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

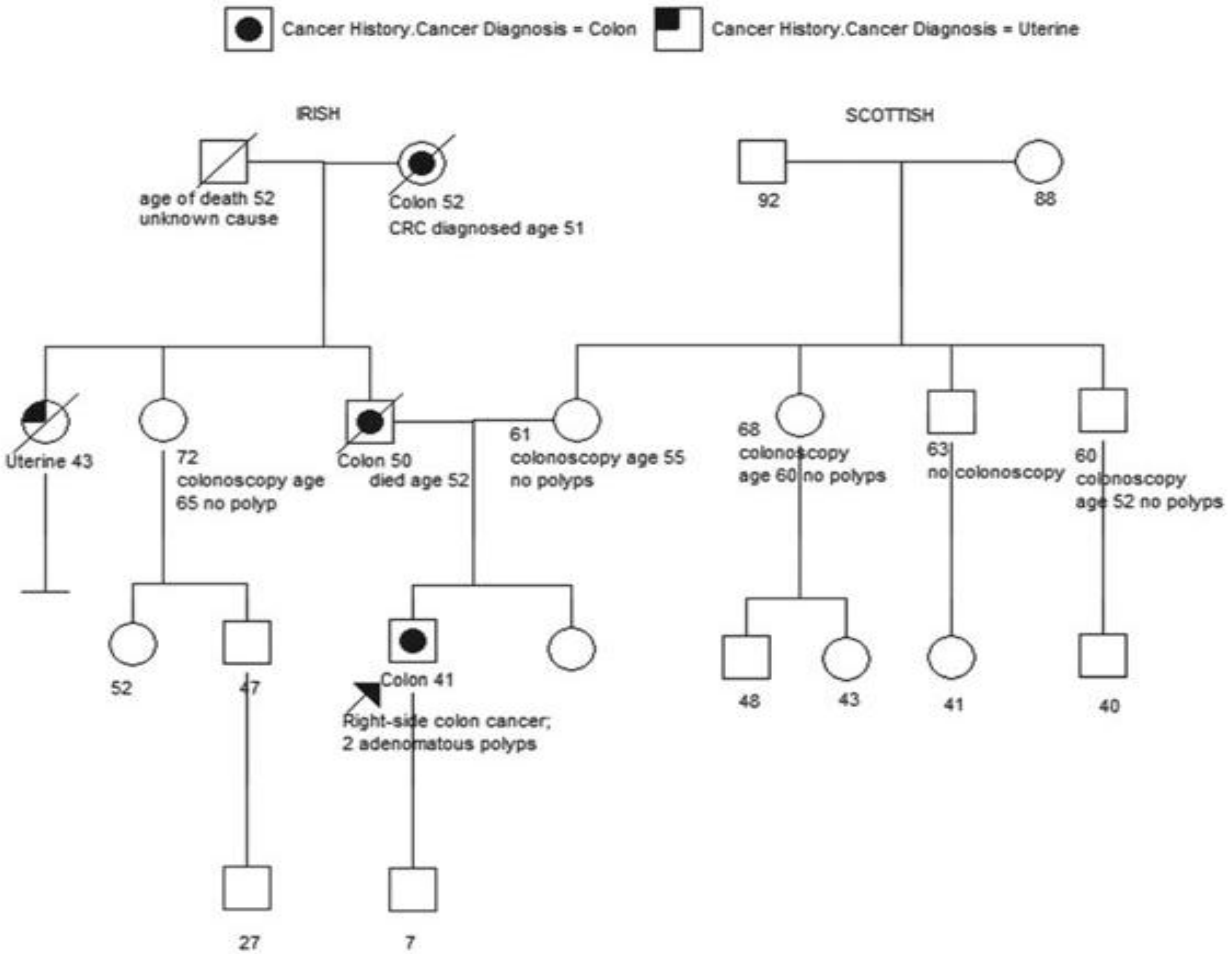

Figure 1. Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).

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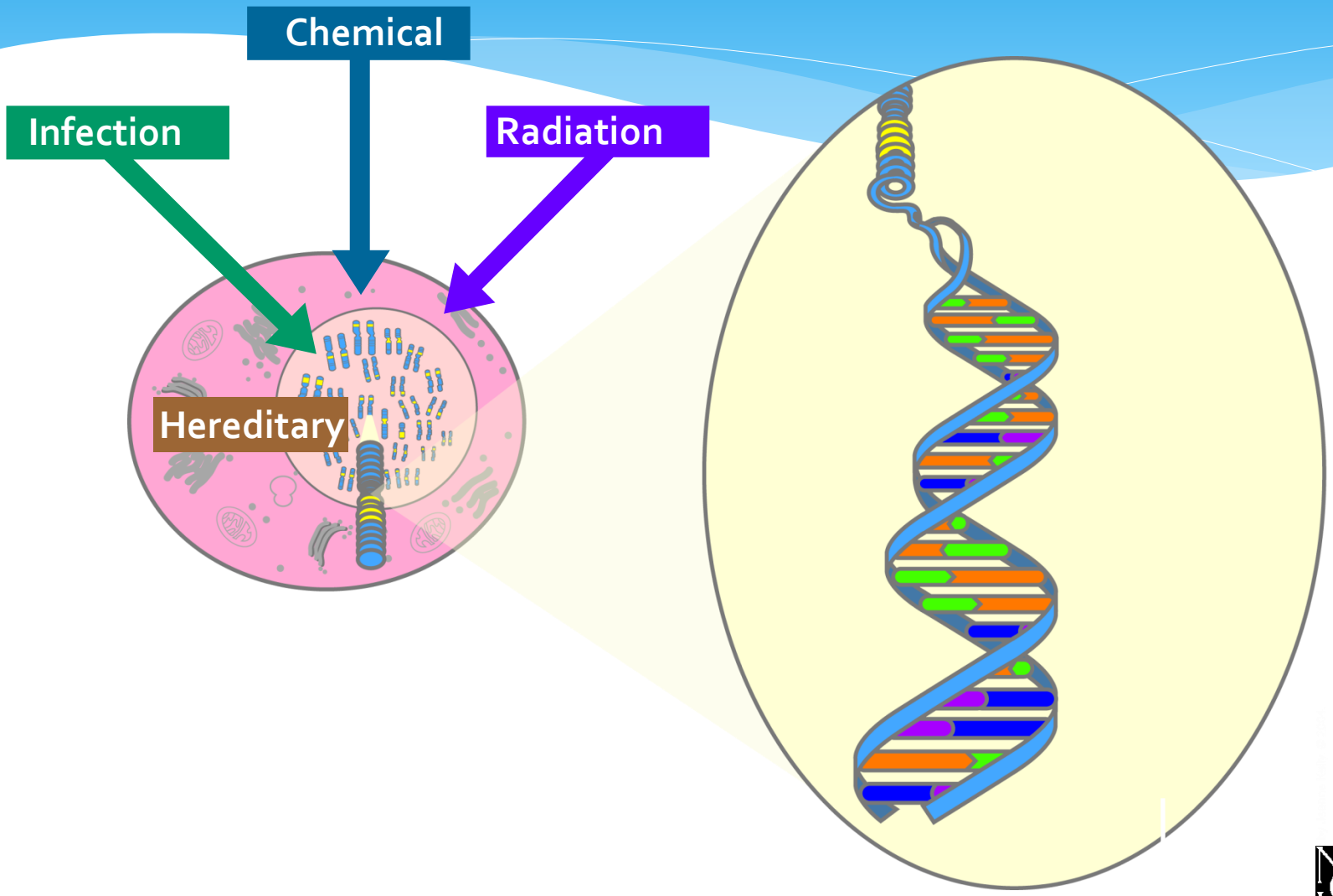
Etiology of Cancer



