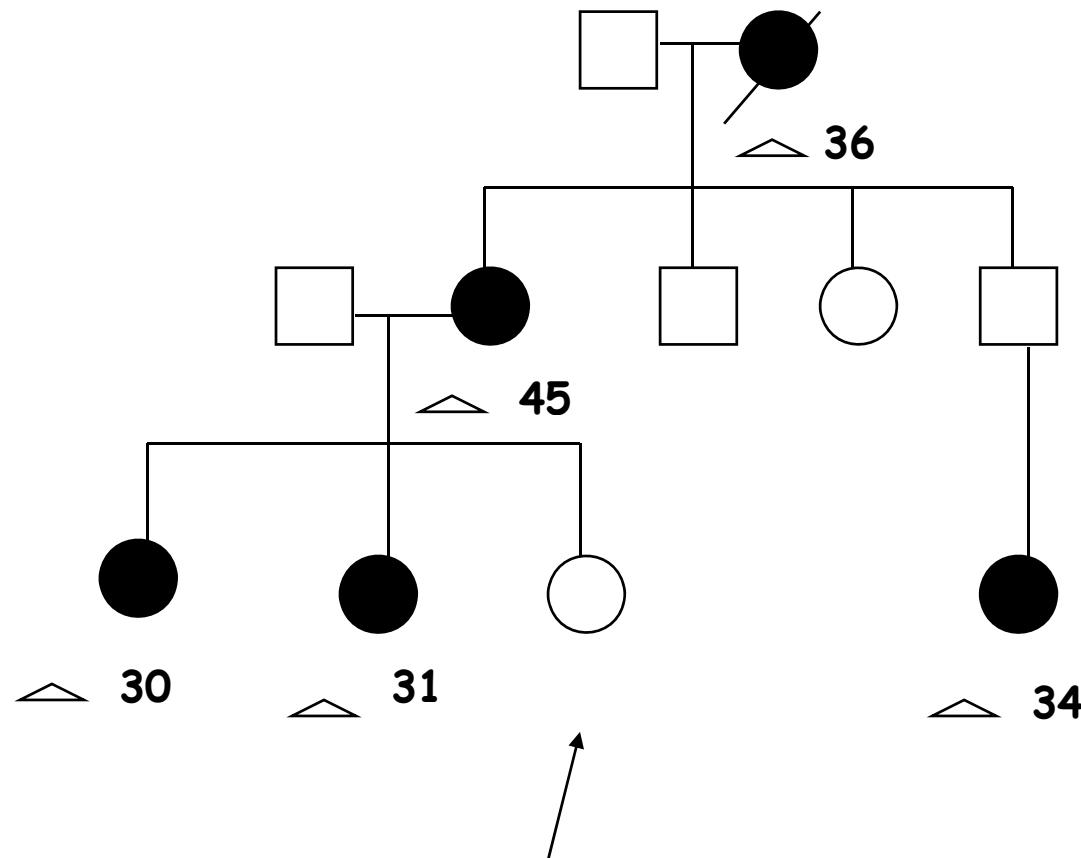


Modified from Aarnio M et al. *Int J Cancer* 64:430, 1995

# High Risk Indicators

- Multiple family members with tumours at same site
- Early age of onset
- History of individuals with multiple primary tumours
- Recognised associations:
  - Breast/ovary
  - Bowel/Endometrium
  - etc.

# Breast Cancer



# NICE - familial breast cancer

## *Mammographic surveillance*

### **High risk:**

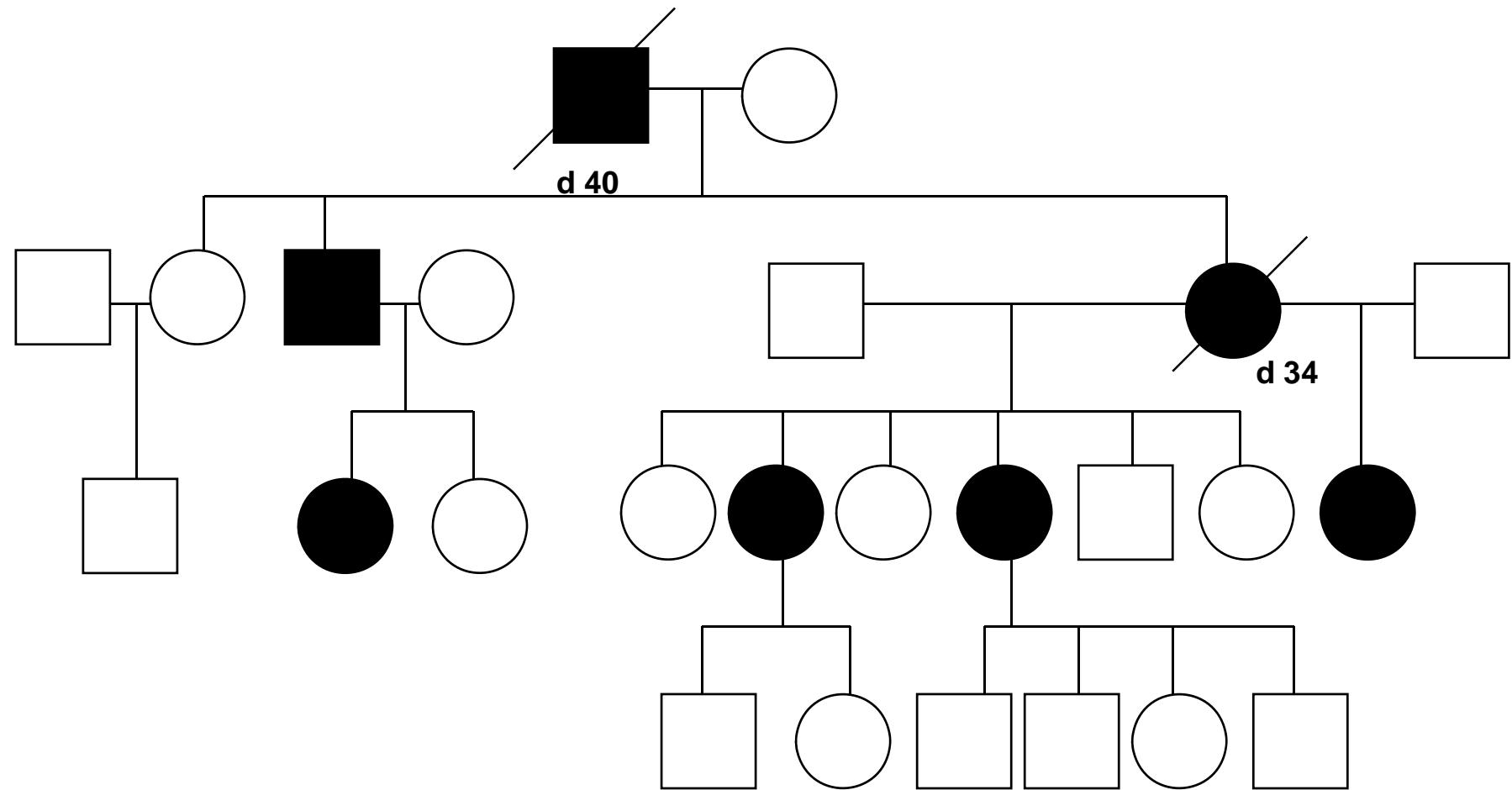
30-40 *individualised strategies*

- Mammography or MRI?

