# Integration of Genomics in Cancer Care

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# Purpose

* **To introduce how genetics and genomics are integrated into cancer care from prevention to treatment**

# Topics

* Etiology of Cancer
* Cancer Risk Assessment
* Tumor Profiling
* Pharmacogenomics
* Targeted Cancer Therapy

# Case Study

* Mr. J – 41 yrs of age, white, Northern European ancestry
* Biopsy: right-sided colon cancer; plus two adenomatous polyps
* No prior cancer history
* Medical history otherwise unremarkable

# Case Study – Mr. J

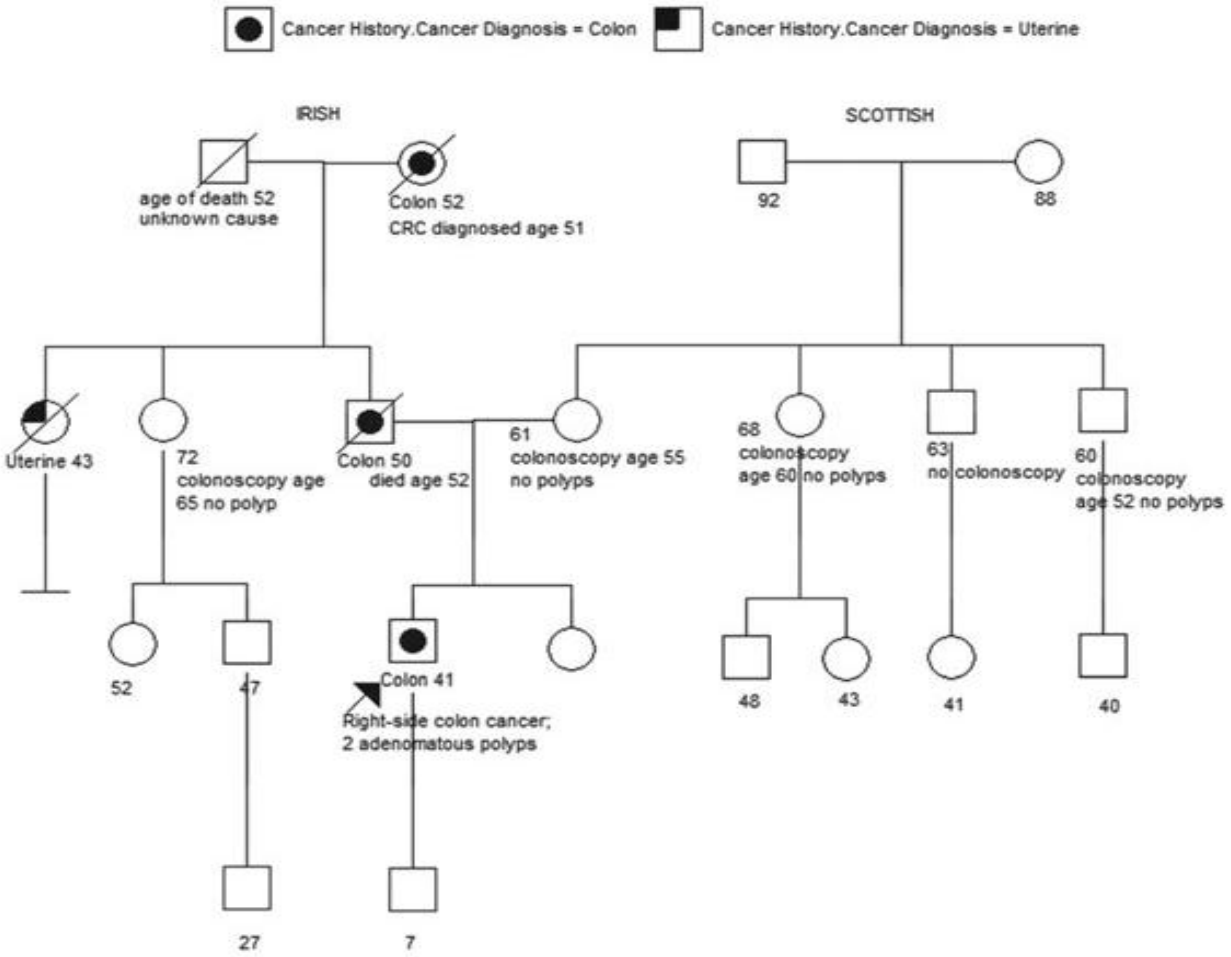
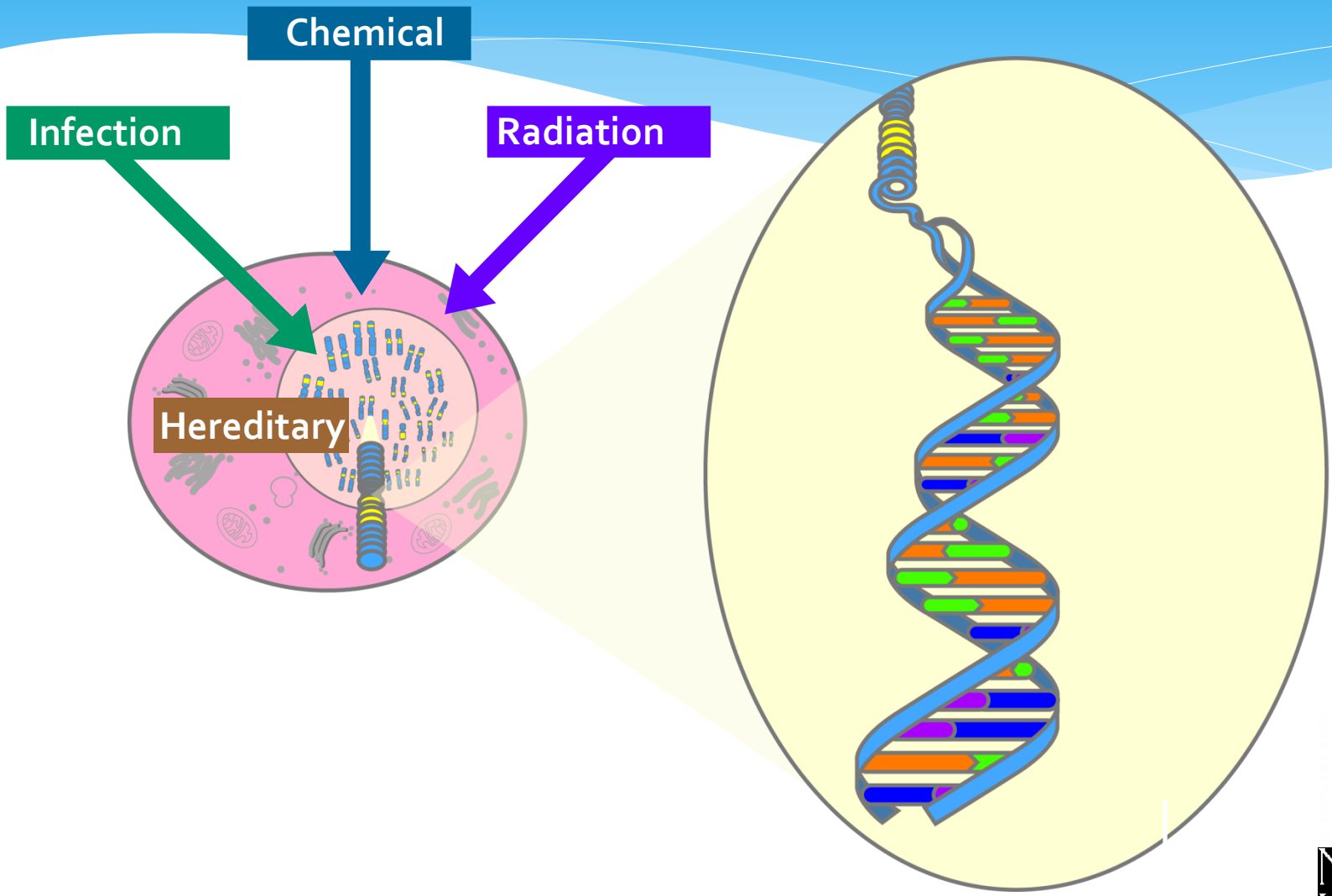