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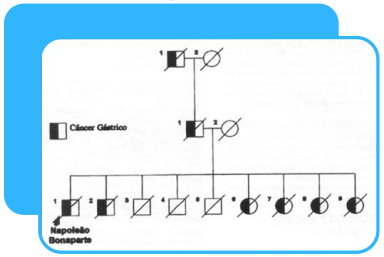
Etiology of Cancer

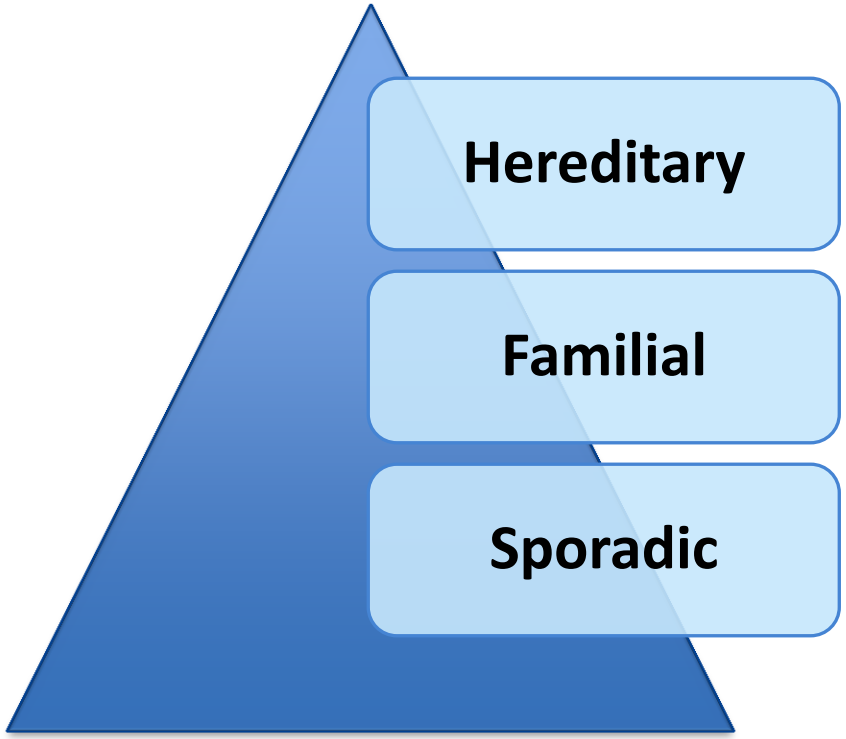
Risk factors

- 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

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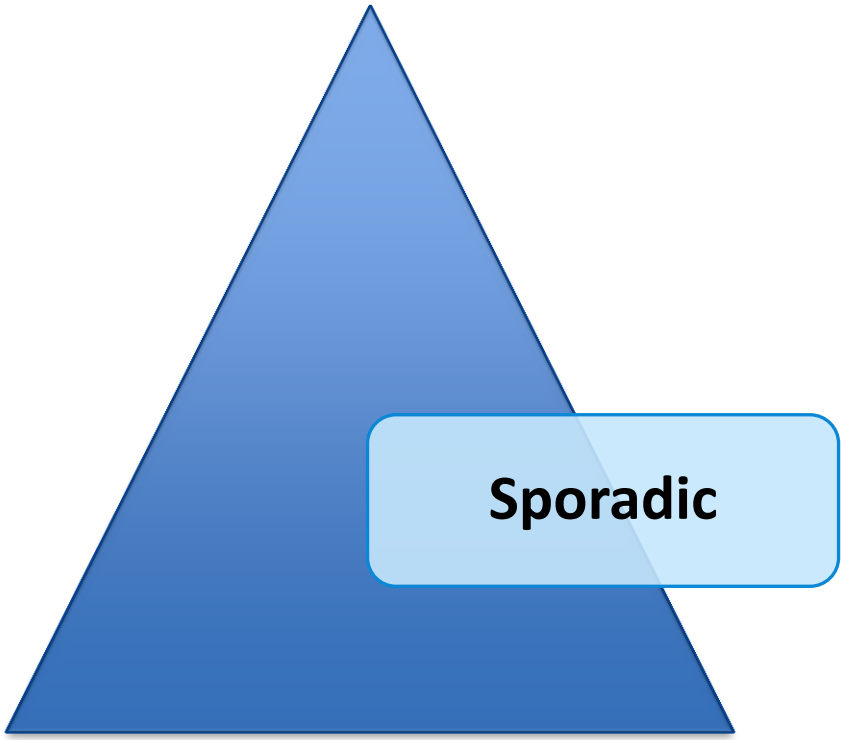
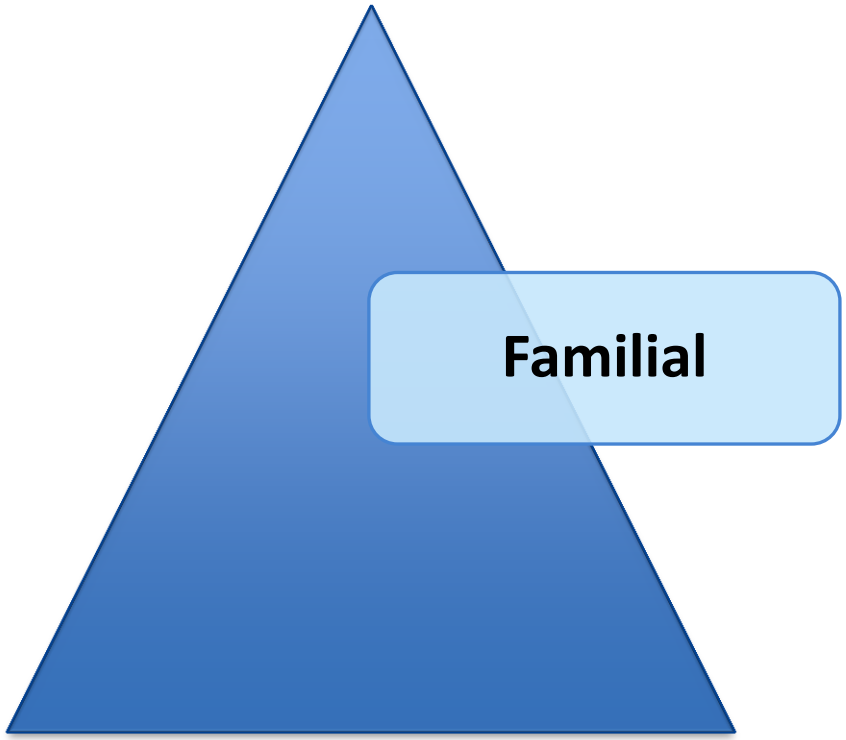


