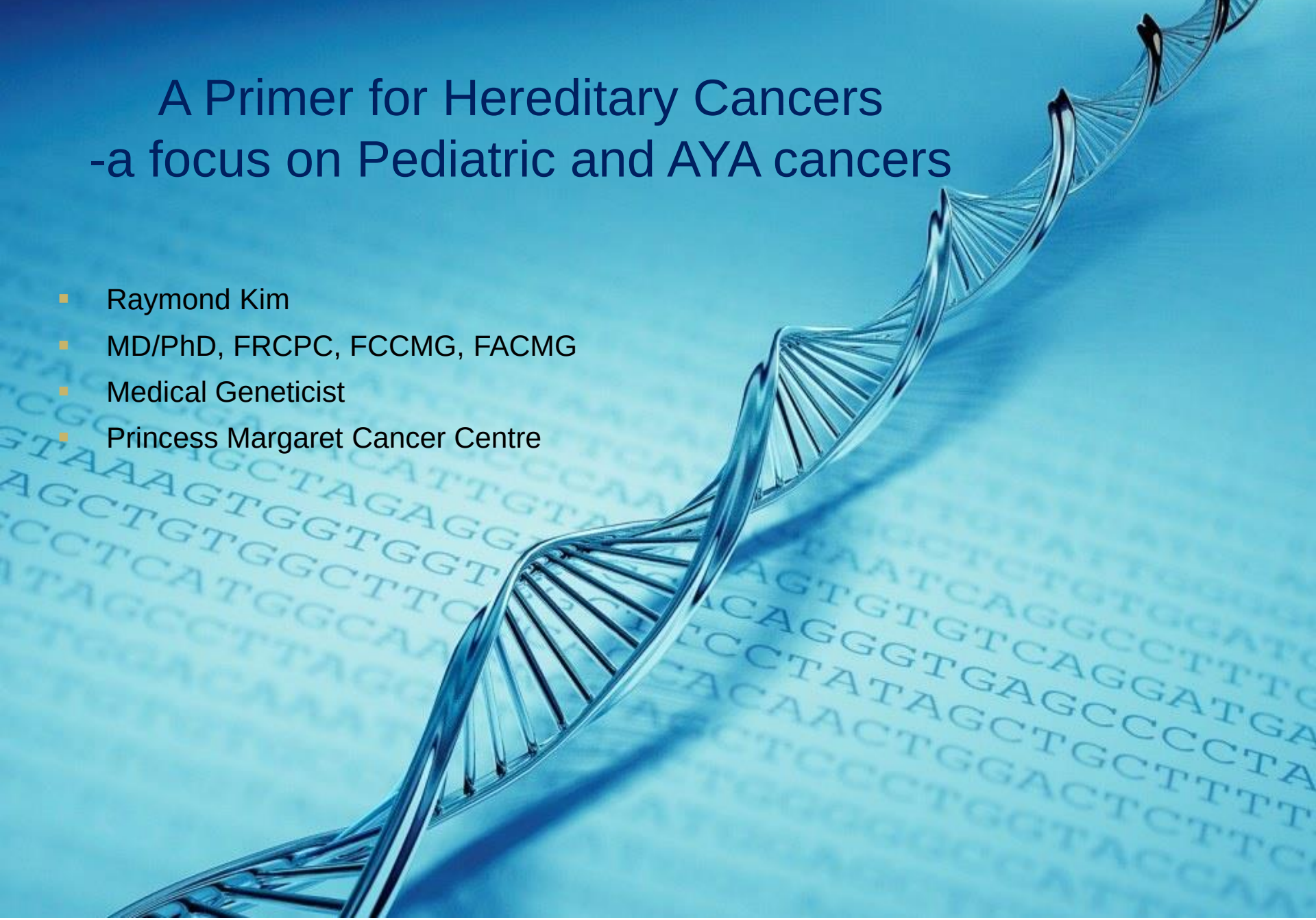
A Primer for Hereditary Cancers -a focus on Pediatric and AYA cancers



- Raymond Kim
- MD/PhD, FRCPC, FCCMG, FACMG
- Medical Geneticist
- Princess Margaret Cancer Centre

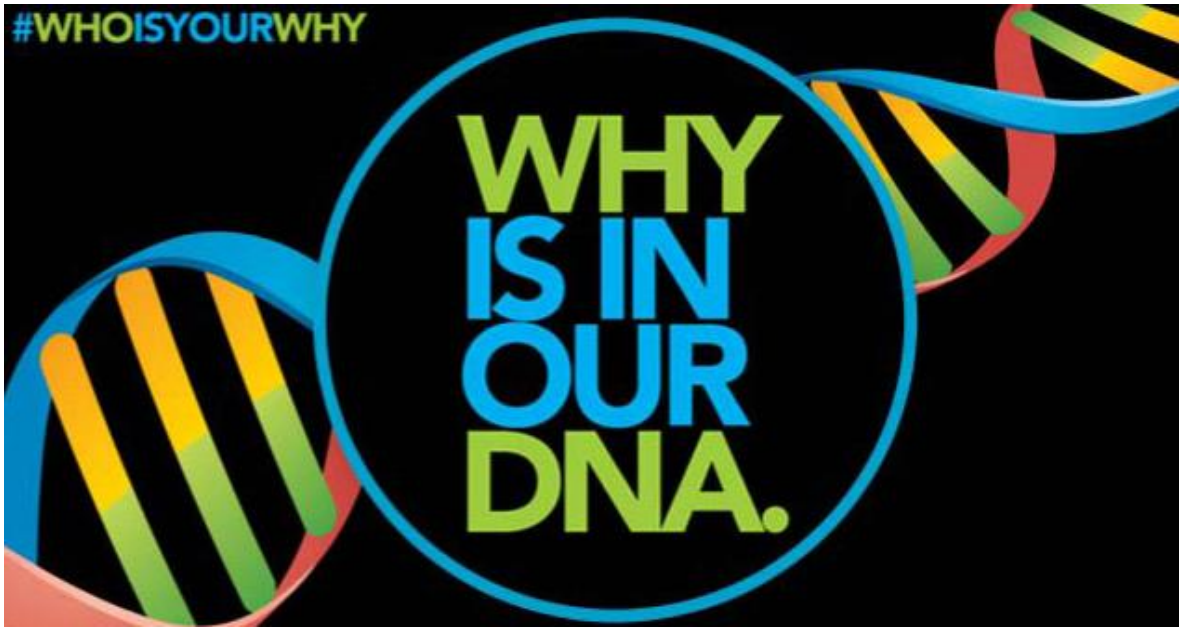
UHN Princess Margaret Cancer Centre

Presenter Disclosure

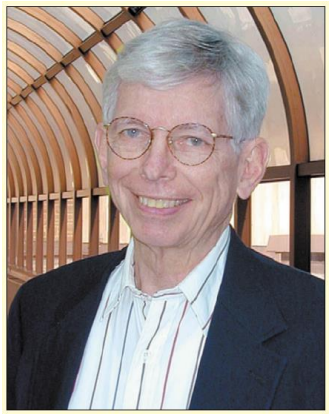
- **Relationships with financial sponsors:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Patents**: N/A
  - **Other:** N/A