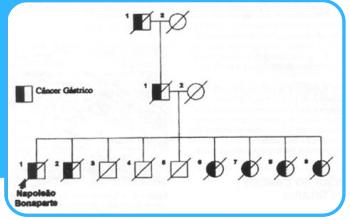

**Figure 1.** Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).

Santos et al 2013

# Etiology of Cancer

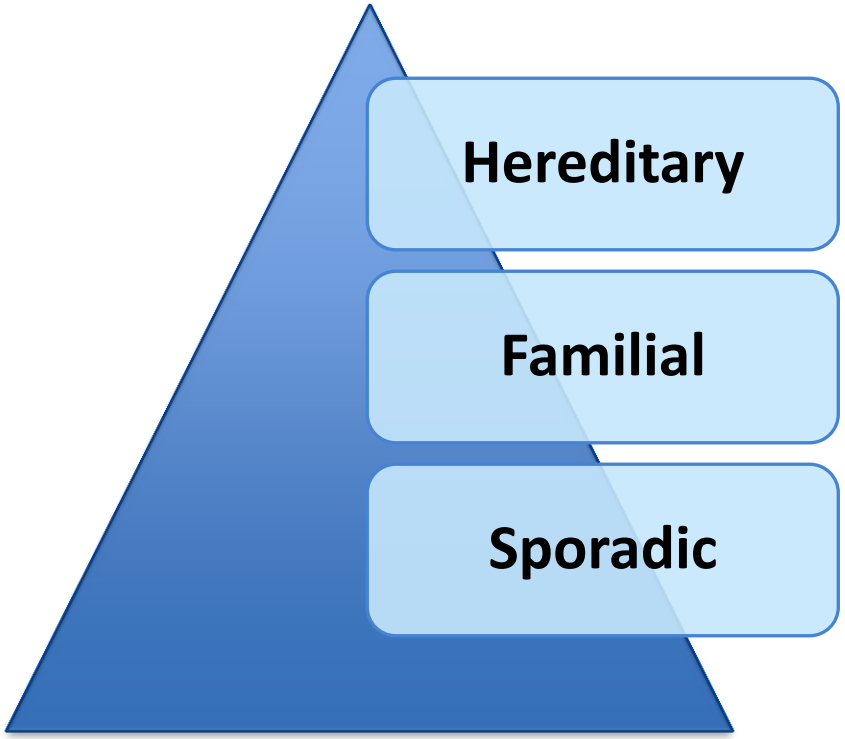


# Etiology of Cancer

- Risk factors
  - Radiation
    - UVB
    - Ionizing
  - Chemical
    - Tobacco
    - Aflatoxin
  - Biological
    - EBV
    - HPV
  - Genetic Susceptibility
    - 

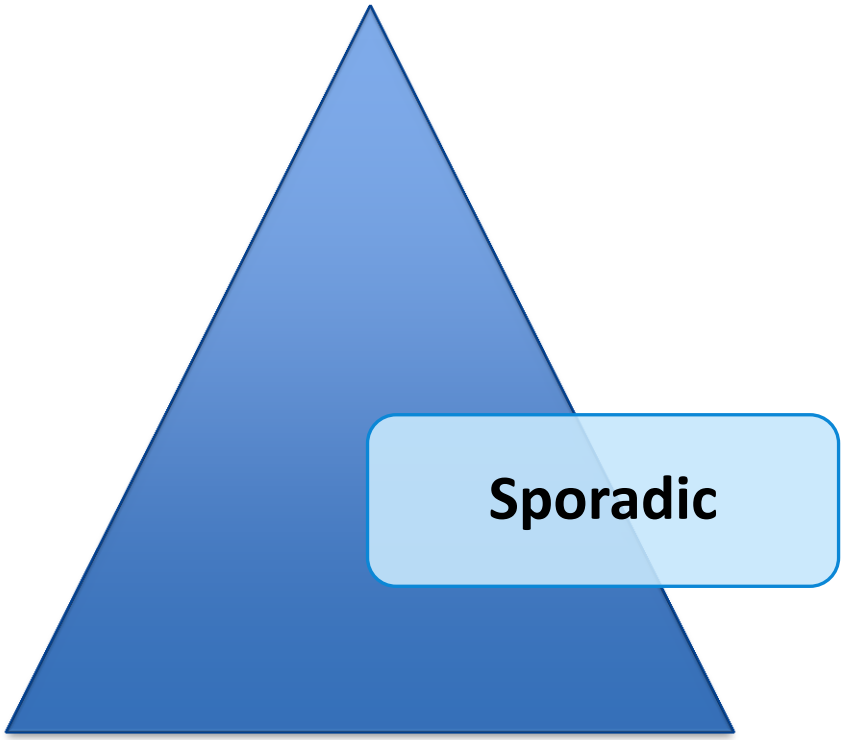
# Etiology of Cancer

**Classification of Tumors Due to Family History (FH)**



# Etiology of Cancer

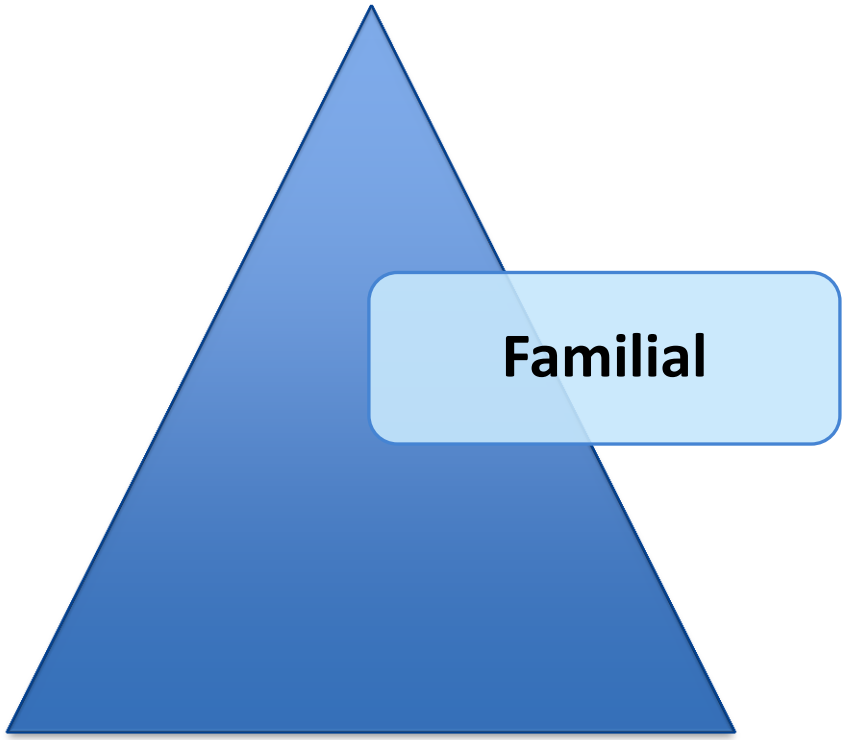
**Classification of Tumors Due to Family History**




**75% of all cancers**
**Age of onset typically that expected for the type of cancer**
**Somatic (acquired) mutations in a specific tissue (e.g., breast, colon)**