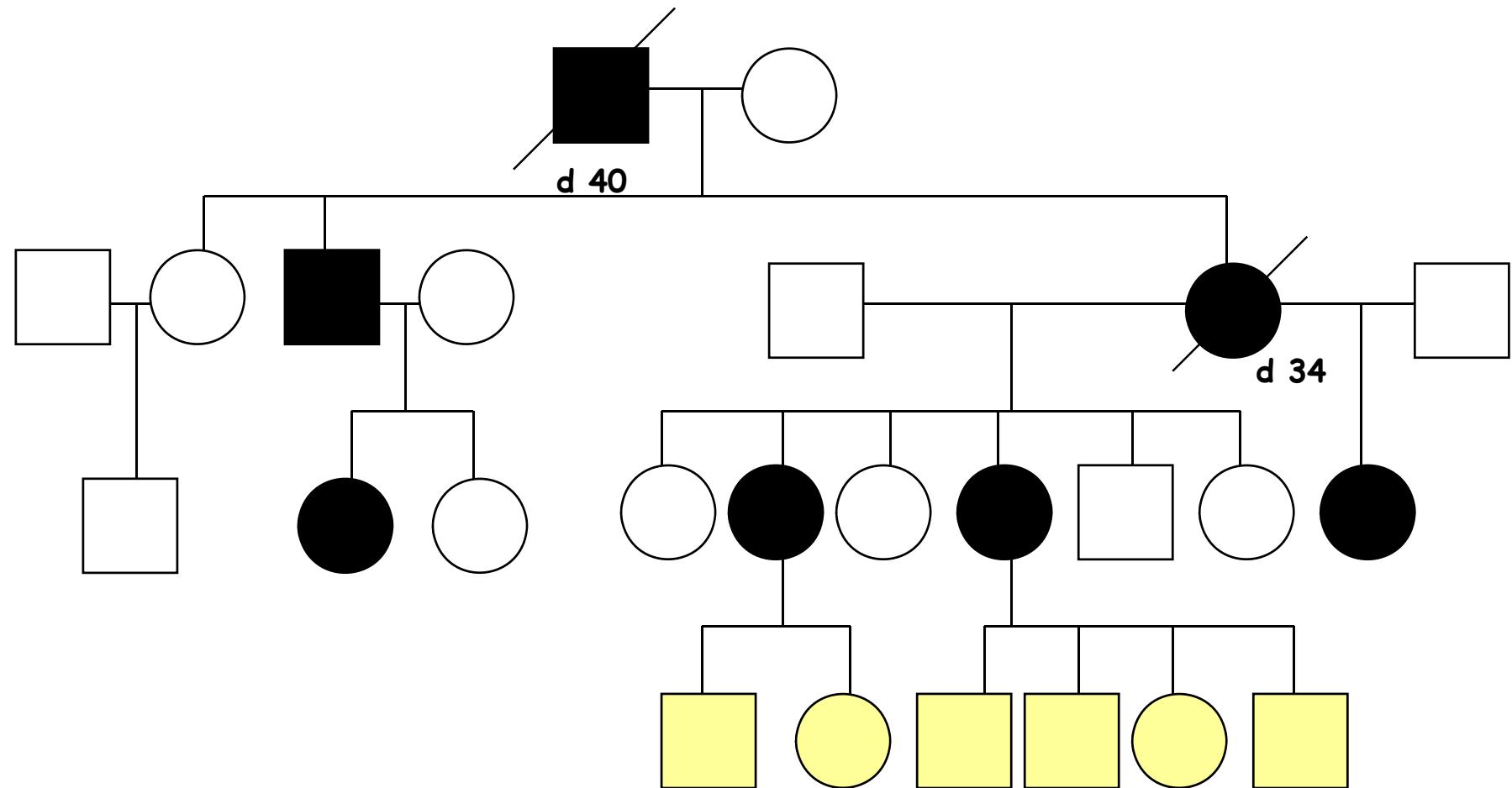
**40-50 annual**

50+ *individualised strategies*

# FAP



# FAP



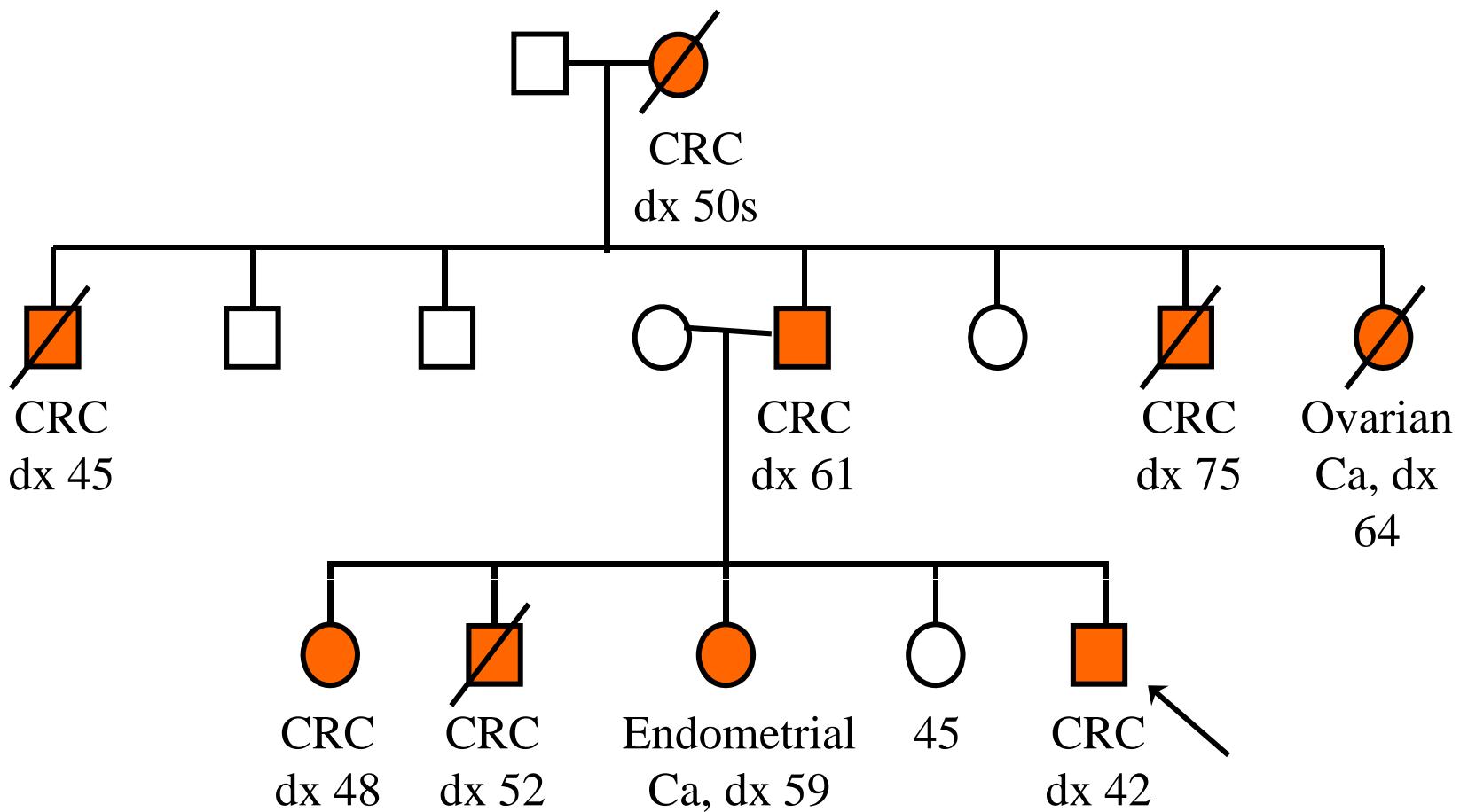
# Genetics of FAP

- Caused by mutations in APC gene (found on chromosome 5)
- ~30% occur as the result of new mutations
- Correlation between position of mutation &:
  - Severity of effect
  - Presence of CHRPEs and desmoids

## FAP: Key Points

- CRC risk is 100% in untreated FAP patients
- Genetic testing identifies most APC mutation carriers