Outline

- Genetic terminology and concepts
- Hereditary cancers
  - When to consider
  - Genetics assessment
- Pathology and genes
- Genetic testing
- Genetic counselling



Cancer is a genetic disease



Proc. Nat. Acad. Sci. USA
Vol. 68, No. 4, pp. 820–823, April 1971

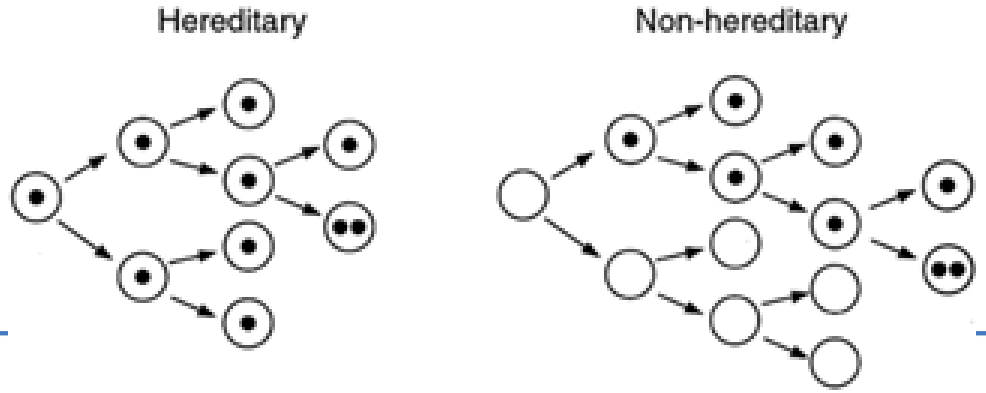
Mutation and Cancer: Statistical Study of Retinoblastoma

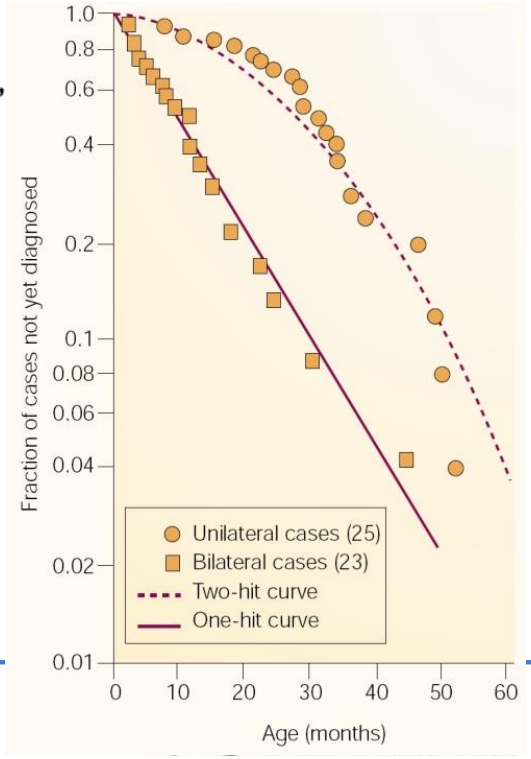
ALFRED G. KNUDSON, JR.

Graduate School of Biomedical Sciences and M. D. Anderson Hospital and Tumor Institute, The University of Texas at Houston, Houston, Texas 77025

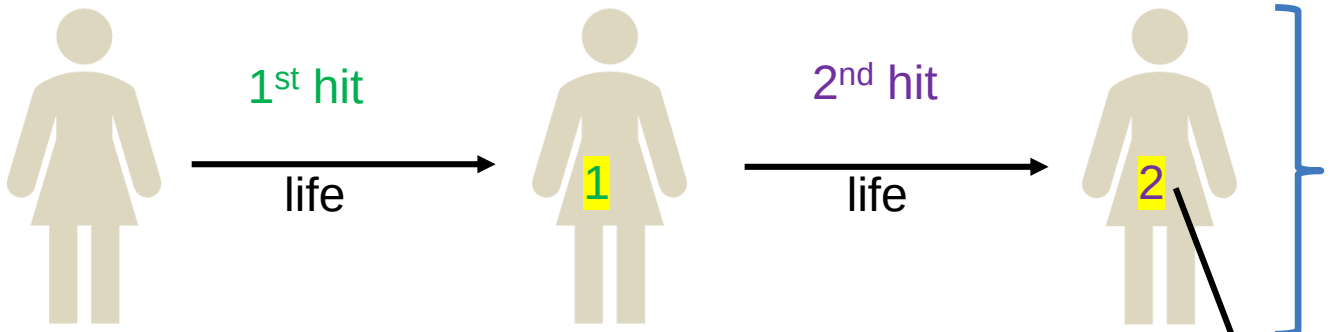
Communicated by James V. Neel, February 8, 1971

RETINOBLASTOMA
TWO MUTATIONS





Sporadic/acquired cancer (90%)

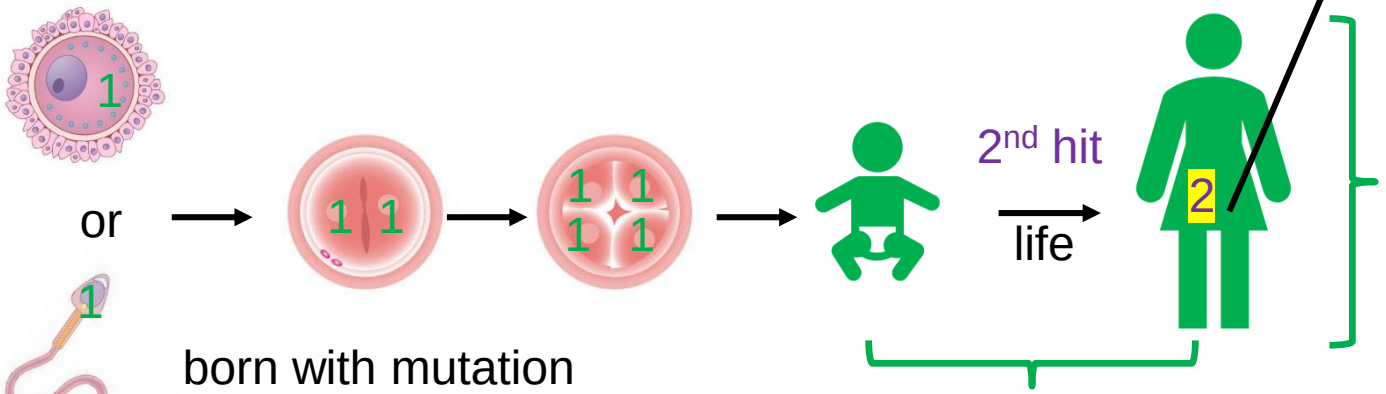


-No other tissues have mutation
-Blood testing no mutations

"normal" genes at birth

Two hits tumour growth, (all cancers*)

Hereditary cancer (10%)