# Etiology of Cancer

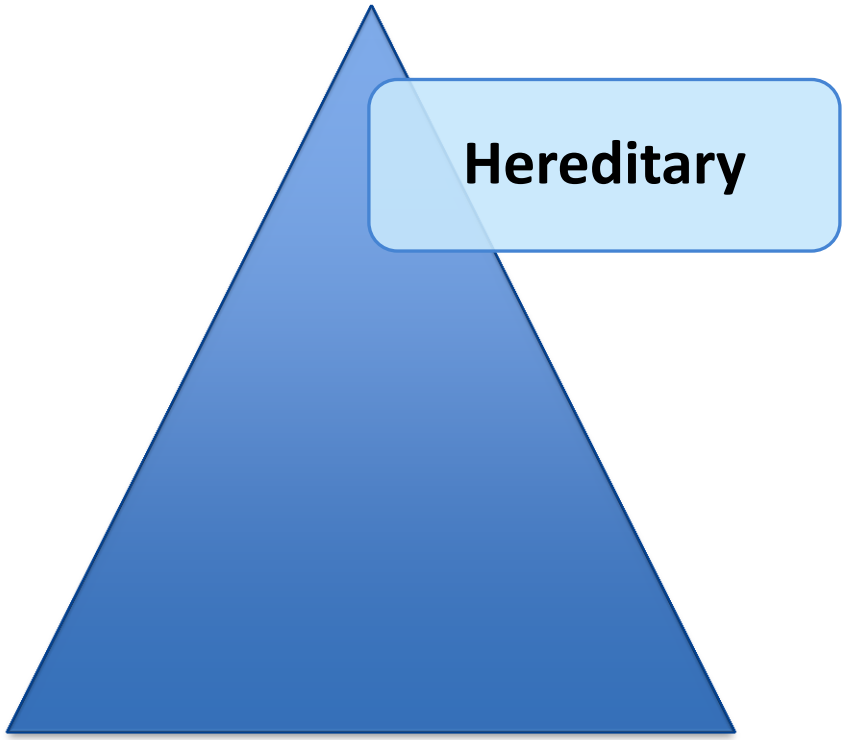
**Classification of Tumors Due to Family History**




**10%-15% of all cancers**
**Same cancer type occuring at excepted age in more than one close relative**
**Shared environmental + genomic influences**

# Etiology of Cancer

**Classification of Tumors Due to Family History**

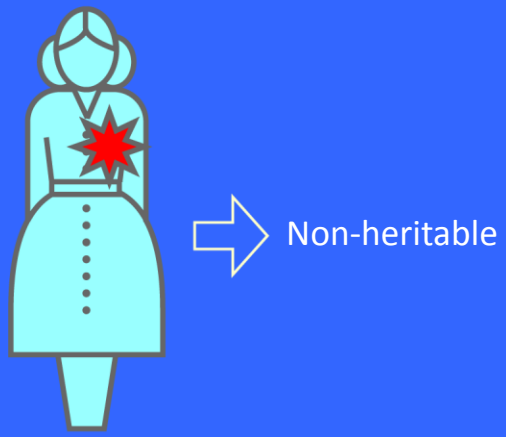



**5%-10 of all cancers**
**Earlier age at onset than usual**
**May or may not have FH of same cancer or other cancers associated with a cancer syndrome**
**Single gene mutation in the germline (egg or sperm)**

# Etiology of Cancer

## Somatic mutations

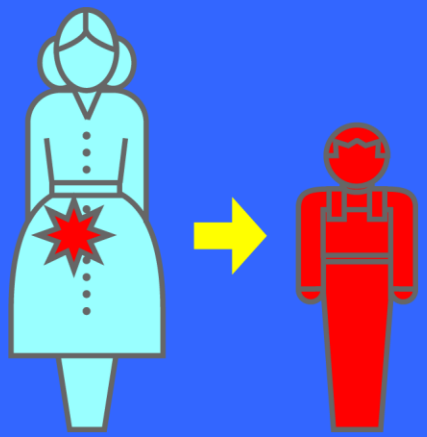
- Occur in non-germline tissues
- Are not heritable




Somatic mutation
(e.g., breast)

## Germline mutations

- Present in egg or sperm
- Are heritable
- Cause cancer family syndromes



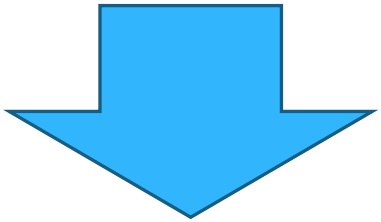
Mutation in
egg or sperm

All cells affected
in offspring

NATIONAL CANCER INSTITUTE
modified

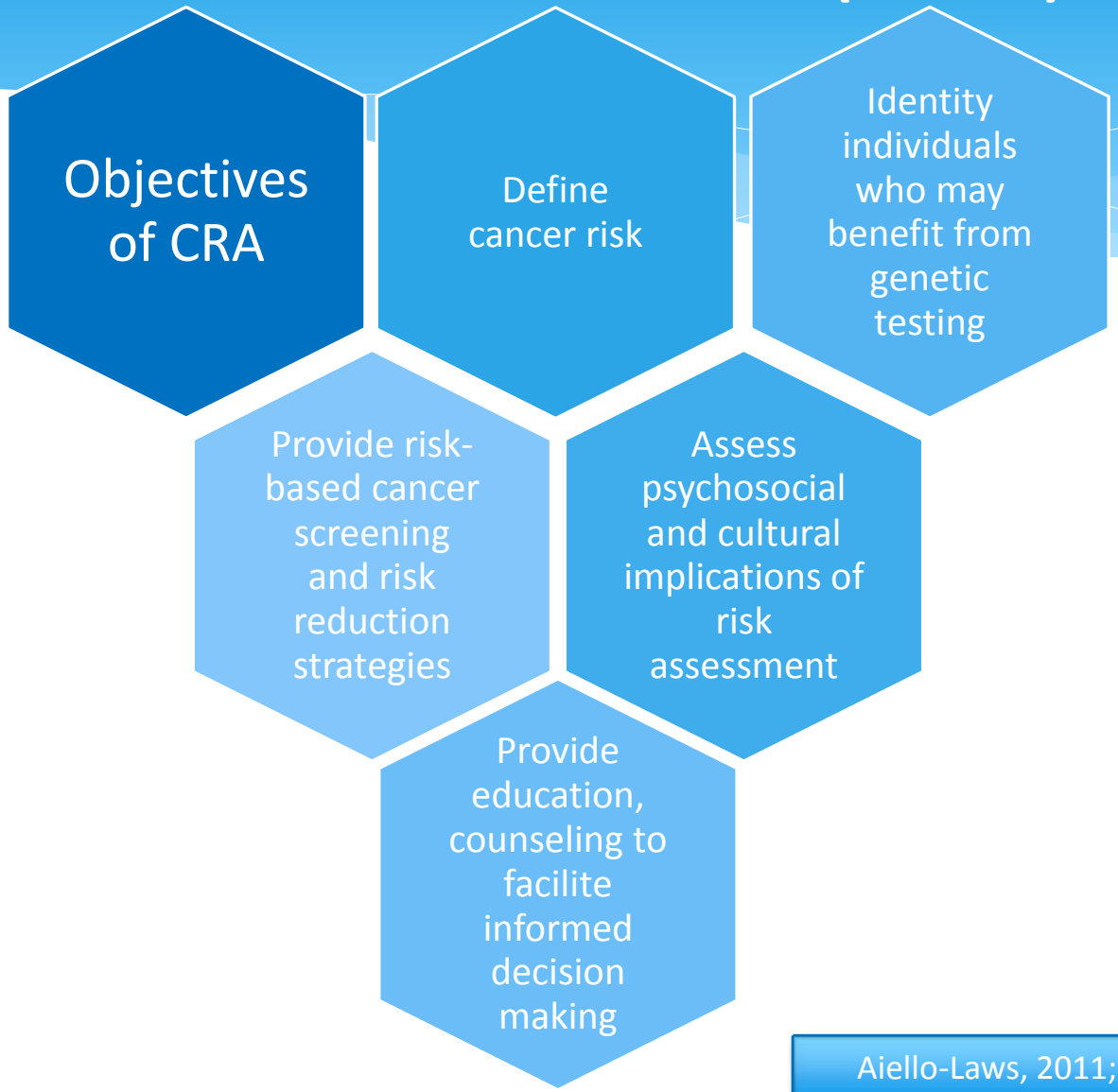
# Etiology of Cancer

How important is to recognize the difference among acquired and heritable genetic mutations?