- Endoscopic surveillance and prophylactic colectomy can improve survival in at-risk patients
- Non-carriers can be spared anxiety and the need for increased surveillance

# Family History is the key to diagnosing HNPCC



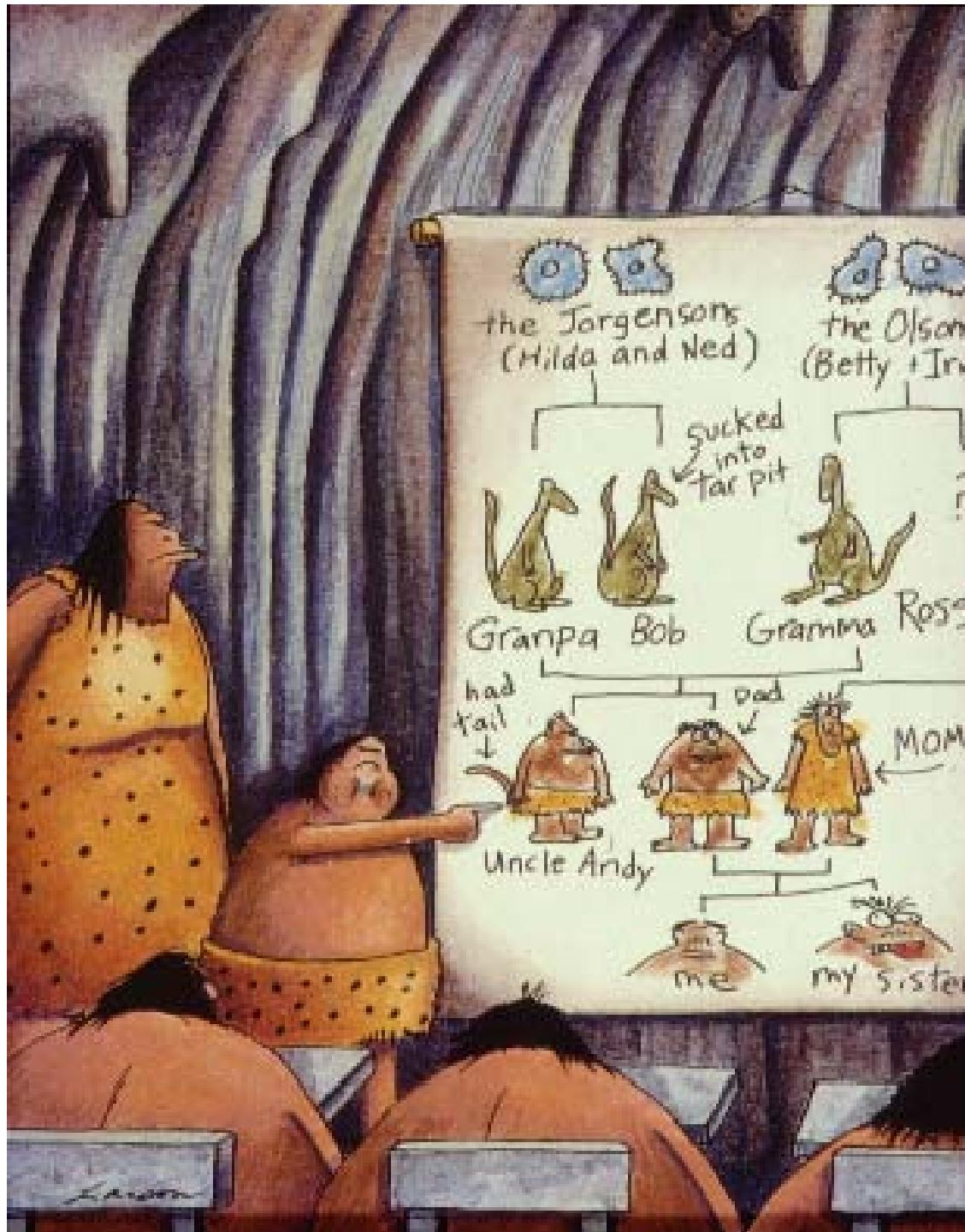
## Genetic Features of HNPCC

- Autosomal dominant inheritance
- Penetrance ~80%
- Genes belong to DNA mismatch repair family
- A number of genes involved  
*(MLH1, MSH2, MSH6, PMS1, PMS2)*