-All tissues have first mutation
-at risk of more cancers

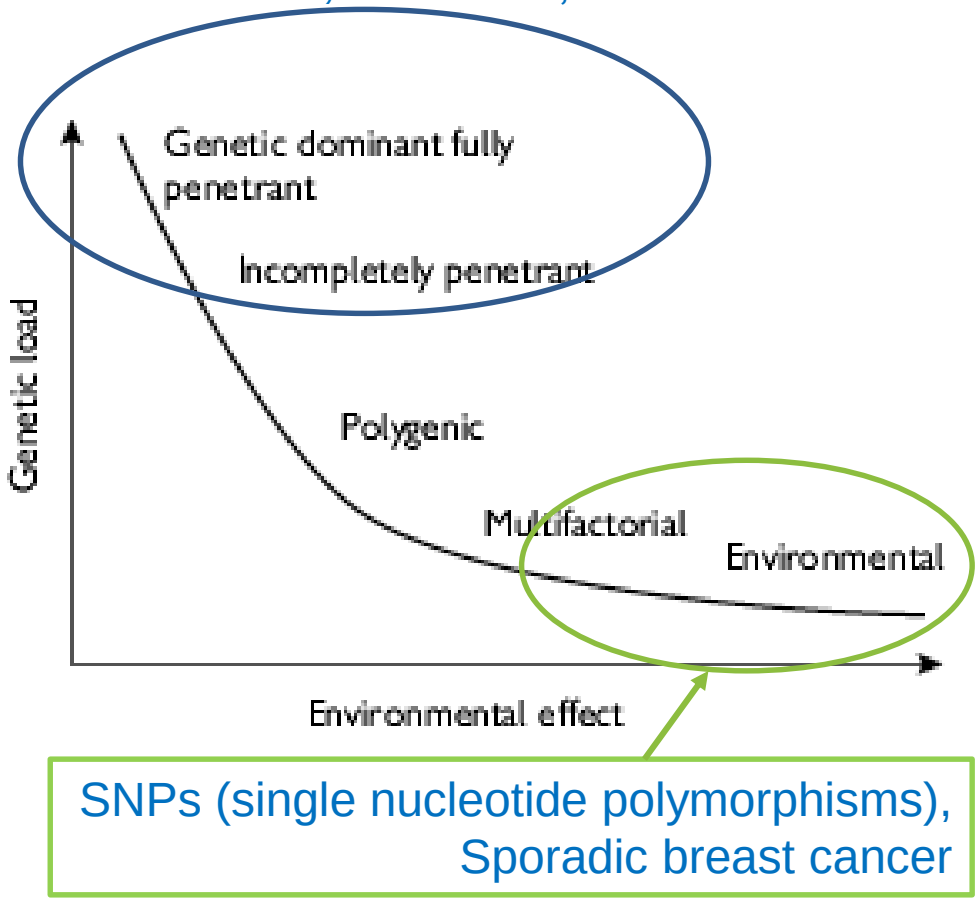
Blood testing mutation detected

Family tree with a pattern
Unusual tumours
Multiple cancers in same individual
Young cancers ~10 years earlier

Who do medical geneticists see?

- All diseases have a genetic component
- Not all diseases require a medical genetics consultation
- Continuum of genetic contribution
  - Many genes interacting with environment (multifactorial)
    - Coronary artery disease
  - Few genes interacting with environment (poly-genic)
    - Diabetes mellitus, IBD
  - **Single gene interacting with environment (incomplete penetrance)**
    - **Hereditary cancer**
  - **Single gene (fully penetrant)**
    - **Huntington disease, Sickle cell anemia**

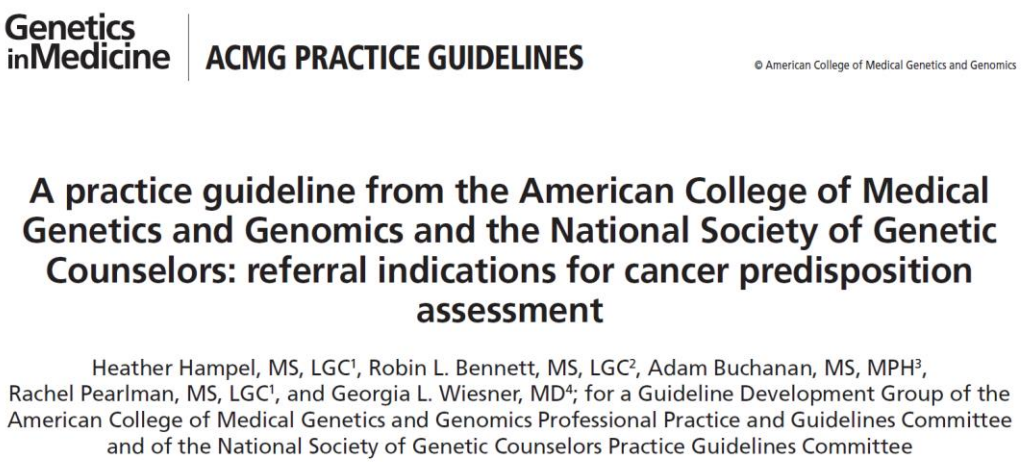
BRCA, CFTR etc, "mutations"



SNPs (single nucleotide polymorphisms), Sporadic breast cancer

Hereditary cancer syndromes

- Over 50 syndromes catalogue in 2008
- Over 300 syndromes entered into OMIM (Online Mendelian Inheritance in Man)
- **<u>Under-recognized and under-referred</u>**
- Germline genetic testing results affect
  - Surveillance
  - Surgical management
  - Eligibility for trials
- Distinct from somatic profiling of the tumour for targeted therapy (non-inherited changes in tumours)


Genetics inMedicine | ACMG PRACTICE GUIDELINES

A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment

Heather Hampel, MS, LGC[1], Robin L. Bennett, MS, LGC[2], Adam Buchanan, MS, MPH[3], Rachel Pearlman, MS, LGC[1], and Georgia L. Wiesner, MD[4]; for a Guideline Development Group of the American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and of the National Society of Genetic Counselors Practice Guidelines Committee

Li-Fraumeni syndrome, the exemplar of Pediatric and AYA cancers

- Choroid plexus Carcinoma
- Adrenocortical carcinoma
- Young Breast Cancer
- Medulloblastoma
- Wilm's Tumour
- Brain cancer
- Rhabdomyosarcoma
- Colon cancer

- Germline Mutation in TP53
- Li-Fraumeni syndrome
- L breast cancer @24
- R breast cancer @25
- R shoulder sarcoma @31
- R lung cancer @44
- Papillary thyroid cancer@44
- c.743G>A; p.Arg248Gln

- Risk of sarcoma, brain, breast cancer, endocrine (100% penetrance in women)
- Whole body MRI, breast MRI, brain MRI, colonoscopy
- Mastectomy, avoid radiation
- Metformin trials