75% of all cancers
Age of onset typically that expected for the type of cancer
Somatic (acquired) mutations in a specific tissue (e.g., breast, colon)

Etiology of Cancer

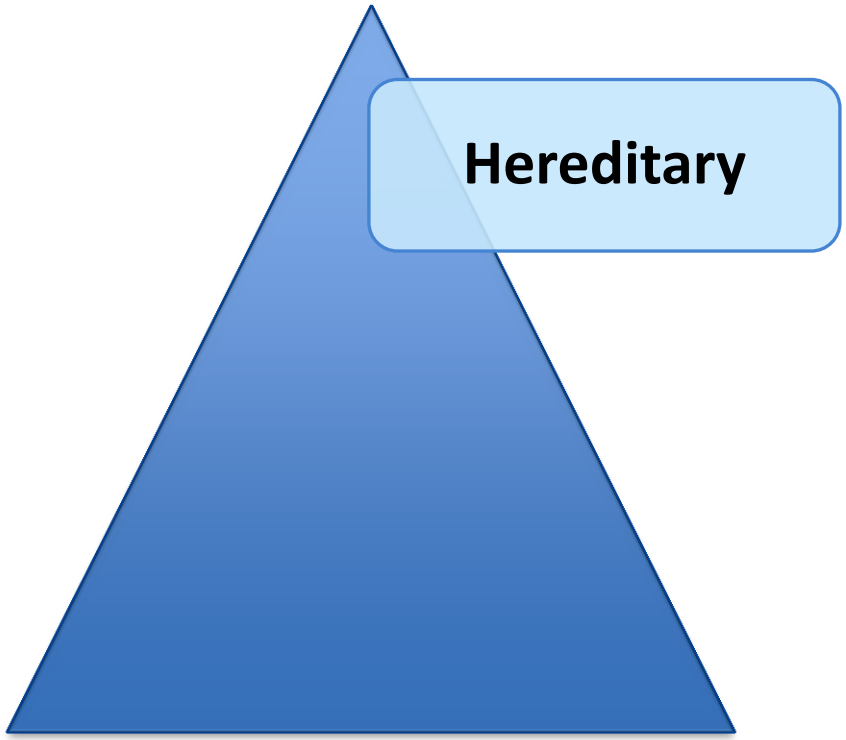
Classification of Tumors Due to Family History



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

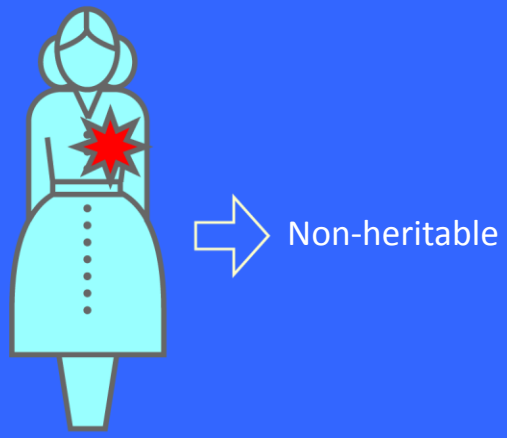


5%-10 of all cancers
Earlier age at onset than usual
May or may not have FH of same cancer or other cancers associated with a cancer syndrome
Single gene mutation in the germline (egg or sperm)

Etiology of Cancer

Somatic mutations

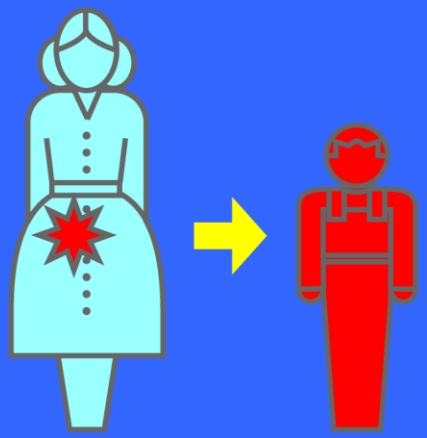
- Occur in non-germline tissues
- Are not heritable



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

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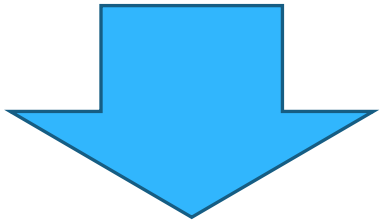
modified