## Amsterdam Criteria

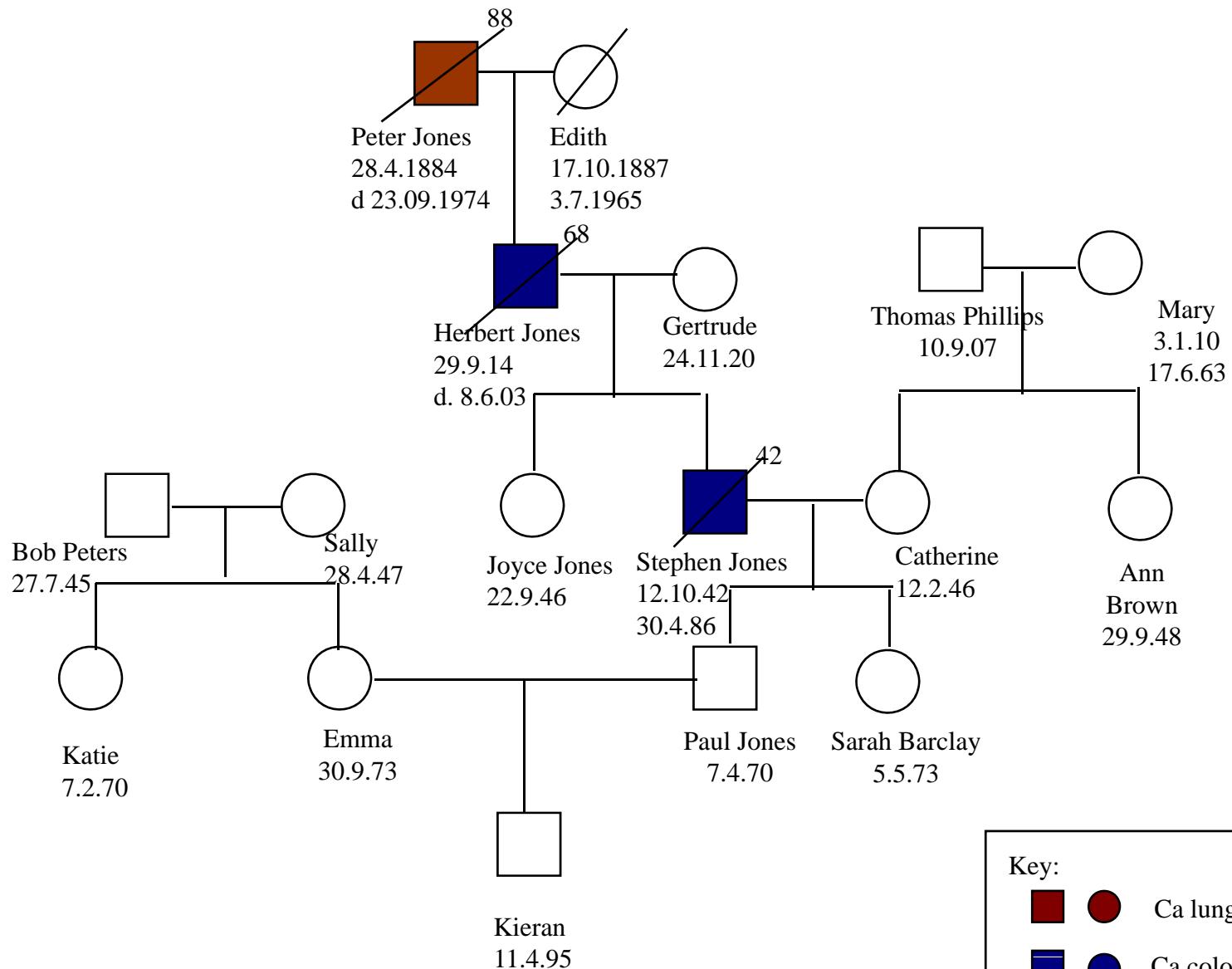
- 3 or more relatives with CRC
  - One case a 1<sup>o</sup> degree relative of the others
  - Two or more generations
  - One CRC by age 50
  - FAP excluded
- 
- Modified Amsterdam criteria: An endometrial cancer can be substituted for one of the CRC

# Taking a Pedigree



**Drawing up the family tree gives information about the relatives and also:**

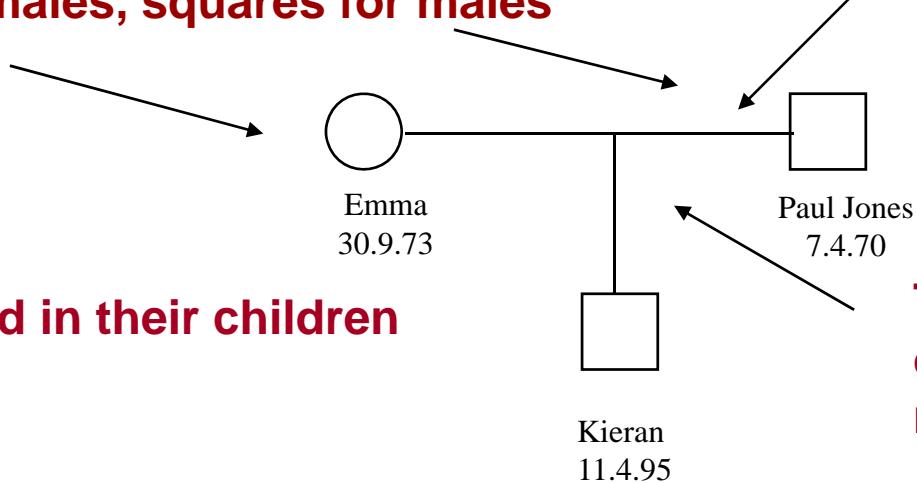
- helps establish the family agenda and dynamics
- may reveal individuals interpretation and beliefs about what is happening in the family
- Has the potential to raise issues of paternity