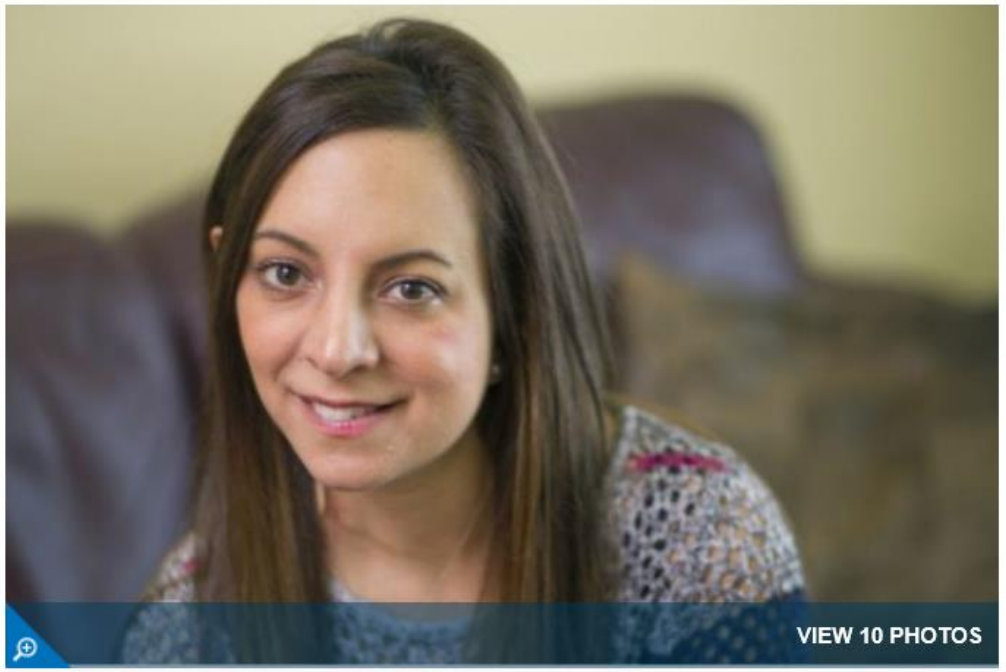
thestar.com
INSIGHT

News / Insight

Five separate cancers. One tenacious Toronto lawyer

Sabrina Fuoco's rare syndrome sparked a pitiless run of cancers. Now she hopes her struggle might help others.

Tweet 78 G+1 7 reddit this!



KEITH BEATY / TORONTO STAR Order this photo

Sabrina Fuoco, 34, had her first cancer diagnosis at age 3. She has refused to let her recurring bouts of the disease change her positive outlook.

UHN Princess Margaret Cancer Centre

Hereditary Breast and Ovarian Cancer ~1/500

- *BRCA1*
  - 40-70% Breast (vs 12%)
  - 20-40% Ovarian (vs 1.5%)
  - 20-30% Prostate (vs 17%)
- Surveillance
  - Breast MRI@25years (OBSP)
  - CA-125 and US not offered
- Management
  - Bilateral Mastectomy
  - Prophylactic Bilateral Salpingo-oophorectomy 35-40
  - Chemoprevention denosumab
  - PARP trials
  - Aspirin

“Synthetic lethality”, from flies to personalized medicine

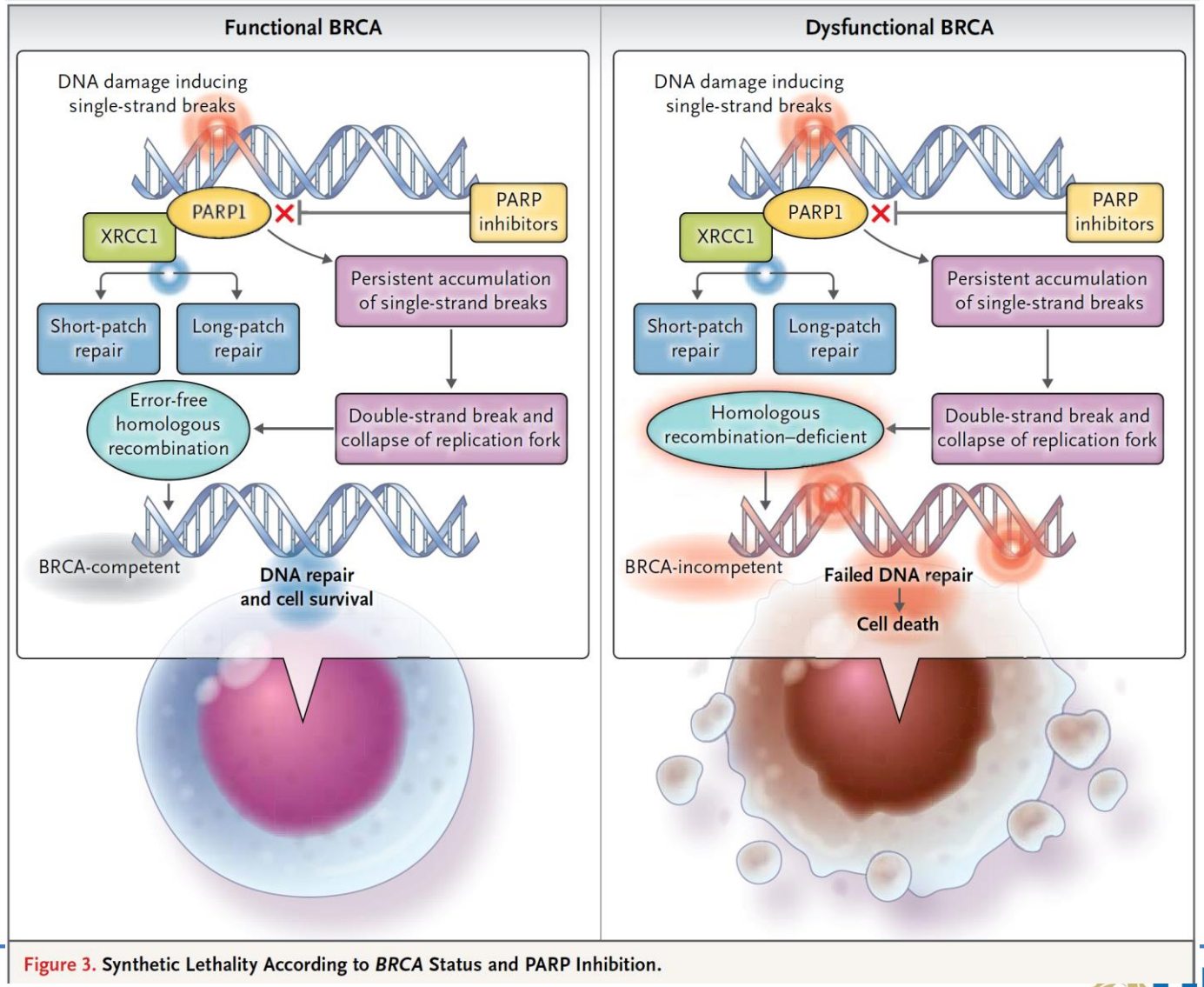
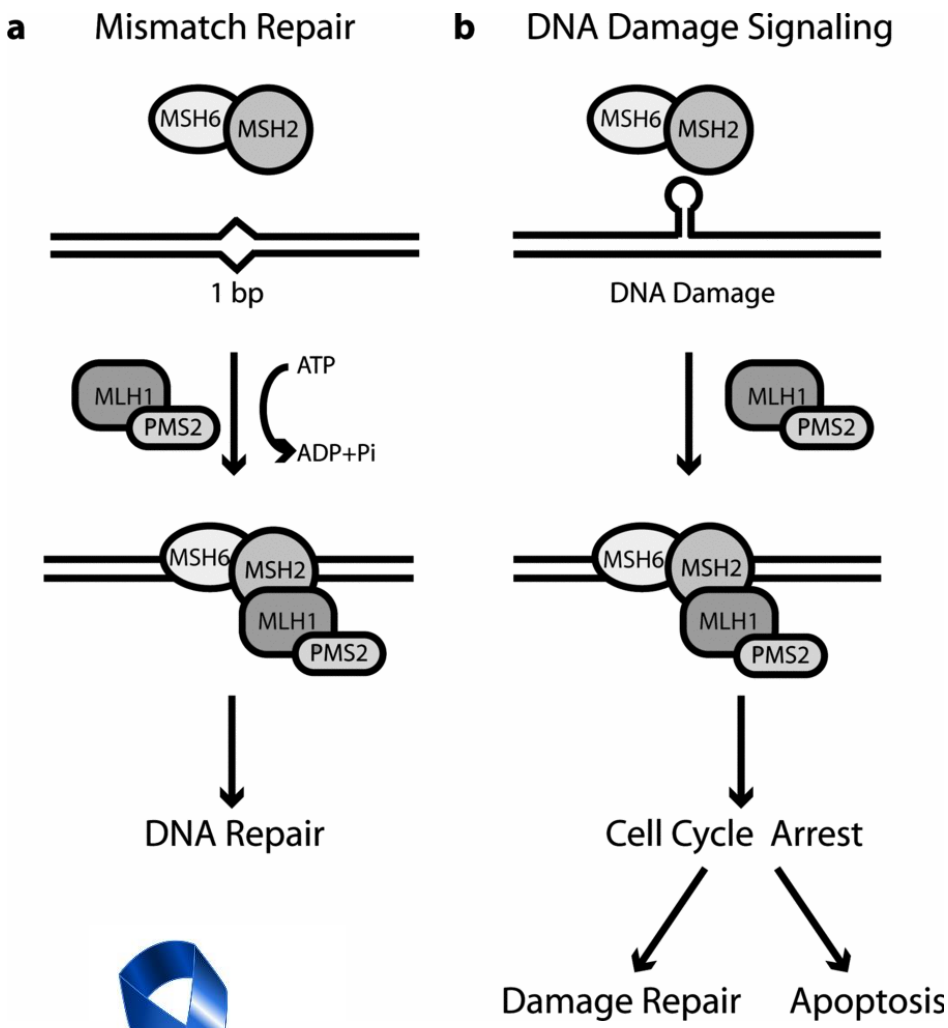