Key to appropriate referral for further evaluation

# Cancer Risk Assessment (CRA)




Aiello-Laws, 2011; Weitzel et al. 2011

# Cancer Risk Assessment

## How to recognize individuals for CRA?

- **Earlier age of cancer onset than expected**
- **Same type of cancer in two or more close relatives**
- **Two or more primary cancers in the same person**
- **Constelation of cancers characteristic of a hereditary syndrome**
- **Male breast cancer, ovarian cancer or medullary thyroid cancer cancer, at any age**
- **Previously identified cancer-associated mutation in the family**

# Case Study – Mr. J

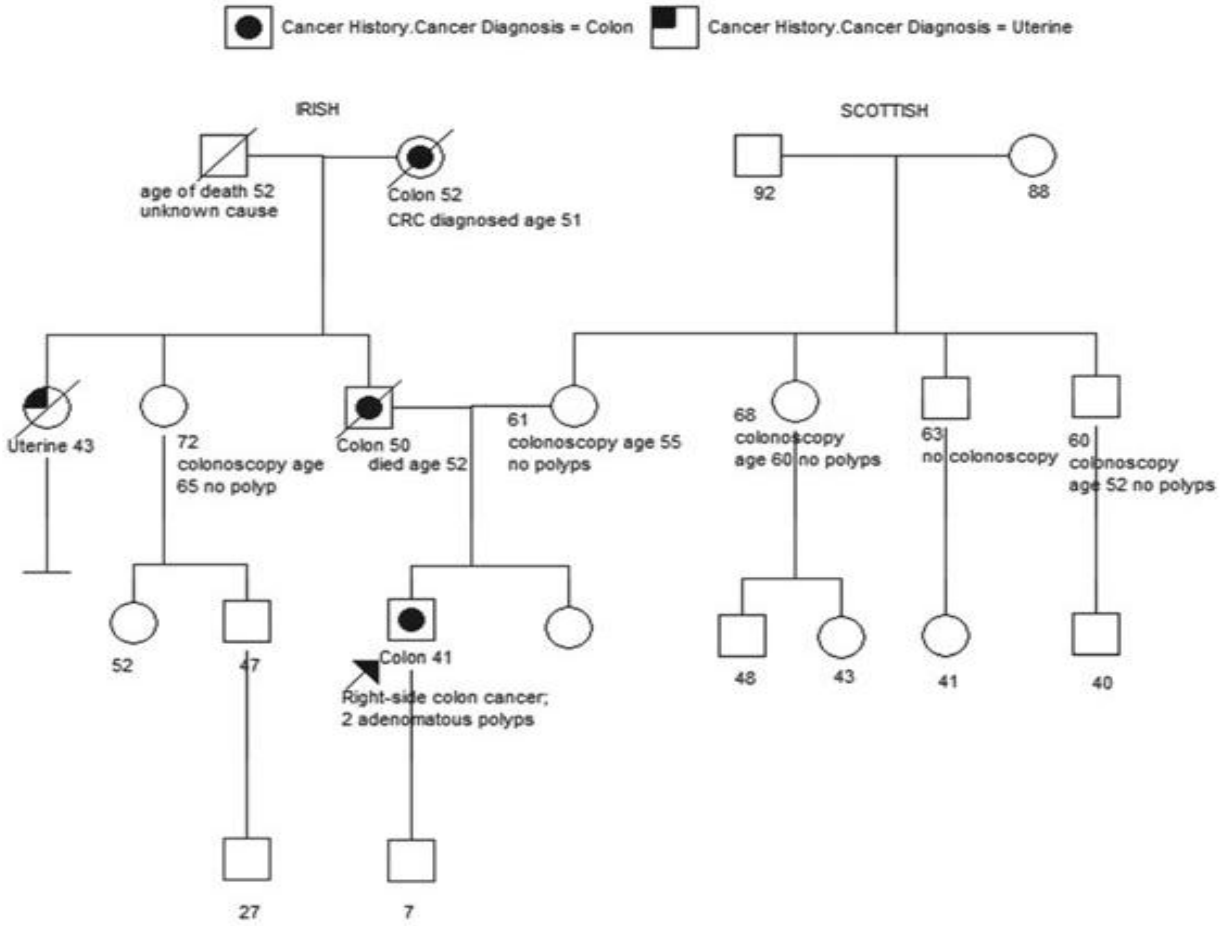



**Figure 1.** Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).

Santos et al 2013

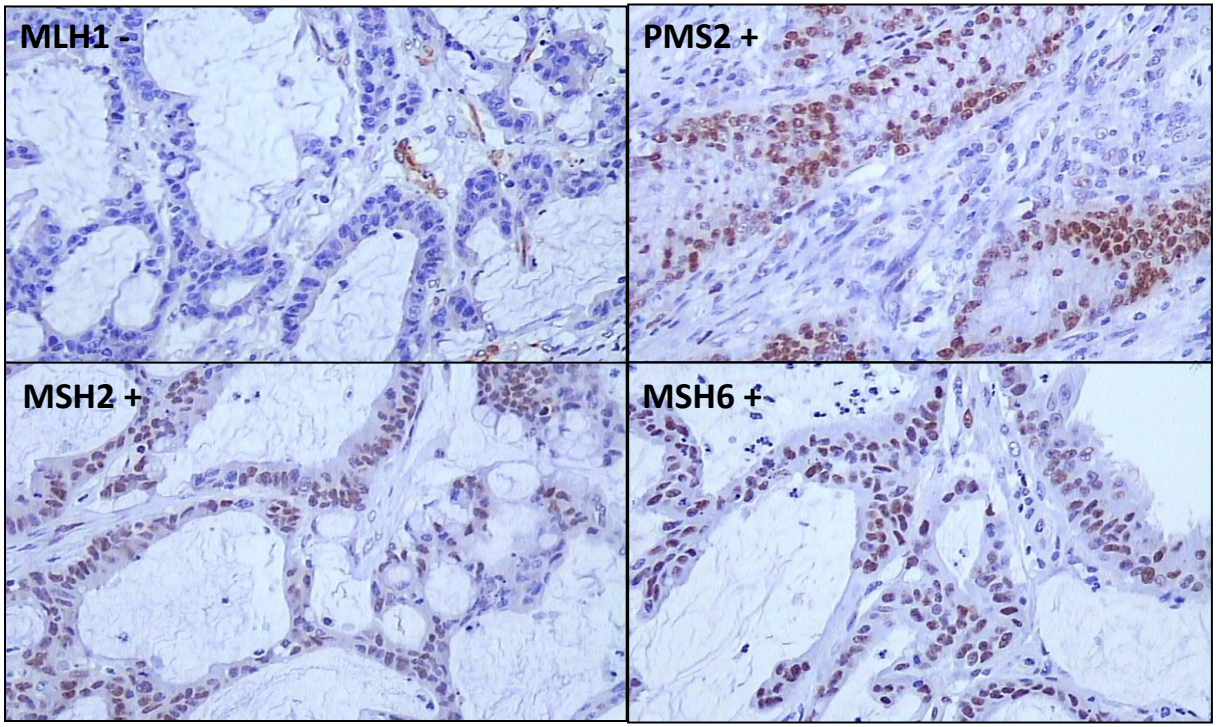
# Tumor Profiling

* **Evaluation of genomic, proteomic and epigenomic expression factors for cancer diagnosis, prognosis and therapeutics**