## Start with the couple being seen

**Use clear symbols: circles for females, squares for males**

**Add in their children**

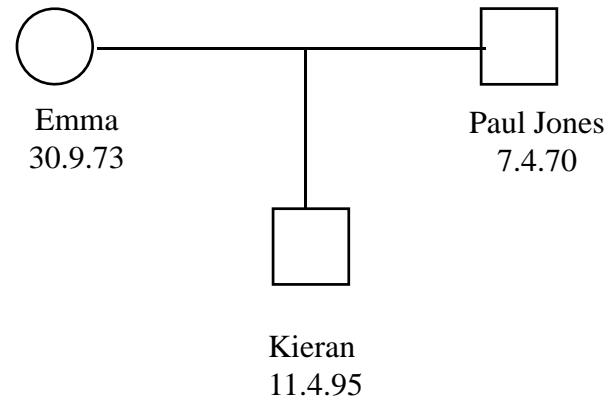


**The horizontal line denotes a relationship (males usually on the left, females on right)**

**The vertical line denotes offspring of the relationship**

**“Have you had any children with other partners?”**

**Record names, dates of birth**

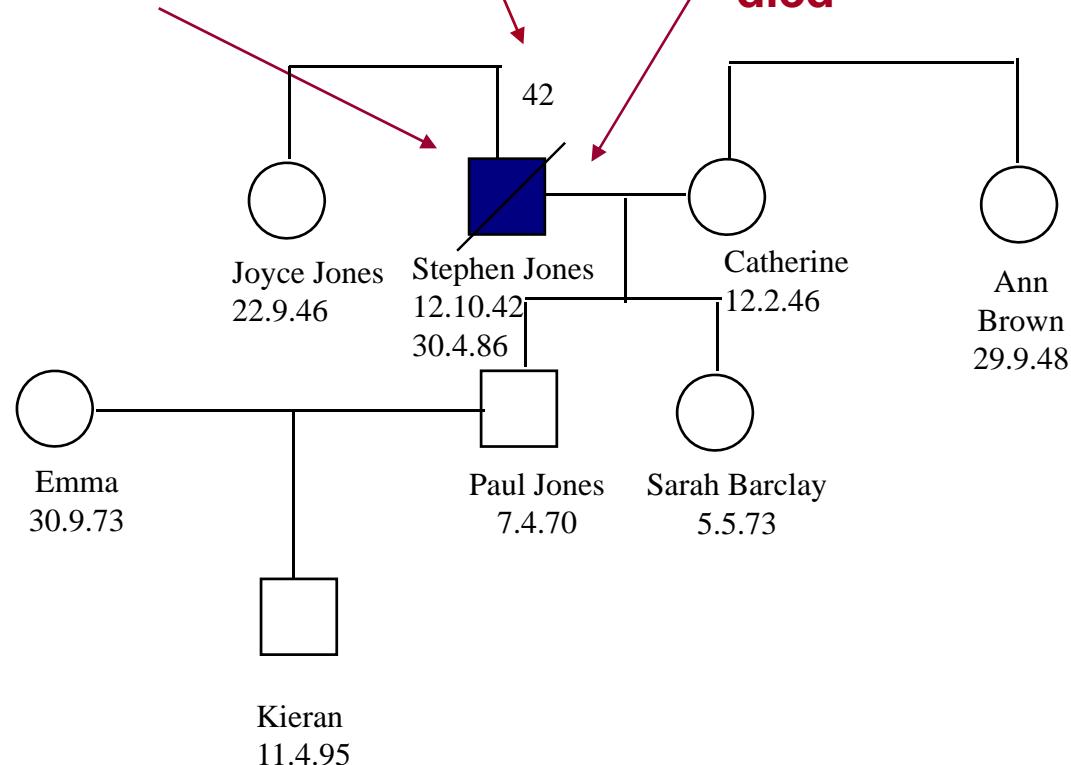


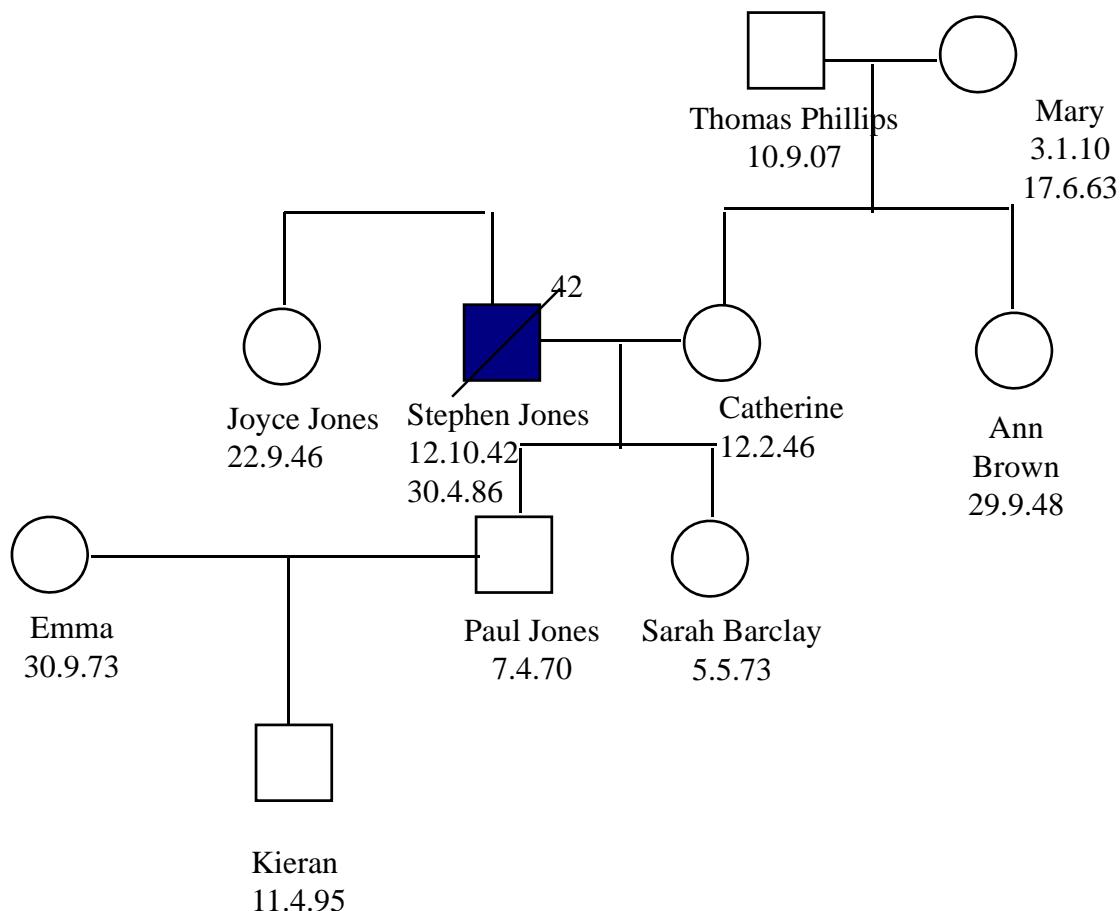
**Choose one parent and ask about:  
brothers and sister and their children  
parents and  
grandparents  
Make sure you ask about ethnicity**

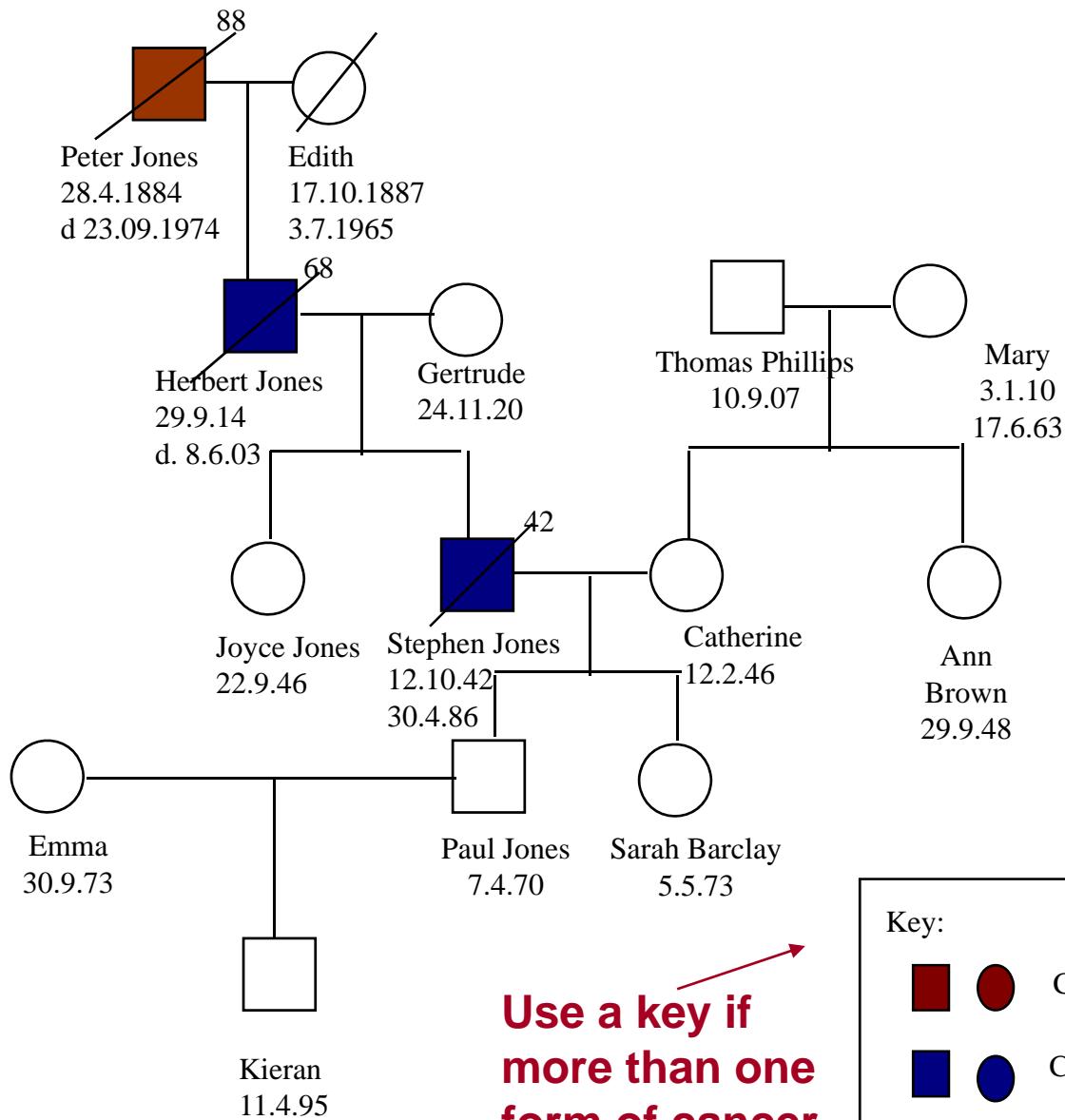
**Colour in the symbol if the person is affected**