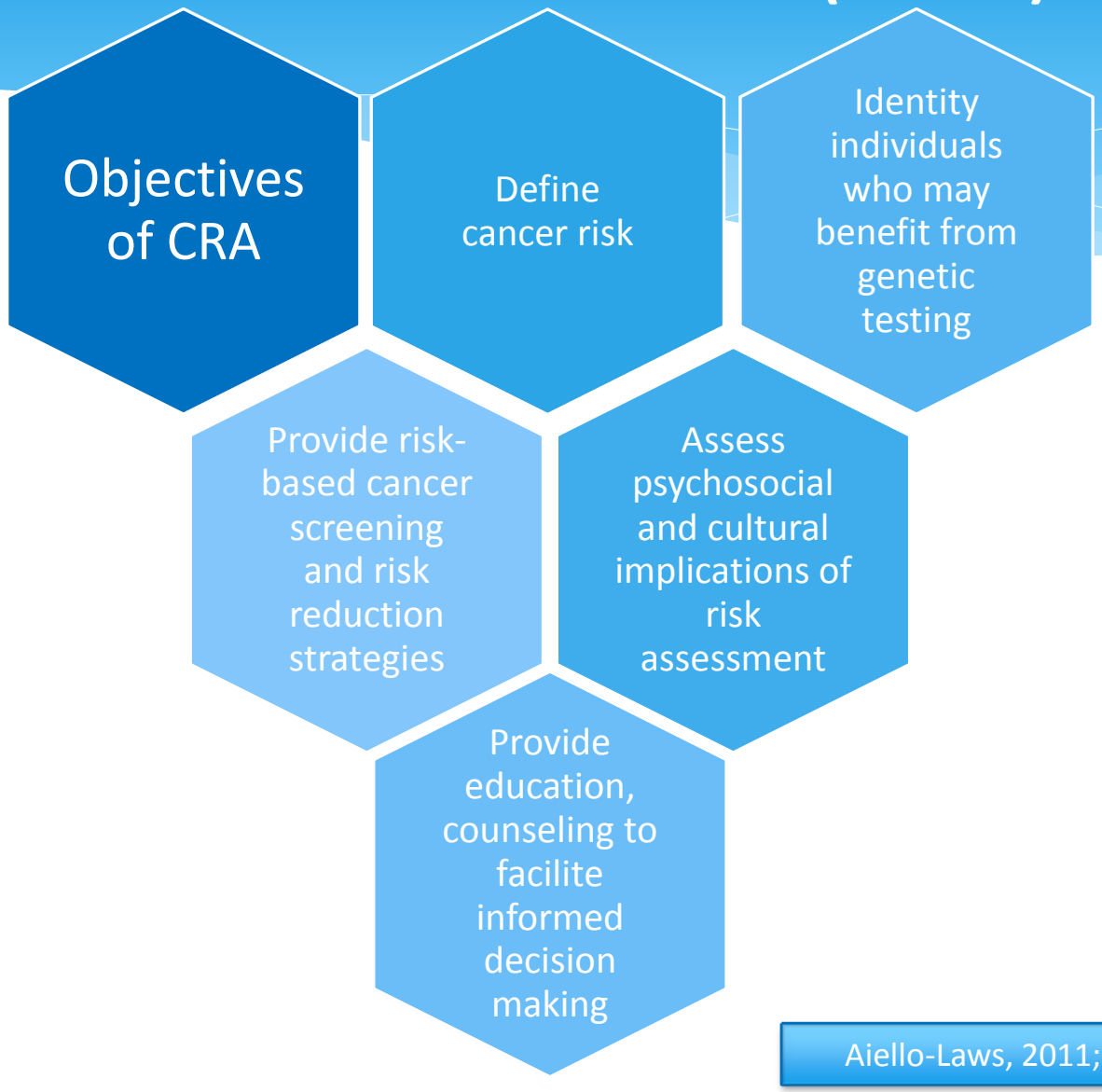
Etiology of Cancer

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

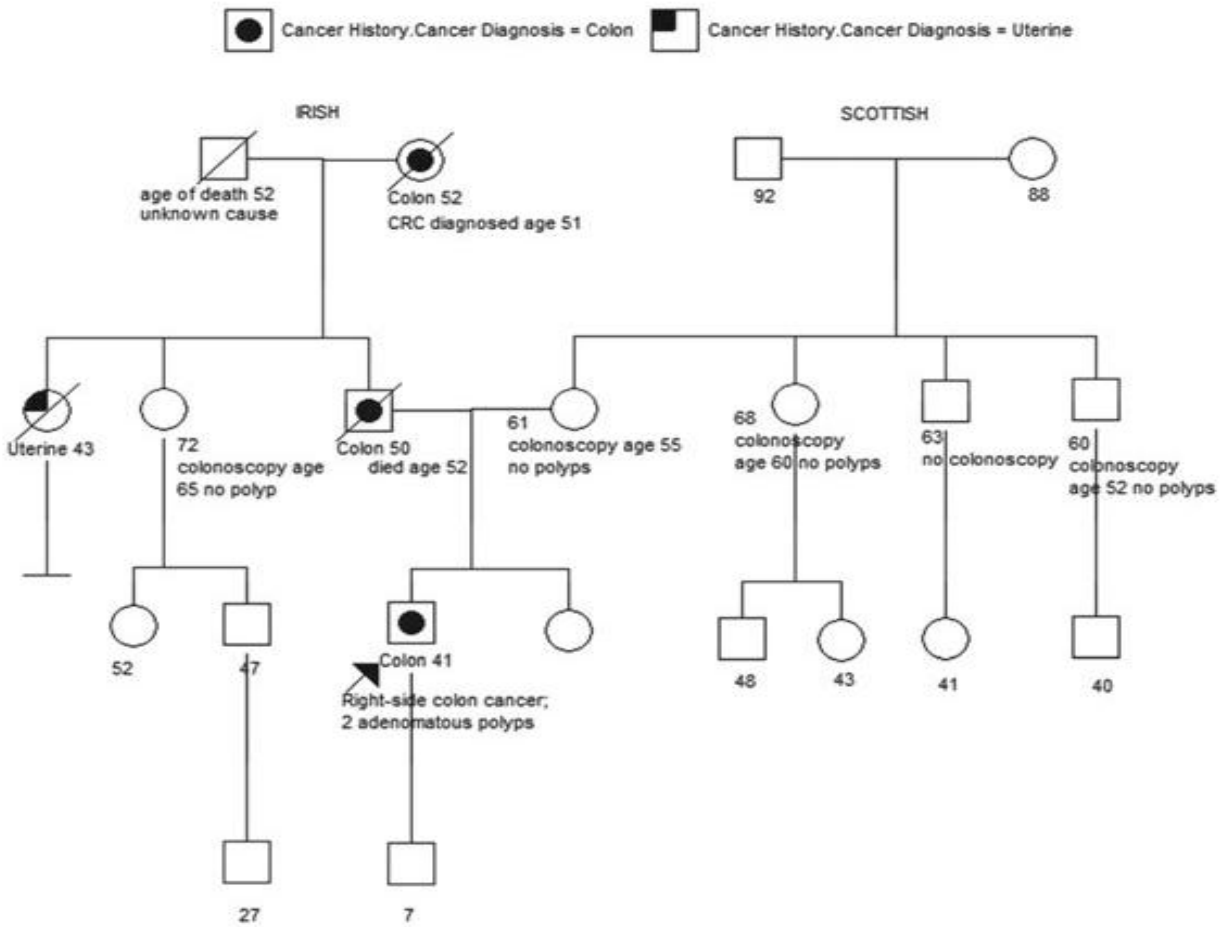


Figure 1. Four-generation pedigree with significant family history of colon and uterine cancers, in the paternal lineage; suspect for Lynch syndrome (fictitious case).