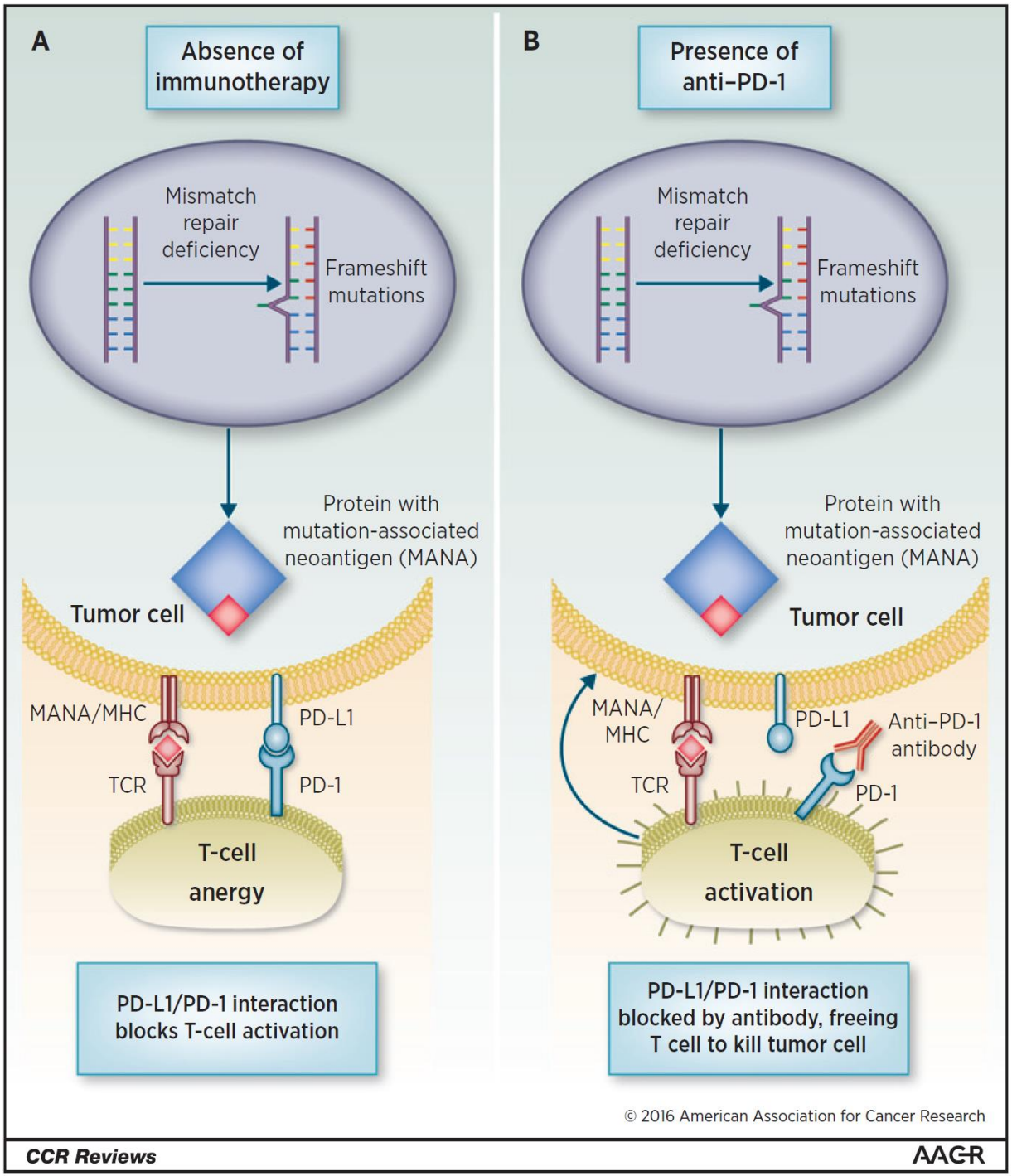
Figure 3. Synthetic Lethality According to *BRCA* Status and PARP Inhibition.