Dacic 2011

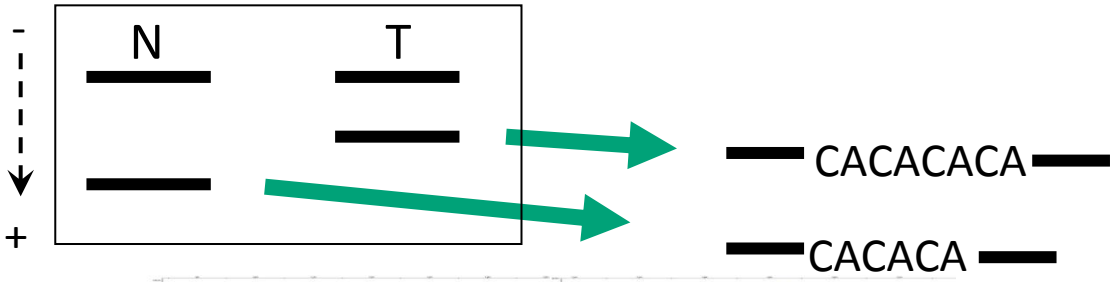
# Case Study – Mr. J

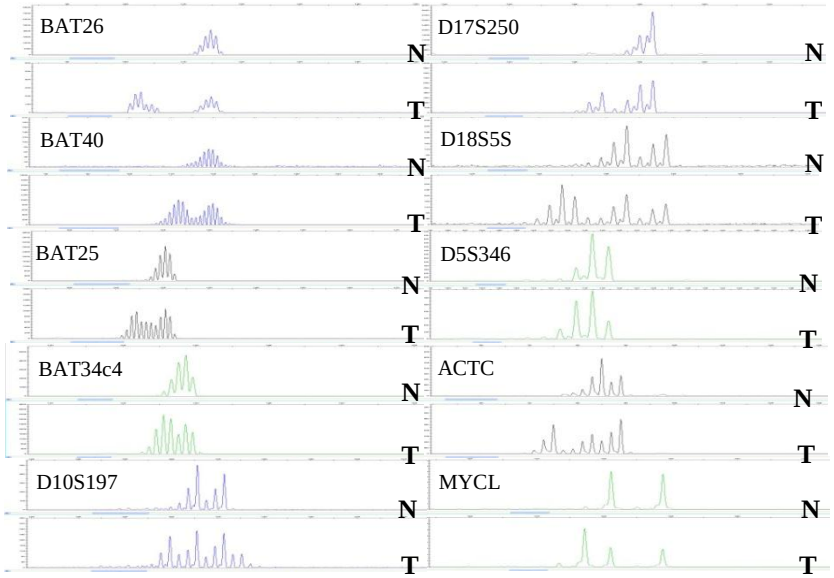
**Immuhistochemistry – test for protein expression of 4 genes associated with colorectal cancer**
**Result: absence of MLH1 expression**



# Case Study – Mr. J

**Other evidence of germline mutation: MSI testing**
**Result: MSI-H (MSI-High)**



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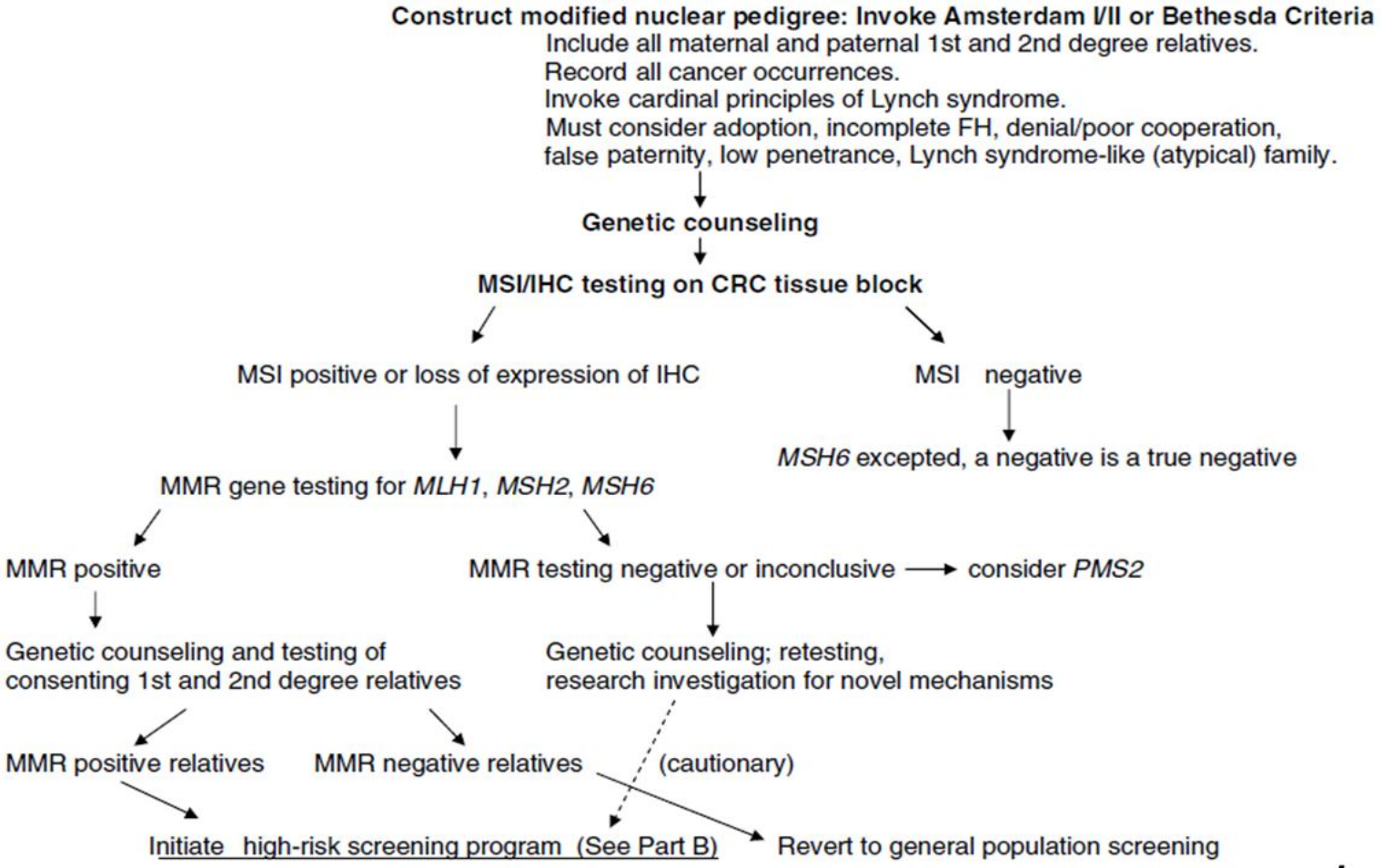
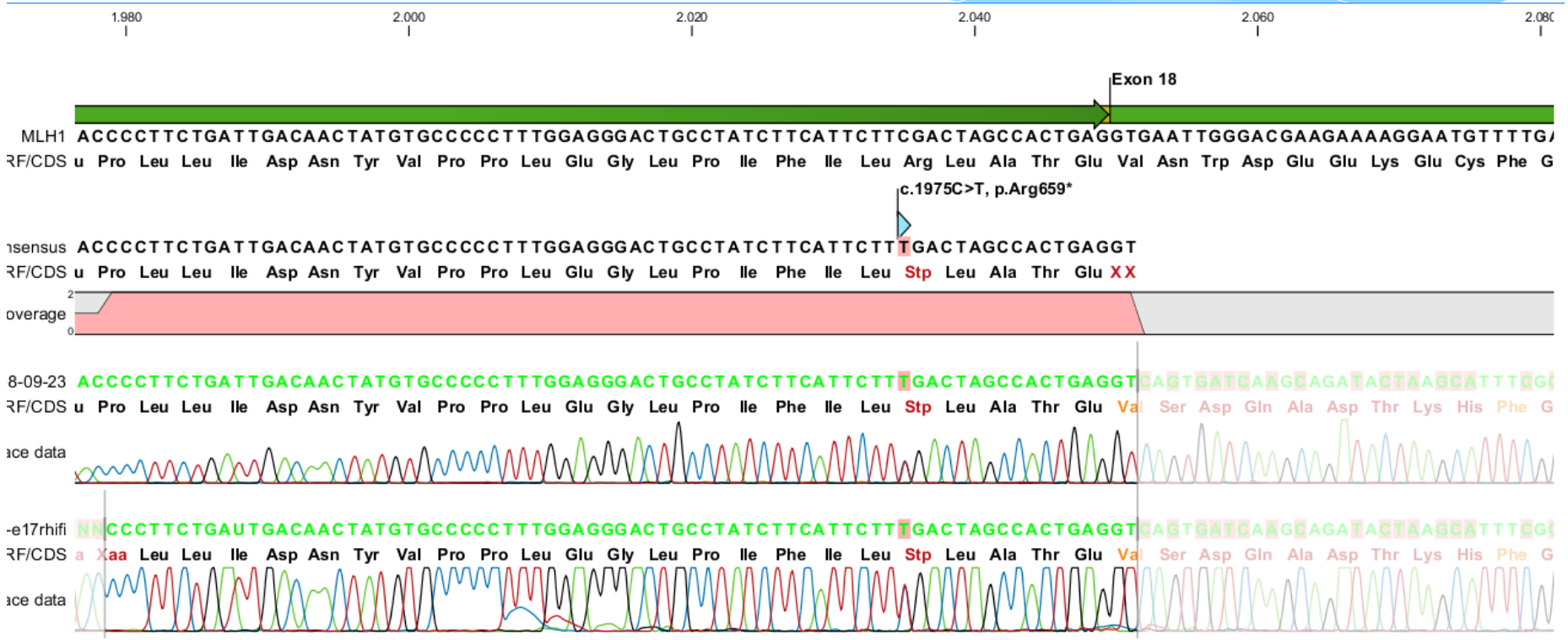