**Add the age at which diagnosis was made**

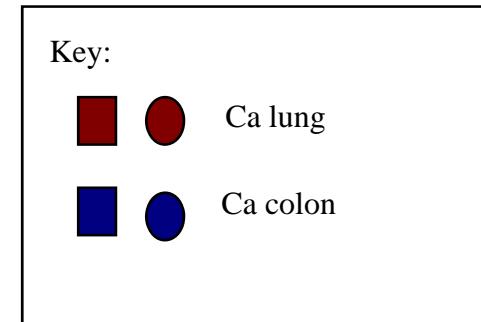
**Put a sloping line through the symbol (from the bottom left hand corner) if the person has died**

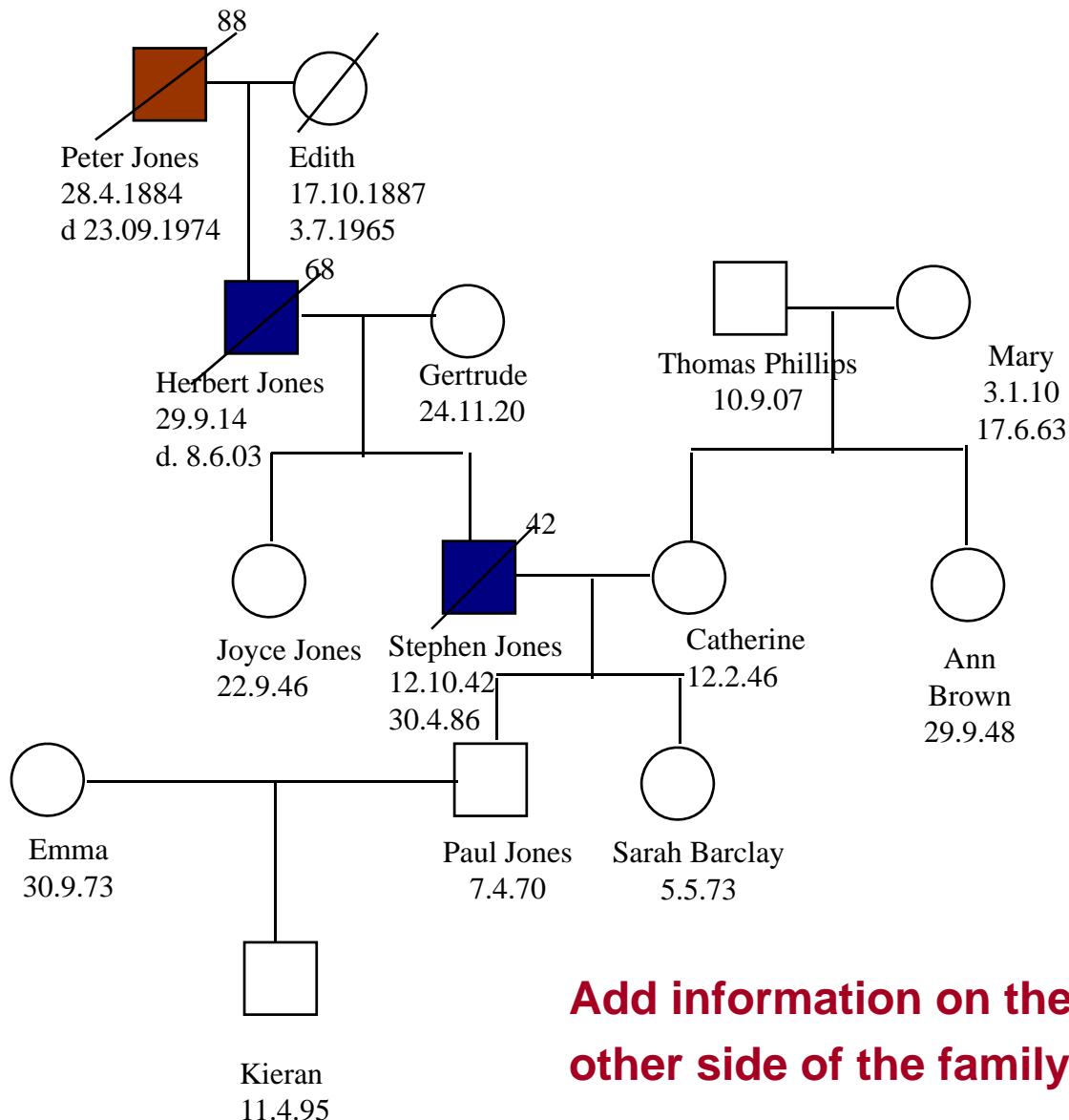




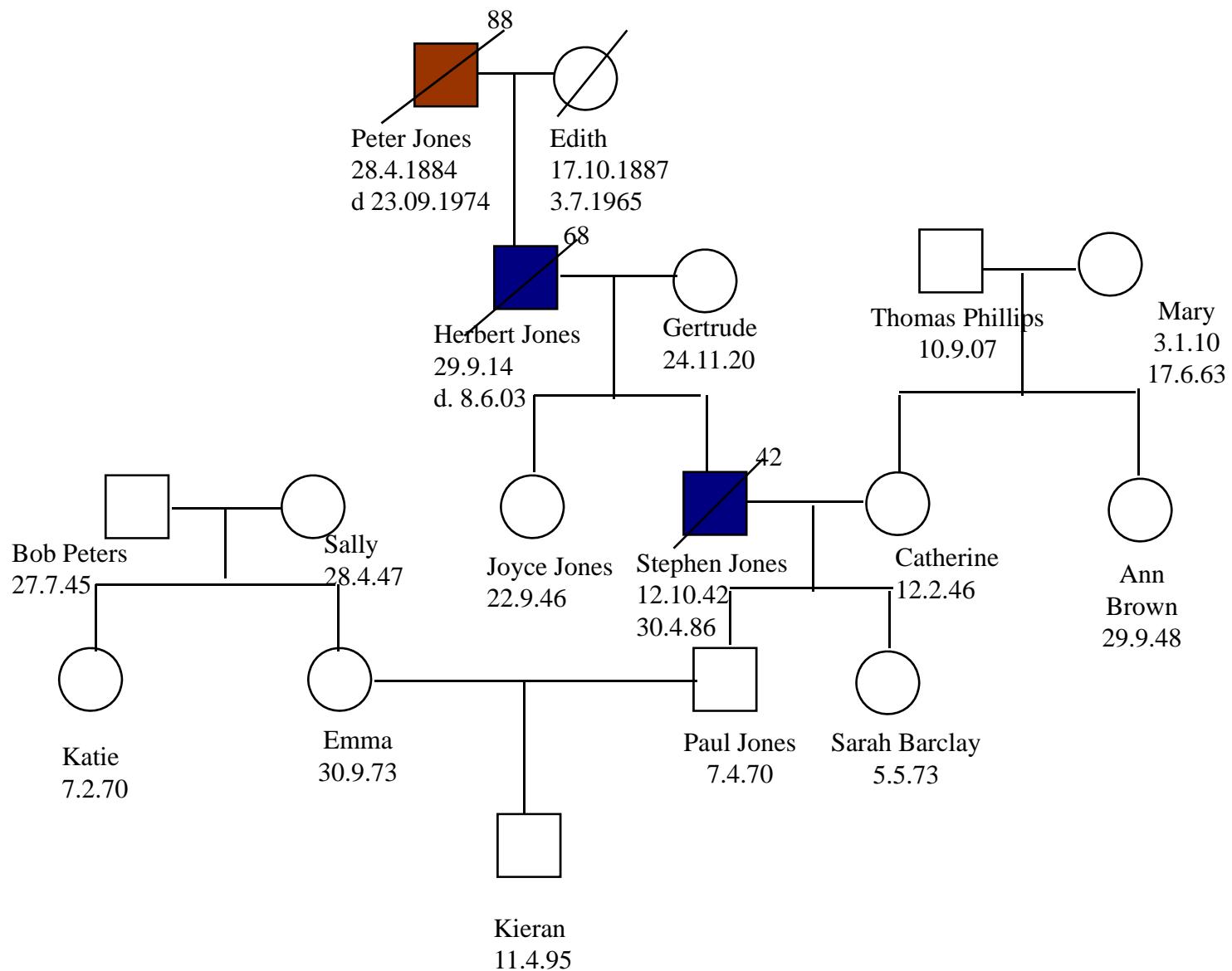


**Use a key if  
more than one  
form of cancer**

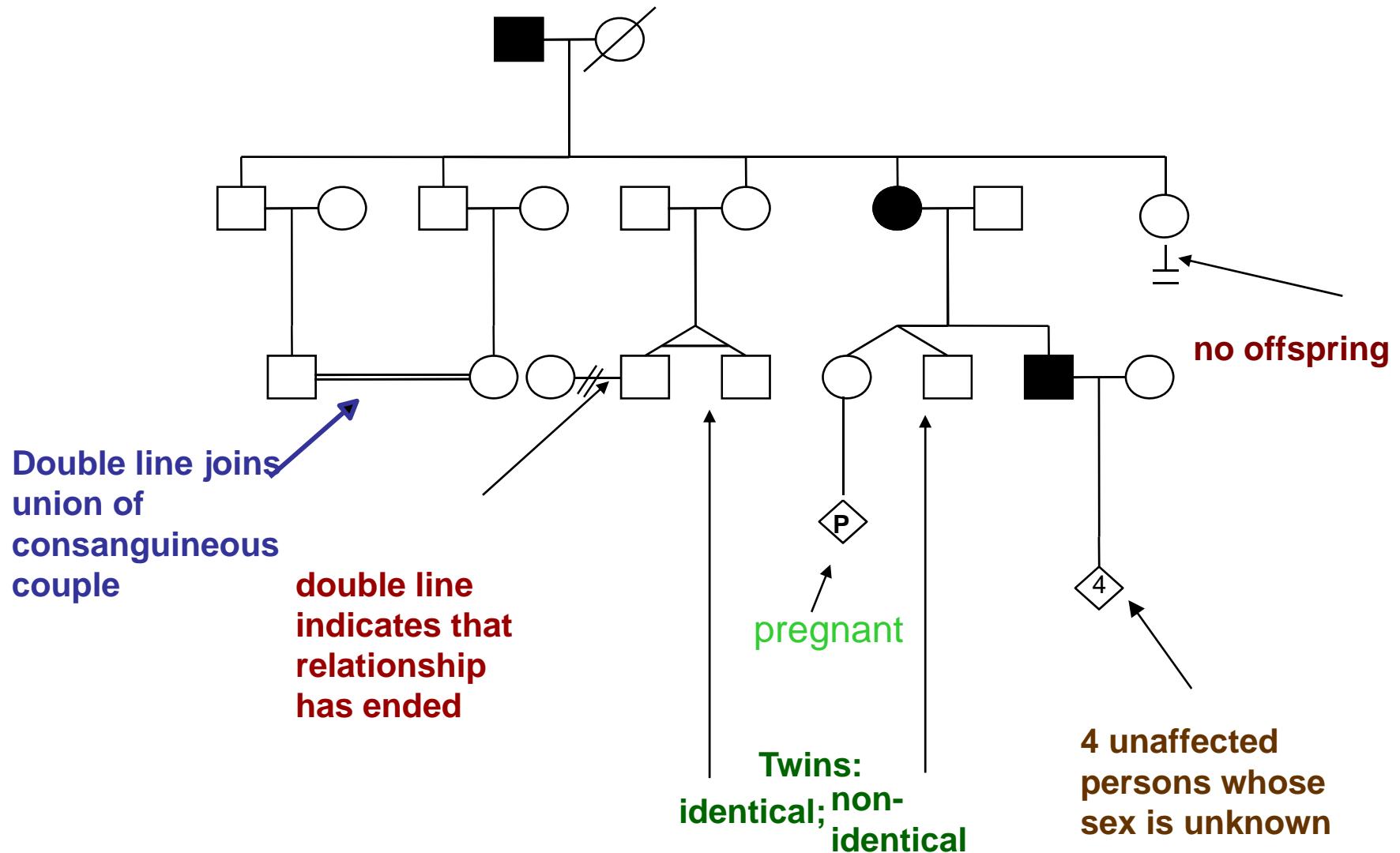




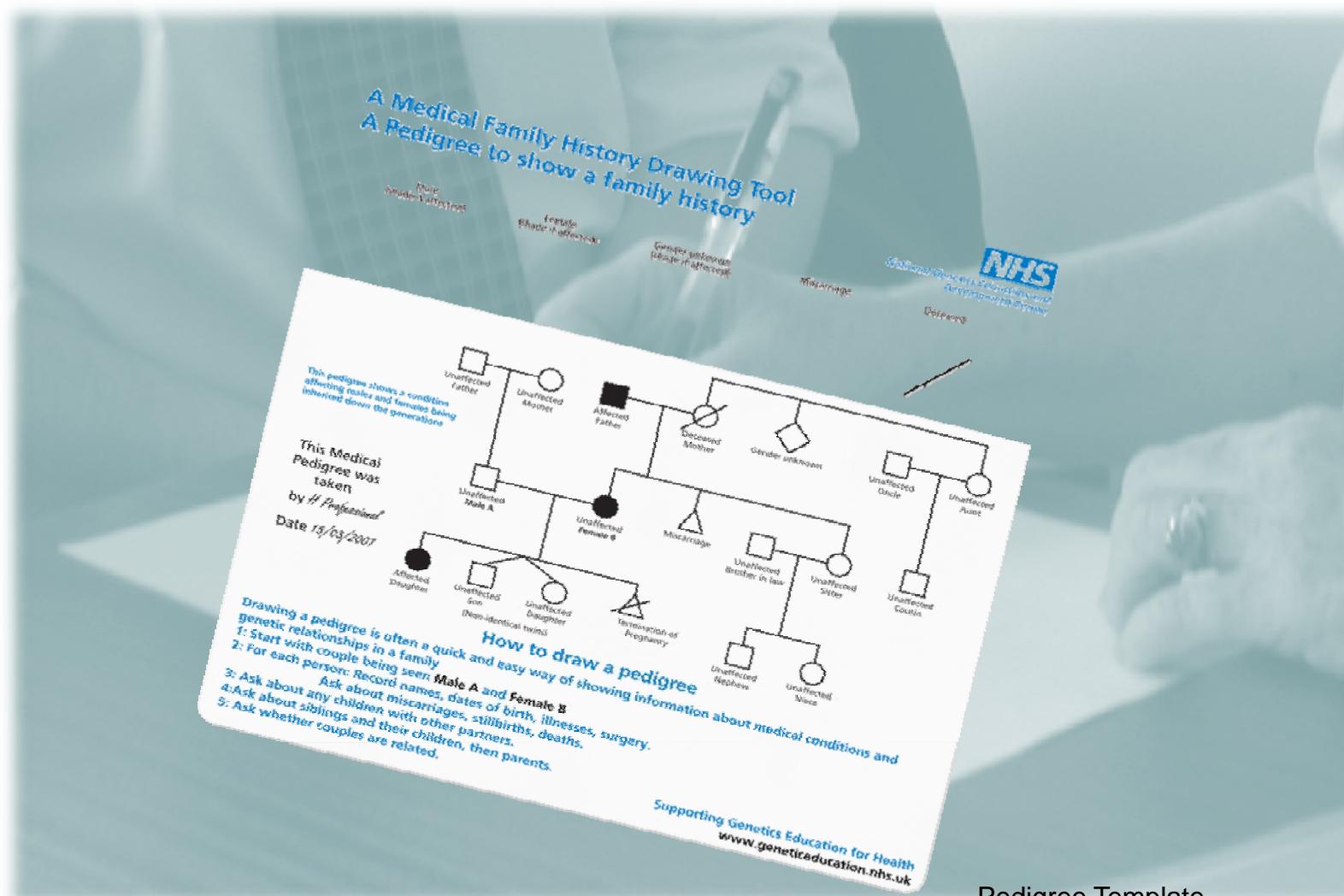
**Add information on the  
other side of the family**



## Other pedigree symbols



# Drawing a pedigree



Pedigree Template-  
One of the resources available from  
the NHS National Genetics  
Education and Development Centre

[www.geneticseducation.nhs.uk](http://www.geneticseducation.nhs.uk)

## Resource database

- Existing resources
- Resources developed by the Centre

The screenshot shows the homepage of the Supporting Genetics Education for Health website. At the top right is the NHS logo and the text "National Genetics Education