Santos et al 2013

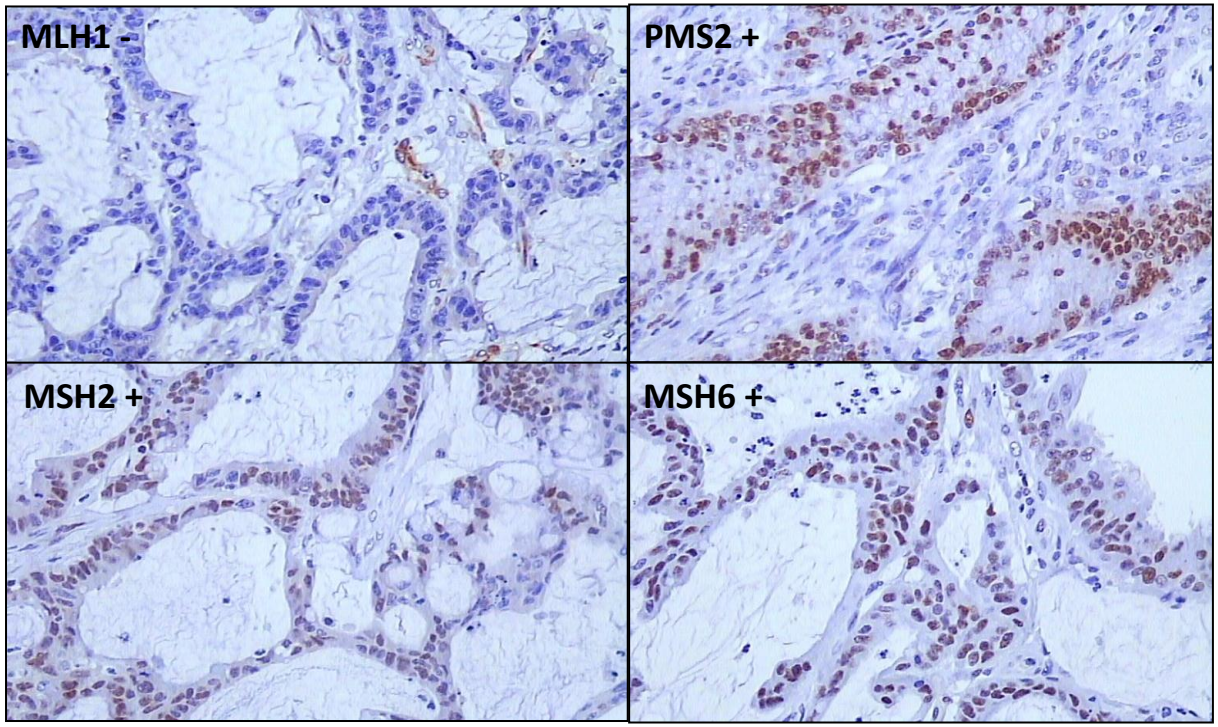
Tumor Profiling

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

Dacic 2011

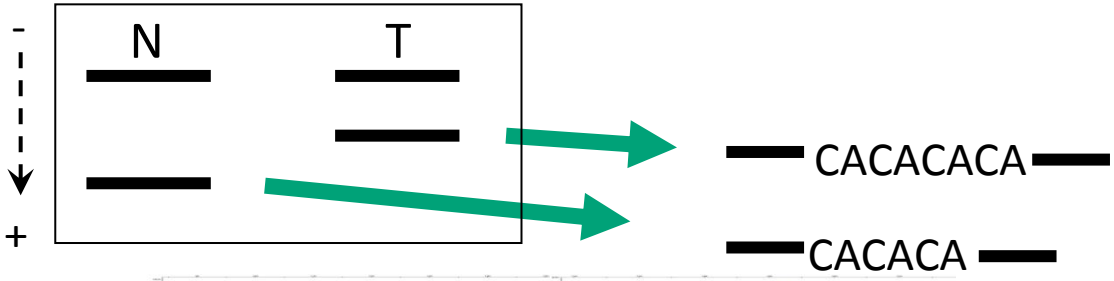
Case Study – Mr. J

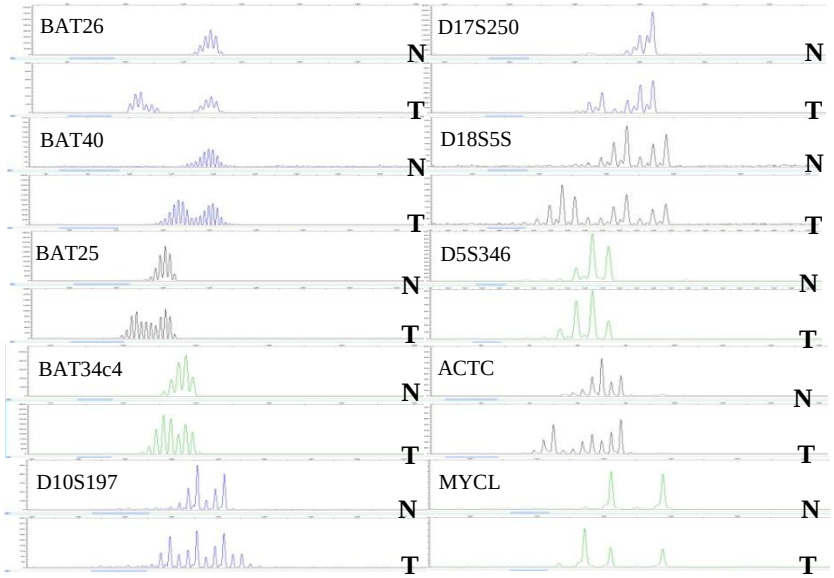
Immuhistochemistry – test for protein expression of 4 genes associated with colorectal cancer
Result: absence of MLH1 expression