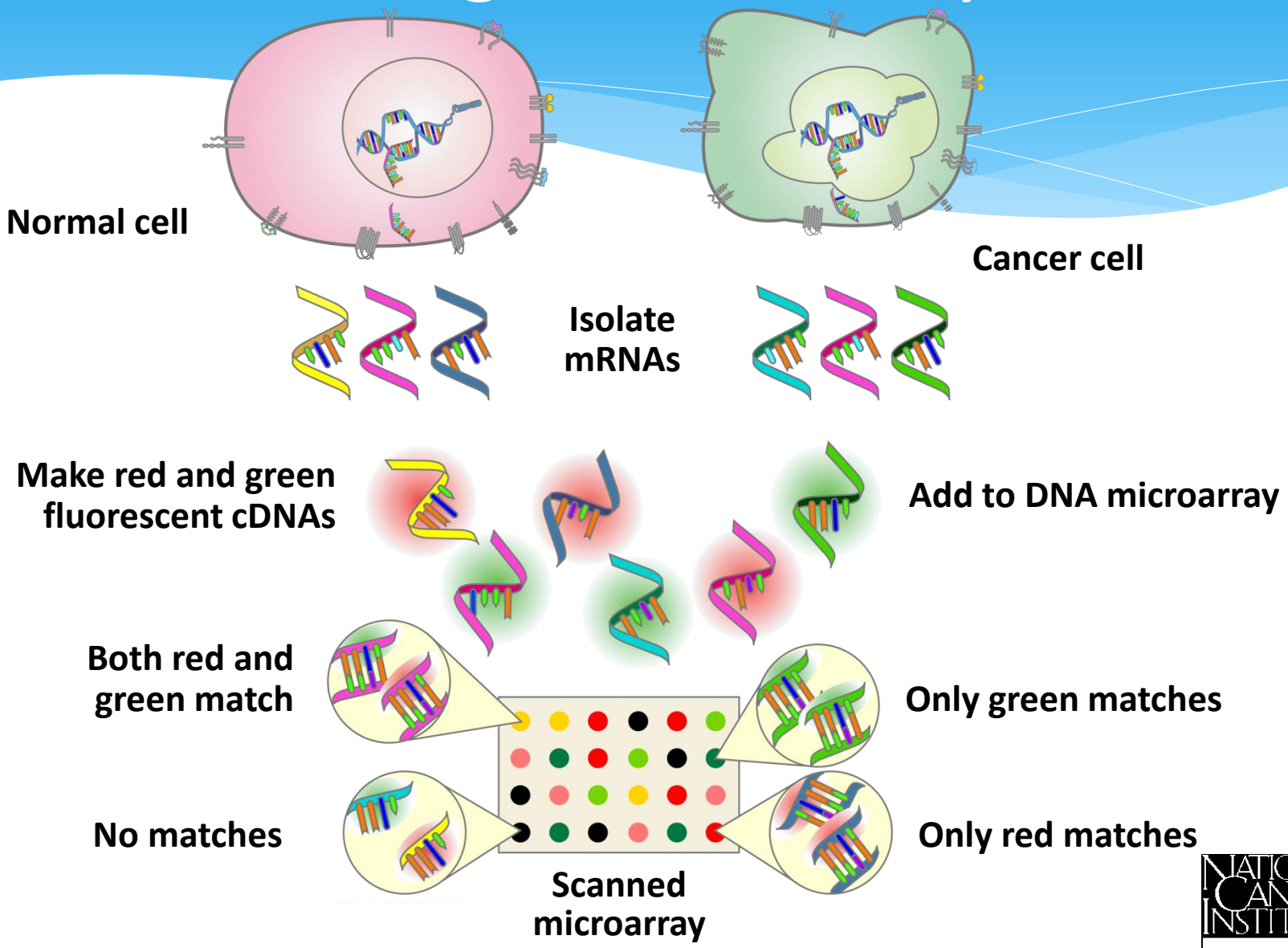

*Lynch et al. (2006)*

# Case Study – Mr. J




Stop codon – exon 17 (c.1975C>T;  p.Arg659*)