and Development Centre". The main navigation menu includes Home, About Us, Learning Genetics, Teaching Genetics, and Genetics in Practice. Below the menu, there's a banner for the "Genetic Progress embedding scientific advances into Healthcare". A section titled "Latest Highlights" lists various resources like "Is my patient's condition inherited?", "A Medical History Drawing Tool for non-genetics health professionals", and "The Genetics of Obesity quick reference sheets for the diabetic clinic". To the right, there are sections for "Resources", "Competences", "Centre Publications", and "Telling Stories". A sidebar on the right contains information about a conference: "Supporting Genetics Education for Health Conference: Connecting Evidence into Practice 15 October 2008, Birmingham". The footer includes links for Sitemap and Lorem ipsum dolor sit amet.

## Searchable

- Search all
- Linked to educational outcomes

The screenshot shows a search result page for "Teaching General Practice Trainees". The left sidebar has categories for Medical Practitioners, Nursing Practitioners, and Learning Outcomes. The main content area is titled "Teaching General Practice Trainees" and includes a sub-section for "Teaching General Practice Trainees". A callout box highlights the third learning outcome: "3. Be able to identify patients with, or at risk of, a genetic condition". Below this, a bulleted list states: "• Be able to take a family history and construct and interpret a pedigree".

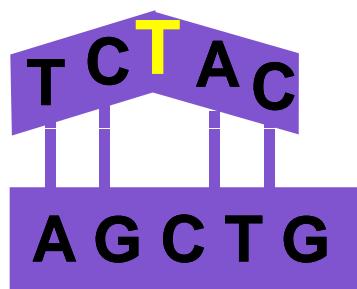


## Evaluated

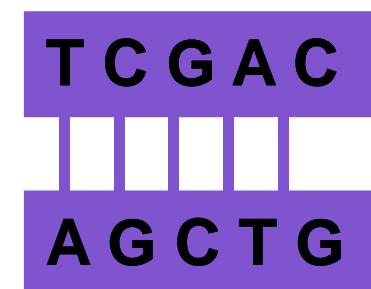
# Genes Associated With Cancer

## 3. DNA damage-response genes: the repair mechanics for DNA

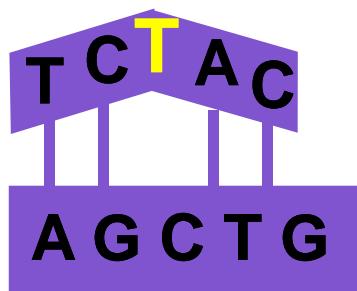
Base pair  
mismatch



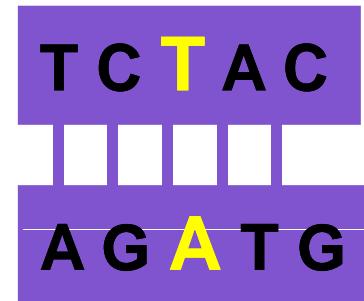
Normal  
DNA repair



# DNA damage-response genes:



Base pair  
mismatch



Mutation  
introduced by  
unrepaired  
DNA