Lynch syndrome

- Mismatch repair pathway deficiency
- Colorectal cancer (50-80%)
- Endometrial (25-60%)
- Ovarian (5-10%)
  - Endometroid, clear cell
- Hepatobiliary (1-5%)
- Adrenocortical carcinoma (3%)
- *MLH1, MSH2, MSH6, PMS2*

- Consider if:
- Amsterdam criteria
  - 3 individuals
  - 2 first-degree relatives
  - 1 under 50
- CRC<35 years of age
- CRC+another Lynch cancer
- Other ongoing screening protocols
- NCCN all CRC<70, UHN endometrial <70
- Annual Colonoscopy ~25y, RRSO, consider endometrial surveillance

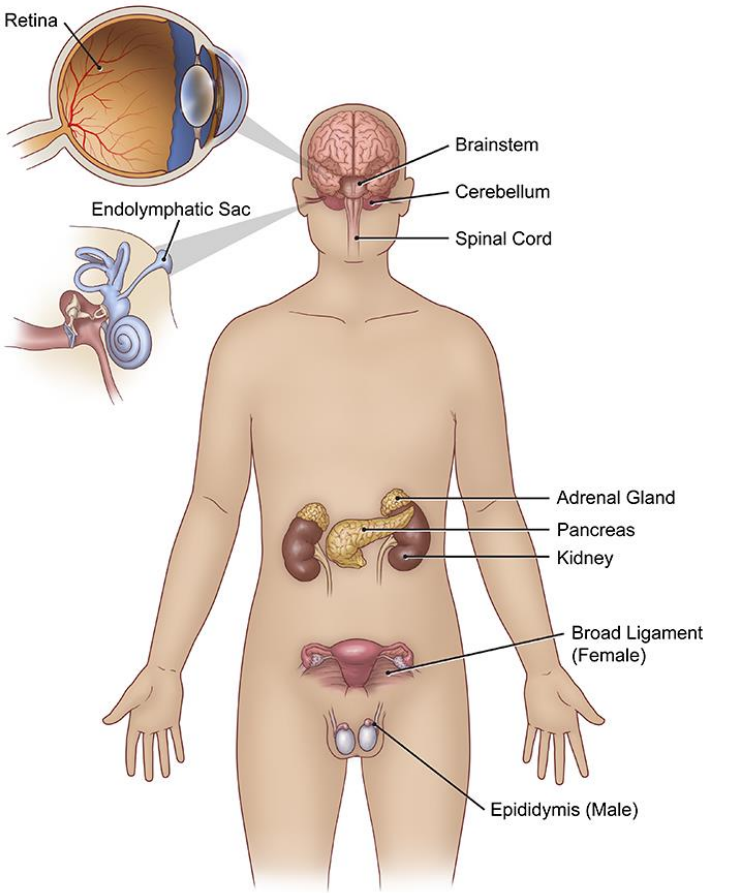




Dudley, ClinCanRes 2016

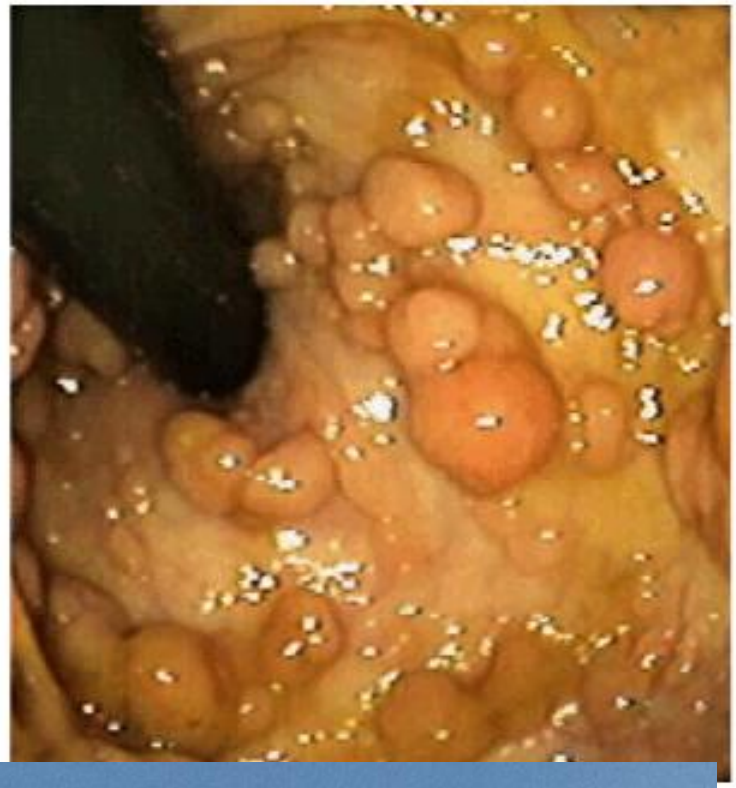
ccRCC, Von Hippel Lindau

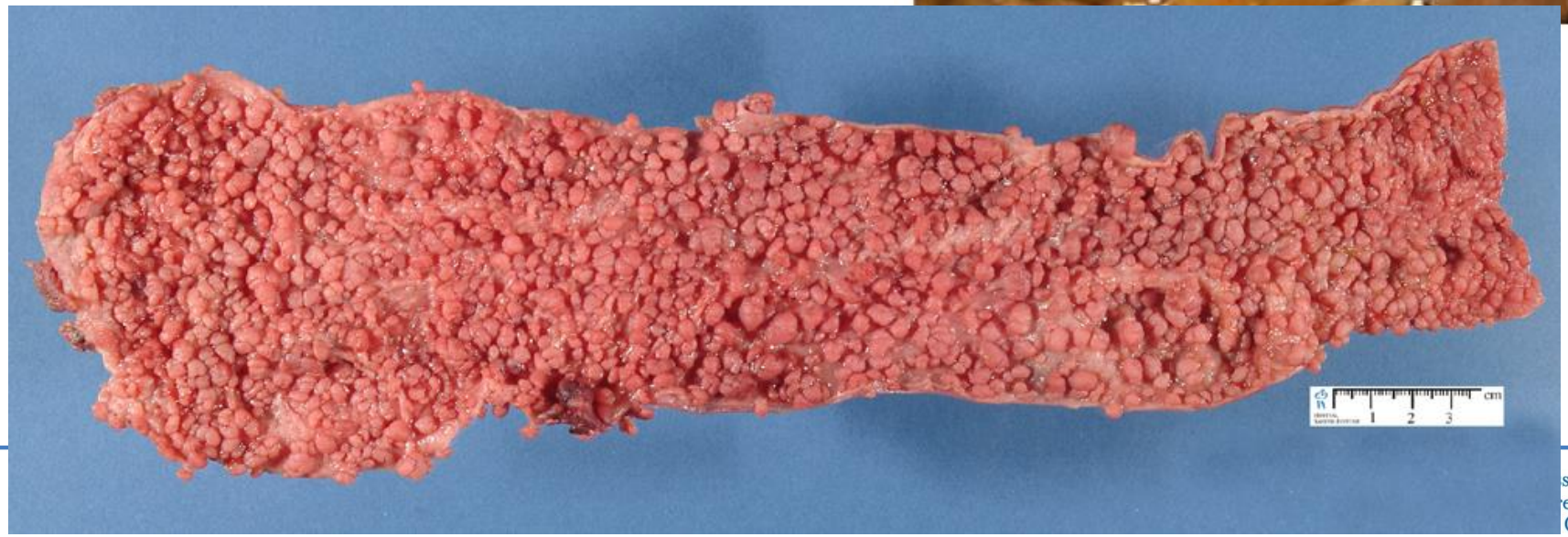
- Multi-system disorder
- Mutations in *VHL* gene responsible for degradation of hypoxia inducible factor 1-alpha (HIF1α)
- Results in hemangioblastomas
  - Eye
  - Brain
  - Spine
- Deafness (endolymphatic sac tumours)
- Pancreatic cysts
- variable expressivity = not all mutation carriers develop all manifestations
- Frameshift mutations result in risk of renal cell carcinoma “type 1”
- Missense mutation result in pheochromocytoma “type 2”