# Tumor Profiling - Microarray



# SNPs and Cancer Risk

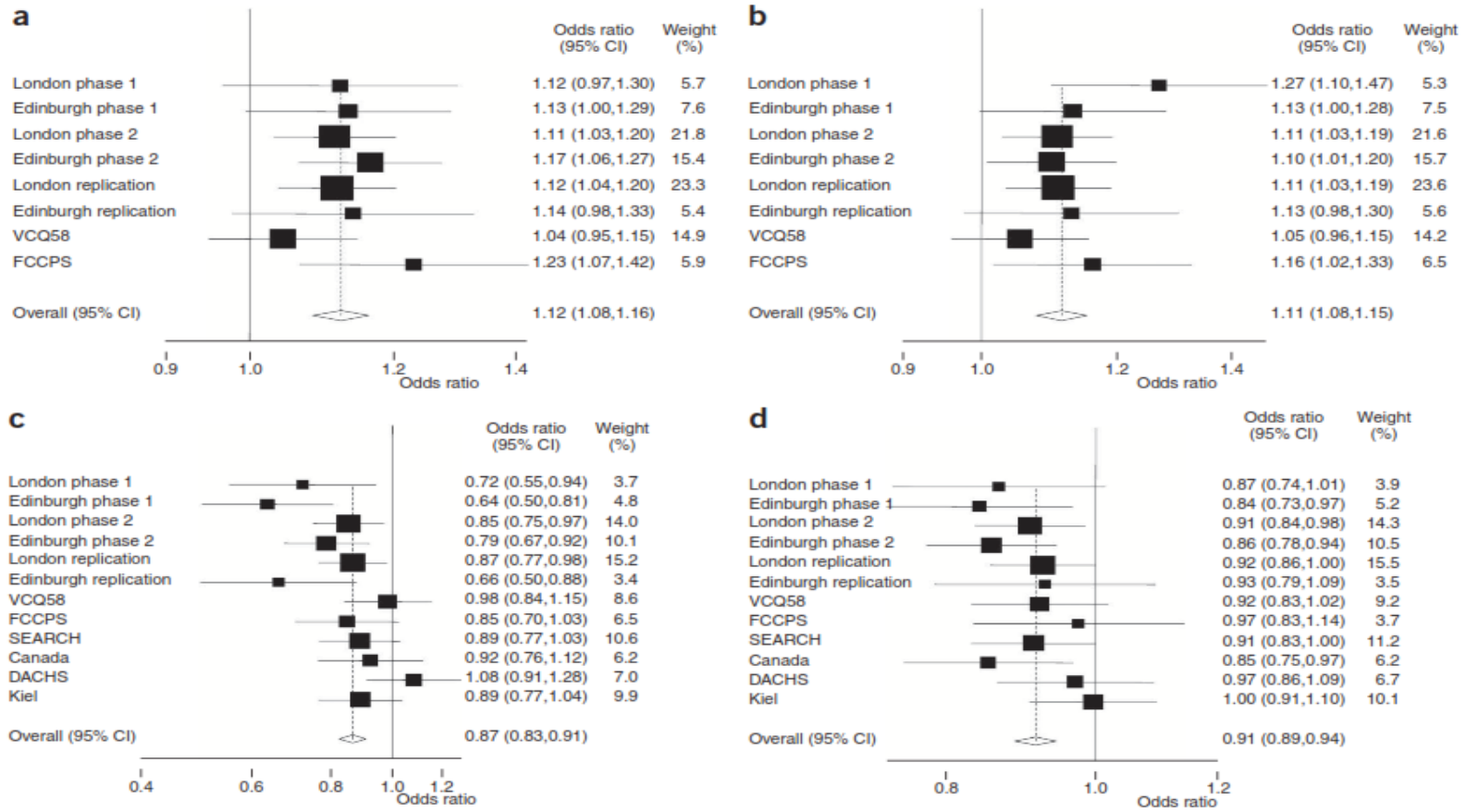
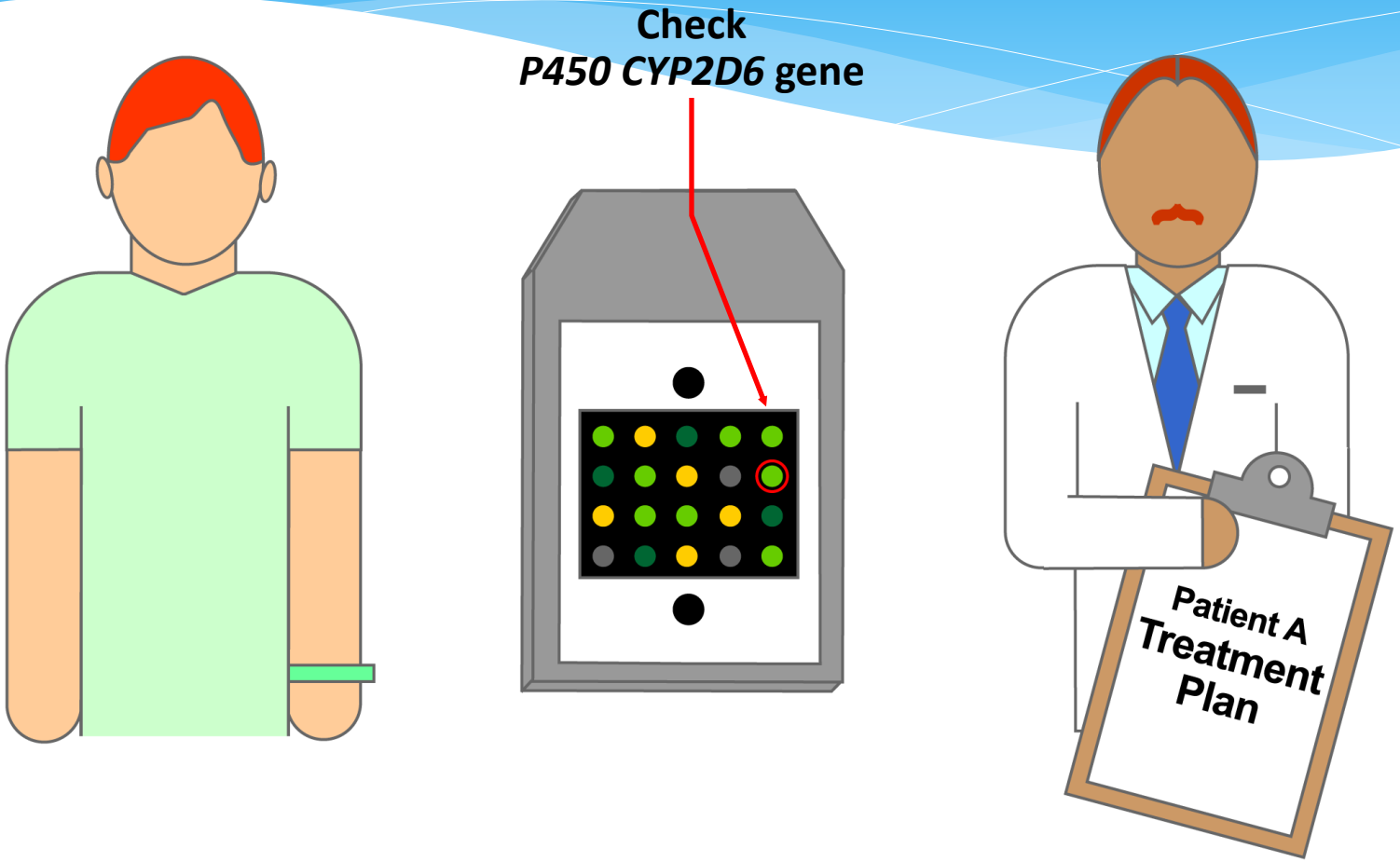