Case Study – Mr. J

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





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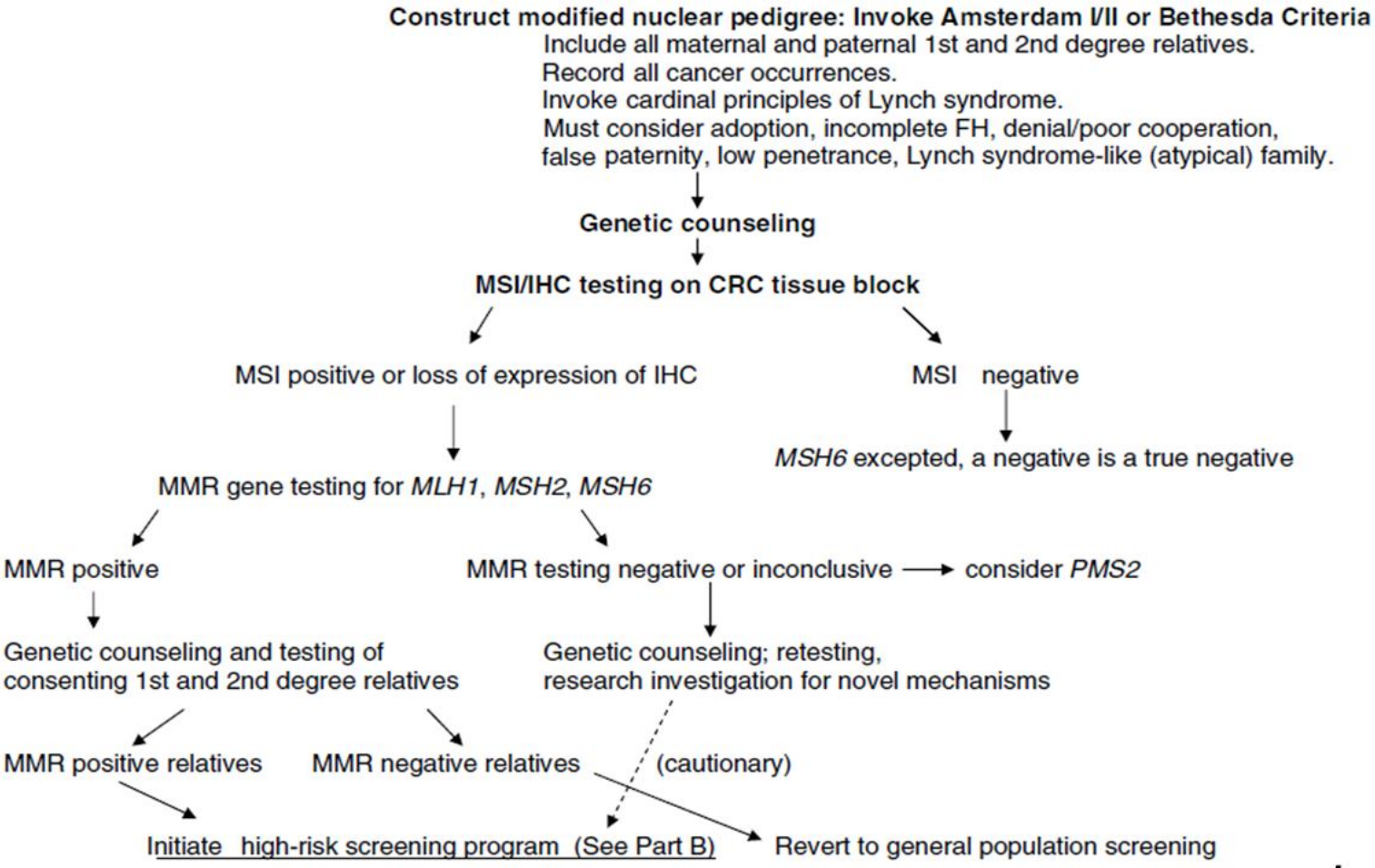
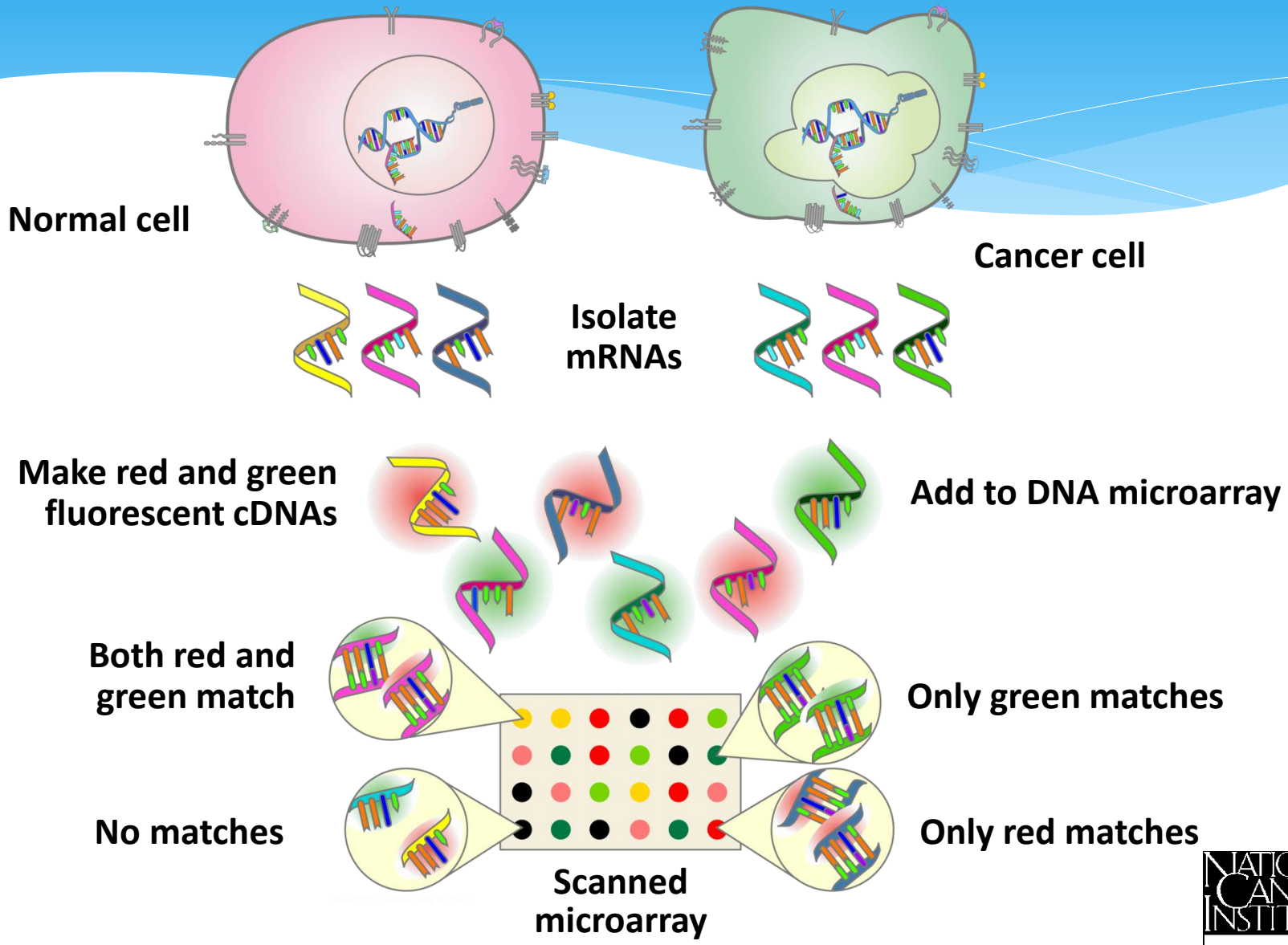


Lynch et al. (2006)