Familial Adenomatous polyposis

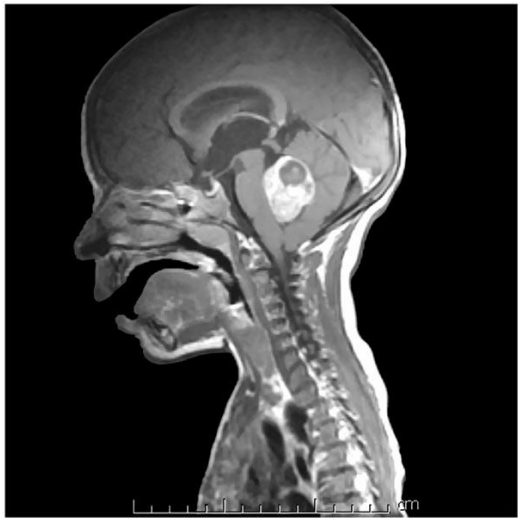
- APC
- ~ 50% mutations carriers develop adenomas by 14 yo
- Genetic testing usually recommended at 10-12 yo
- Untreated FAP leads to ~100% risk colorectal cancer
- Annual colonoscopy at 10 years, colectomy in late teens

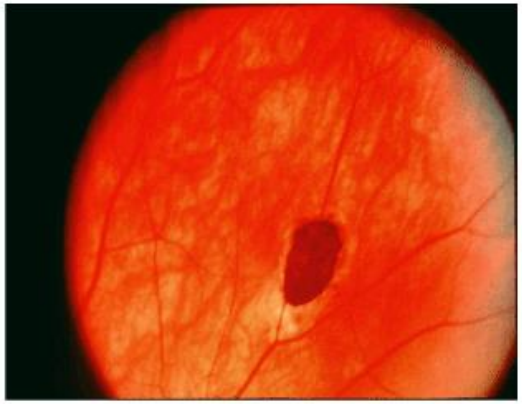




FAP Extracolonic manifestations:

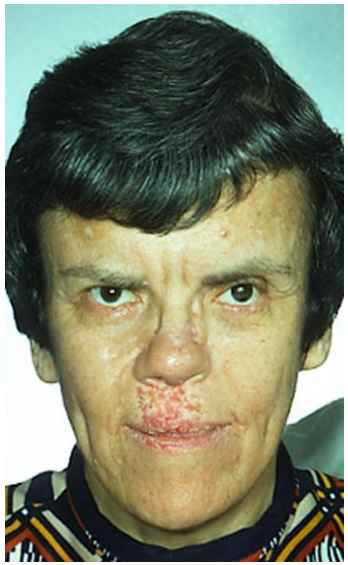
- Congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Epidermoid cysts
- Abnormal dentition
- Desmoid tumors
- Malignant tumors (hepatoblastoma, medulloblastoma, thyroid cancer)
- Osteomas

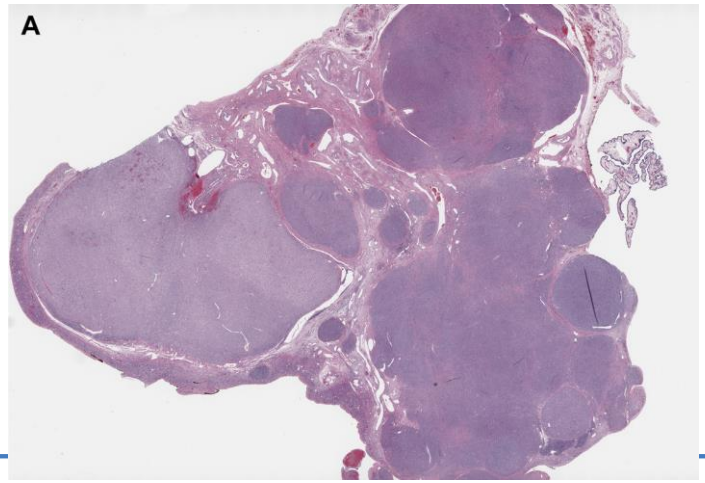


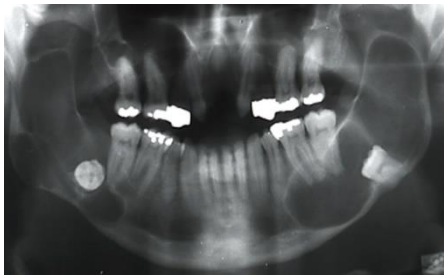


Ovarian fibromas, Gorlin syndrome

- Nevoid basal cell carcinoma syndrome (PTCH gene)
- Jaw cysts
- Coarse facial features, milia
- Macrocephaly
- Bifid ribs
- Medulloblastomas
- Meningiomas, post XRT
- Palmar pits
- Ovarian fibromas



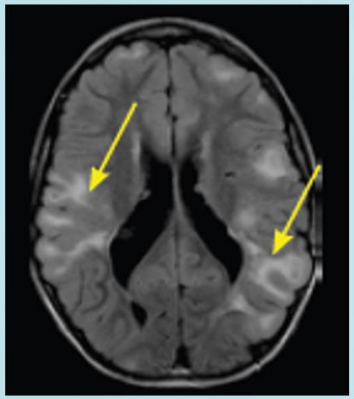




Tuberous Sclerosis (*TSC1-harmatin/TSC2-tuberin*), multisystem disorder -brain, skin, kidney