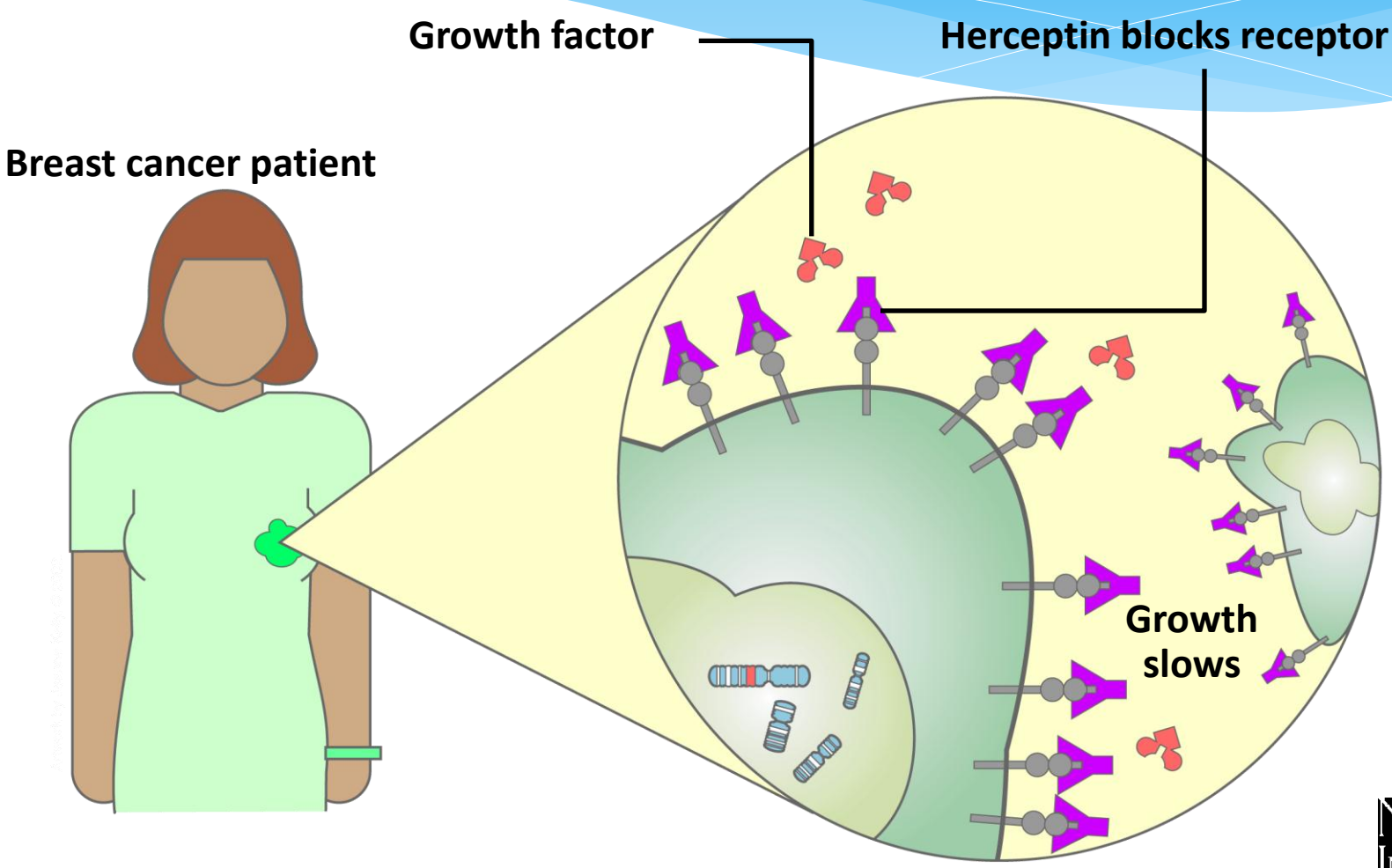

**Figure 2** Forest plot of effect size and direction for the four SNPs associated with CRC. (**a**) rs961253. (**b**) rs4444235. (**c**) rs10411210. (**d**) rs9929218. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% CIs. The diamond (and broken line) represents the summary OR computed under a fixed-effects model, with the 95% CI given by its width. The unbroken vertical line is at the null value (OR = 1.0).

Houlston et al 2008

# SNPs and Pharmacogenomics



# Targeted Therapy - Trastuzumab



# Targeted Therapy

**Table 1.** Selected Genetic Markers and Their Application in Cancer Treatment

| Tumor | Genetic marker | Description-application | Drug-implication |
|---|---|---|---|
| Breast | *HER2* amplification | *HER2*-positive tumors indicates need for additional therapy. | Trastuzumab, lapatinib |
| Breast | OncotypeDx® | Microarray analysis of 21 genetic markers. Identifies if patients with early stage ER-positive, lymph node negative, *Her2*-negative tumors may benefit from adjuvant chemotherapy. | Chemotherapy evaluation |
| Colorectal cancer | OncotypeDx® | Microarray analysis of 12 genetic markers. Identifies if patients with stage II disease may benefit from adjuvant chemotherapy. | Chemotherapy evaluation |
| | *KRAS* mutation | Tumors with a *KRAS* mutation do not respond to treatment with EGFR monoclonal antibodies. *KRAS* status should be evaluated prior to treatment. | Cetuximab, panitumumab contraindicated |
| | *UGT1A1*28* | Patients with a germline *UGT1A1* variant are at risk for higher toxicity (especially neutropenia, diarrhea). | Irinotecan; consider dosage adjustment or alternate drug |
| Leukemia | *BCR-ABL* | Ph + CML; Ph + ALL. Presence of a BCR-ABL gene mutation indicates response to tyrosine kinase inhibitor therapy. | Imatinib, dasatinib, nilotinib |
| Non-small-cell lung cancer | *EGFR* mutation | *EGFR* mutation is associated with a better response to an EGFR-tyrosine-kinase inhibitor. | Erlotinib, geftinib |
| Breast, ovarian | *BRCA1/BRCA2* mutation | Patients with a germline *BRCA* gene mutation who have disease progression following initial therapy may respond to treatment with PARP inhibitors. | Olaparib, for example |
| Melanoma | *BRAF* V600E mutation | Tumors with this *BRAF* mutation are sensitive to a kinase inhibitor | Vemurafenib indicated |

*Note.* ER = estrogen receptor; EGFR = epidermal growth factor receptor; Ph = Philadelphia chromosome; CML = chronic myelogenous leukemia; ALL = acute lymphoblastic leukemia; PARP = poly ADP ribose polymerase.

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# Case Study – Mr. J

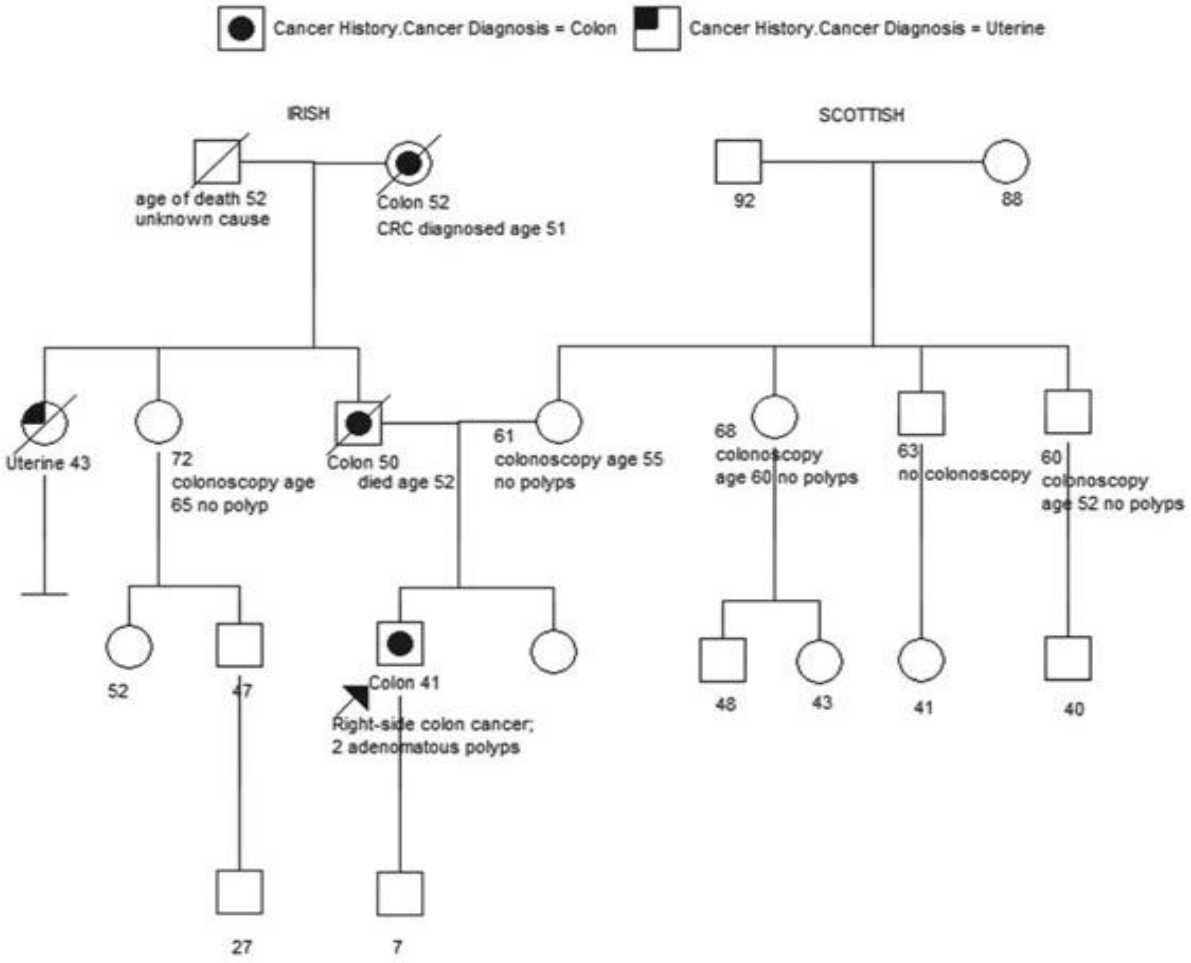


**Figure 1.** Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).

Santos et al 2013

# Case Study – Mr. J

* **MSI – Important to guiding treatment decision-making in early stage colon cancer**
* **IHC – Important to guiding genetic testing strategy**
* **Mutation detection – Important to guiding genetic counseling/testing for at-risk family members**

# Closing Remarks

* **Genomic care is now central to the care of patients with cancer**
* **Nurses must be aware of developments in genomics and its impact in the cancer care continuum to help educate patients and support informed decision-making**