Case Study – Mr. J

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

Tumor Profiling - Microarray



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SNPs and Cancer Risk

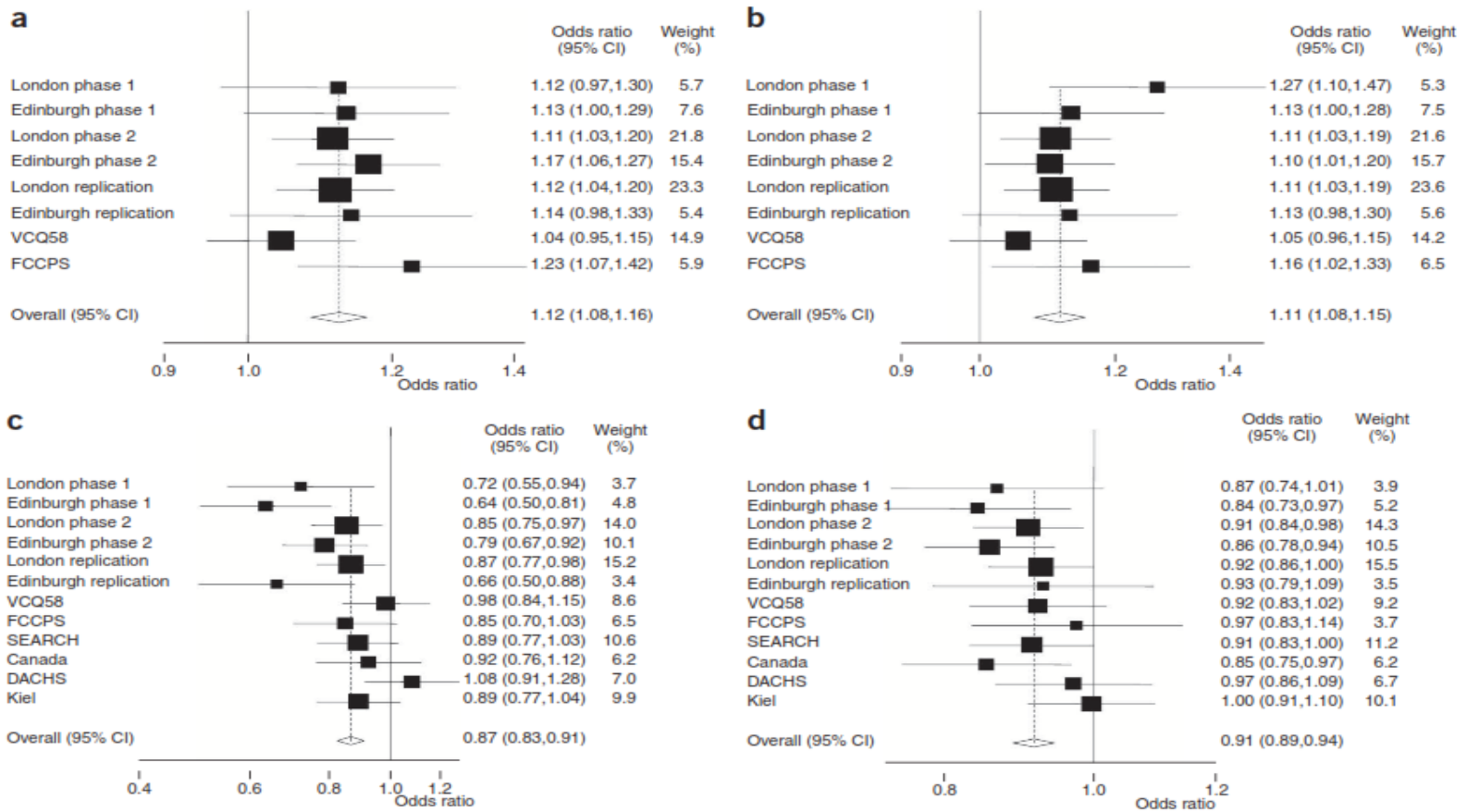
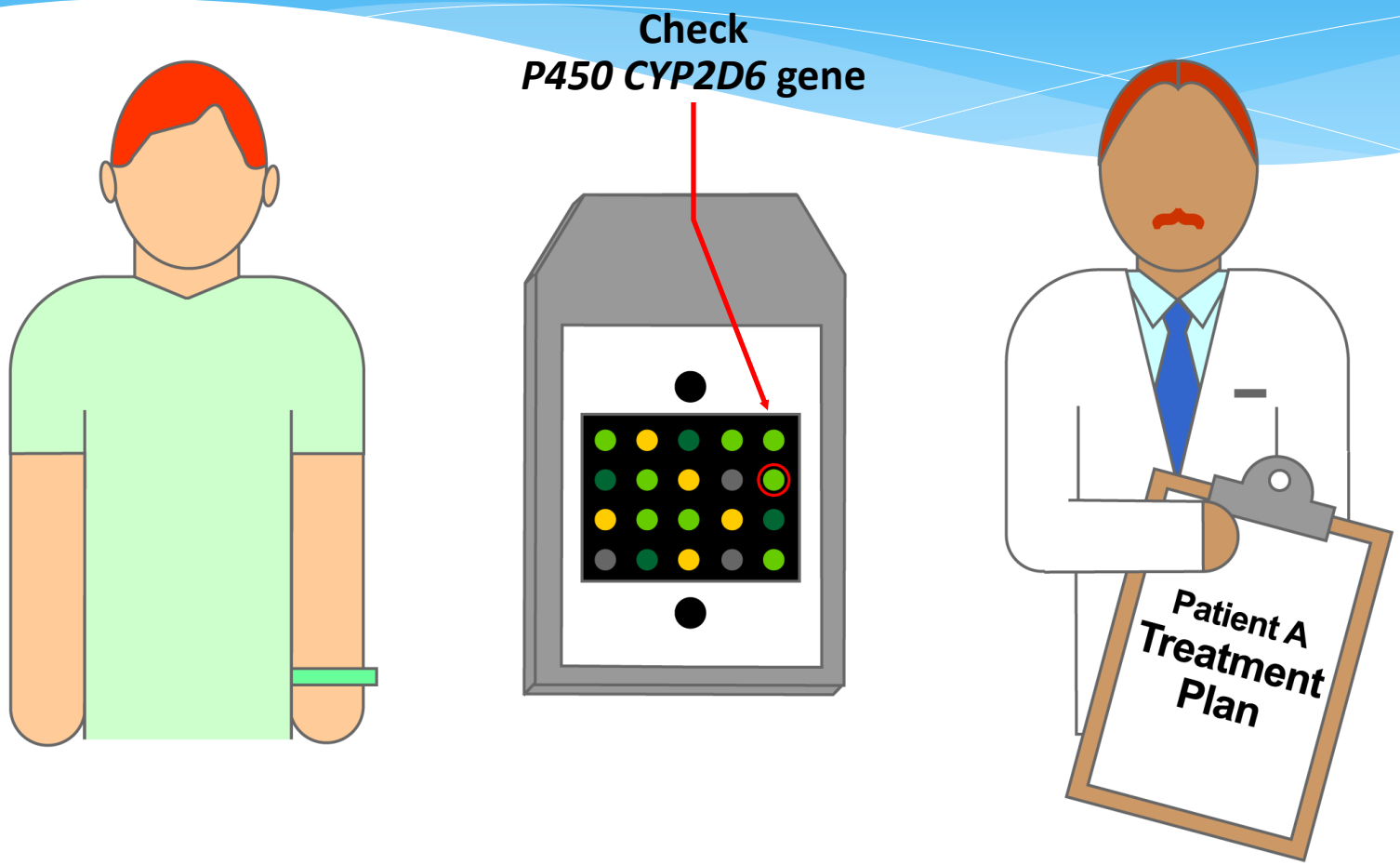


Figure 2 Forest plot of effect size and direction for the four SNPs associated with CRC. (**a**) rs961253. (**b**) rs4444235. (**c**) rs10411210. (**d**) rs9929218. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines 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



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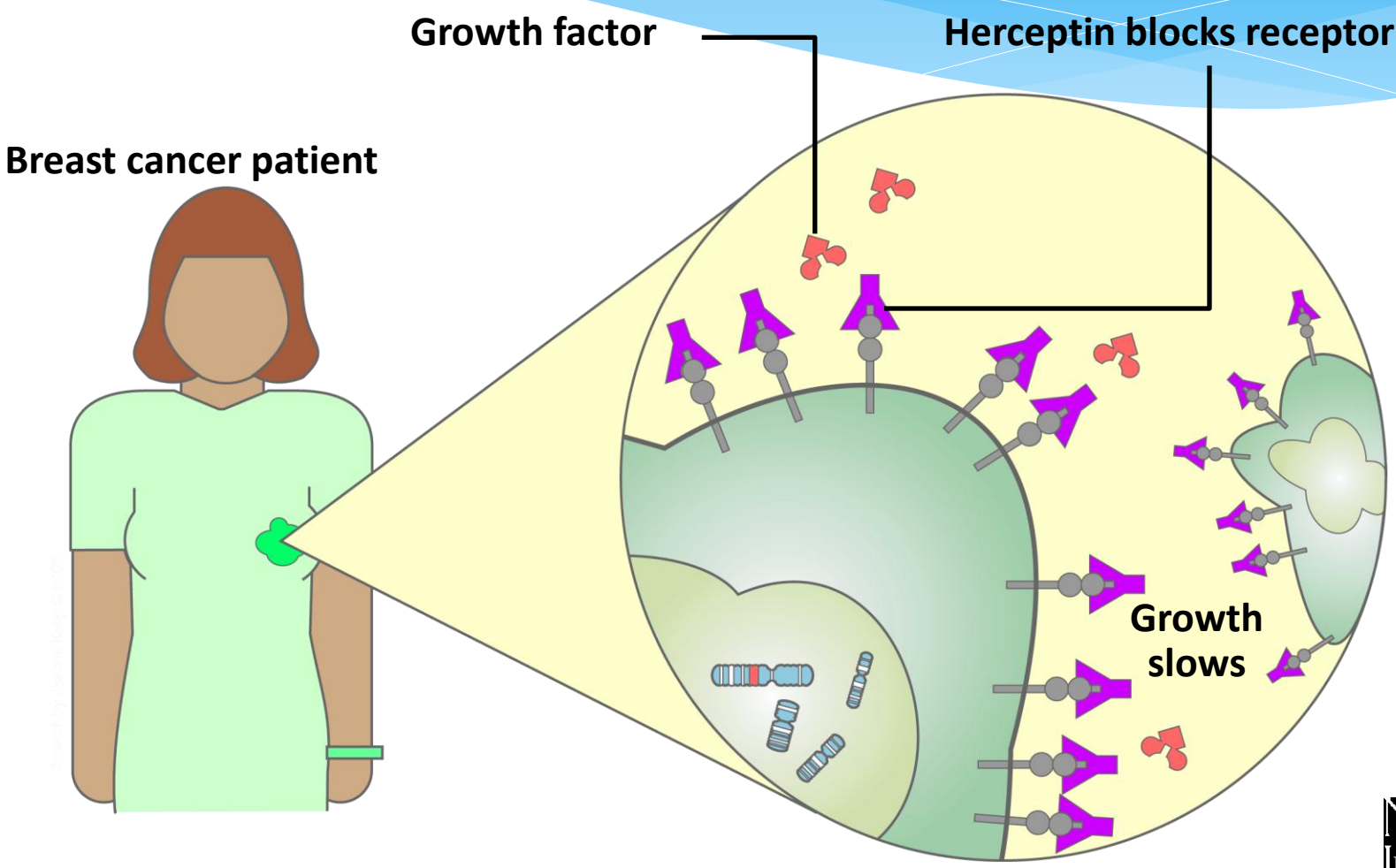
Targeted Therapy - Trastuzumab



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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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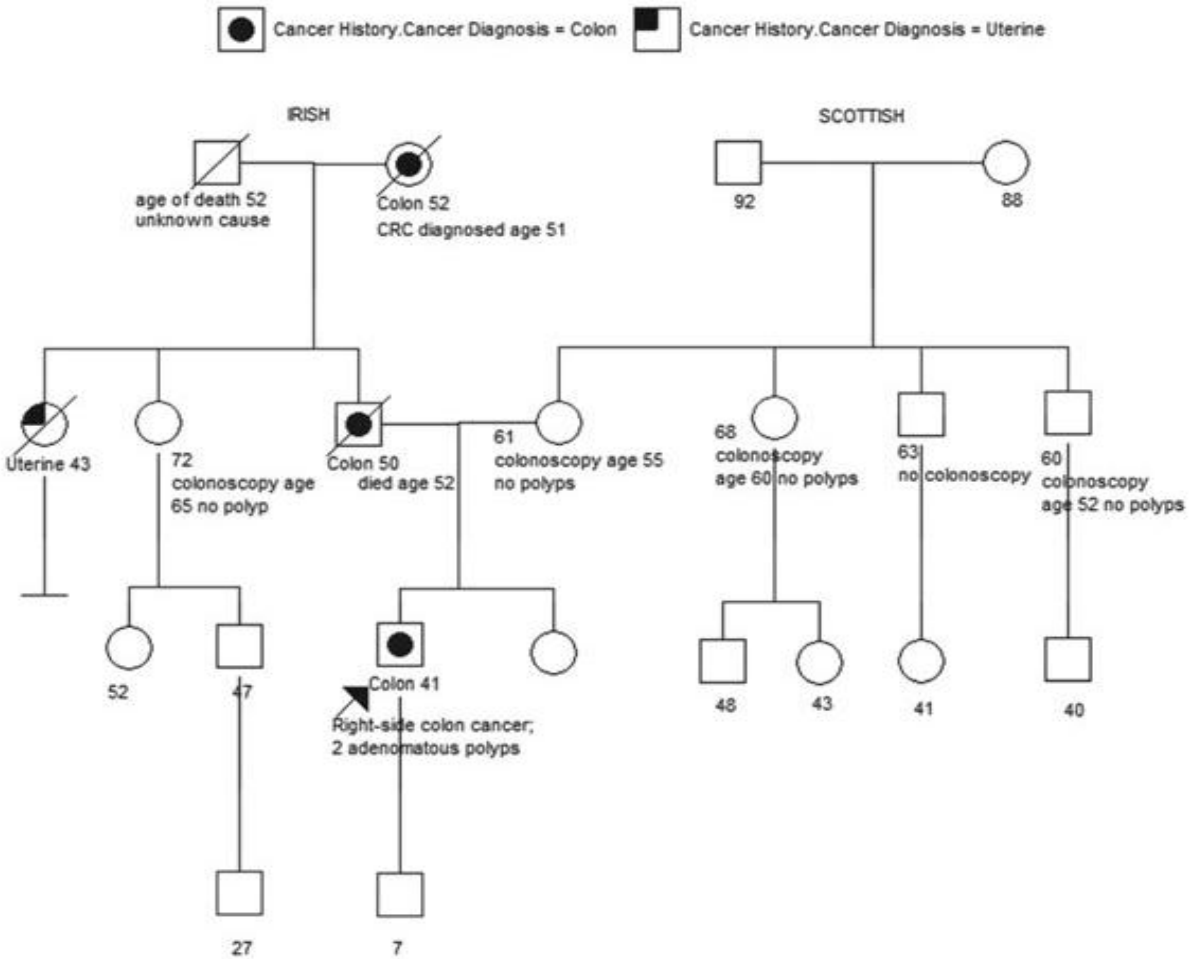
Case Study – Mr. J



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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**