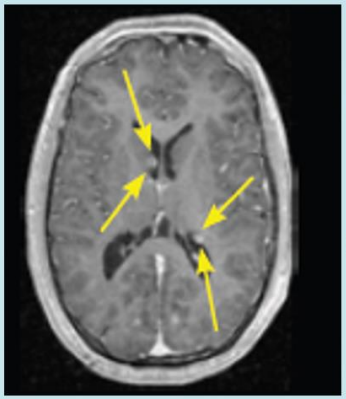
Brain tumours

Cortical tubers



- Abnormal neuron growth results in seizures

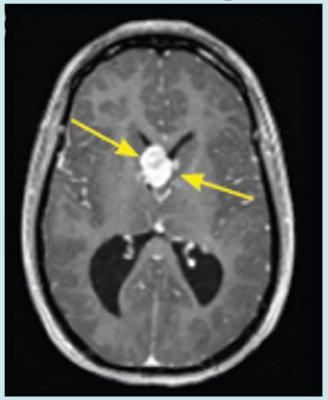
Subependymal Nodules



Numerous SENs distributed on the wall of the lateral ventricles

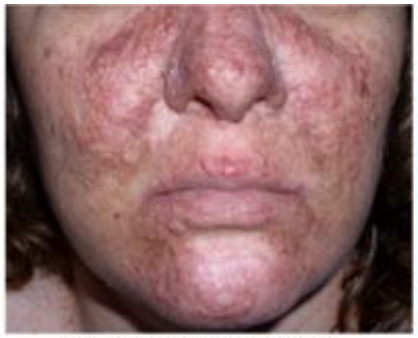
- Benign tumours, asymptomatic

Subependymal giant-cell astrocytoma

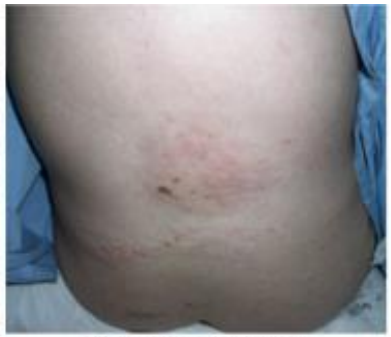


- Well circumscribed, slow-growing, low-grade tumours
- Can obstruct CSF circulation, leading to hydrocephalus

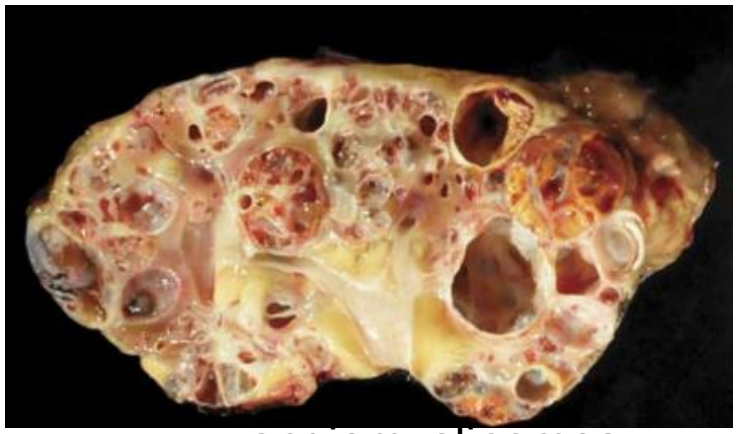
Skin, kidney cysts, lung and uterine LAM



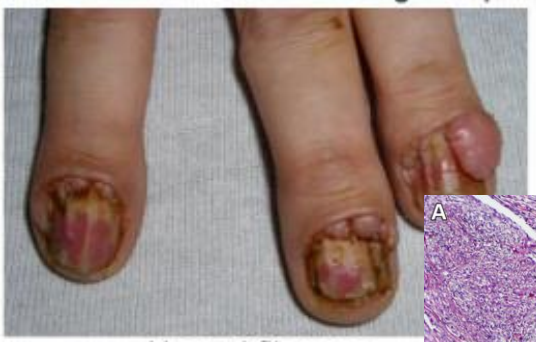
Adenoma sebaceum



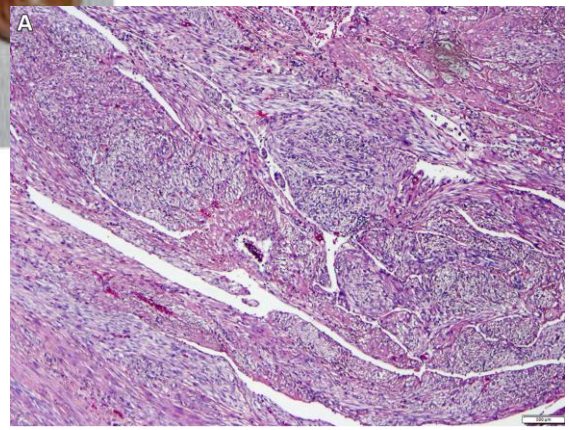
Shagreen patch

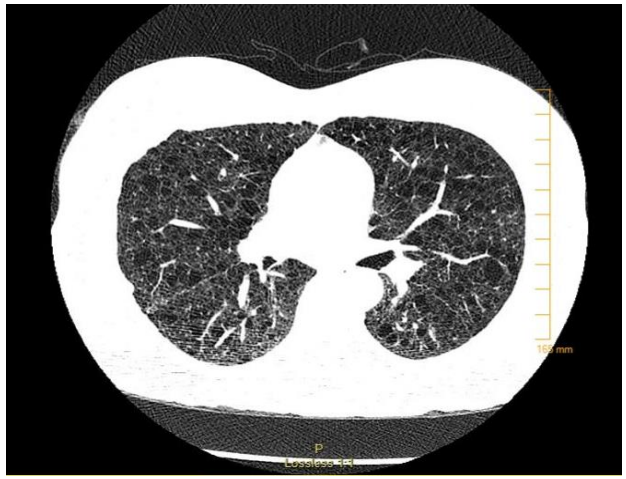


angiomyolipomas



Ungual fibromas

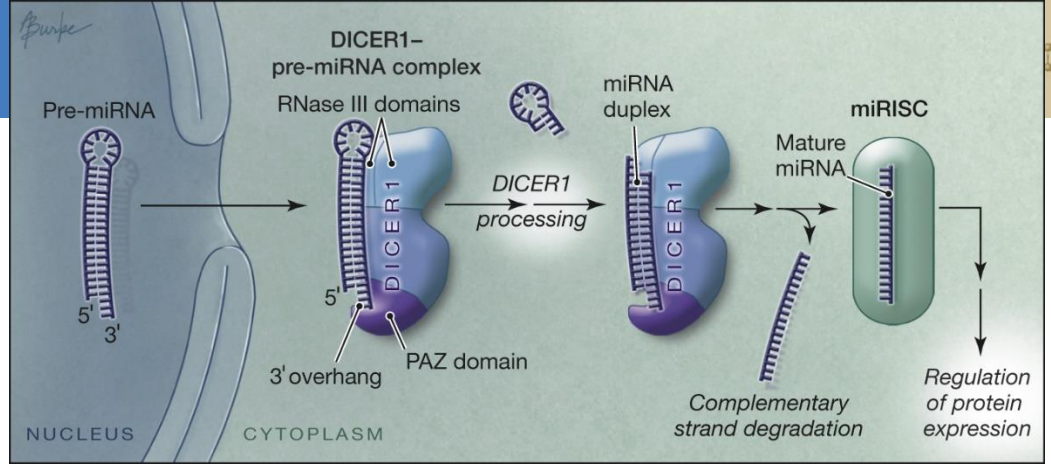


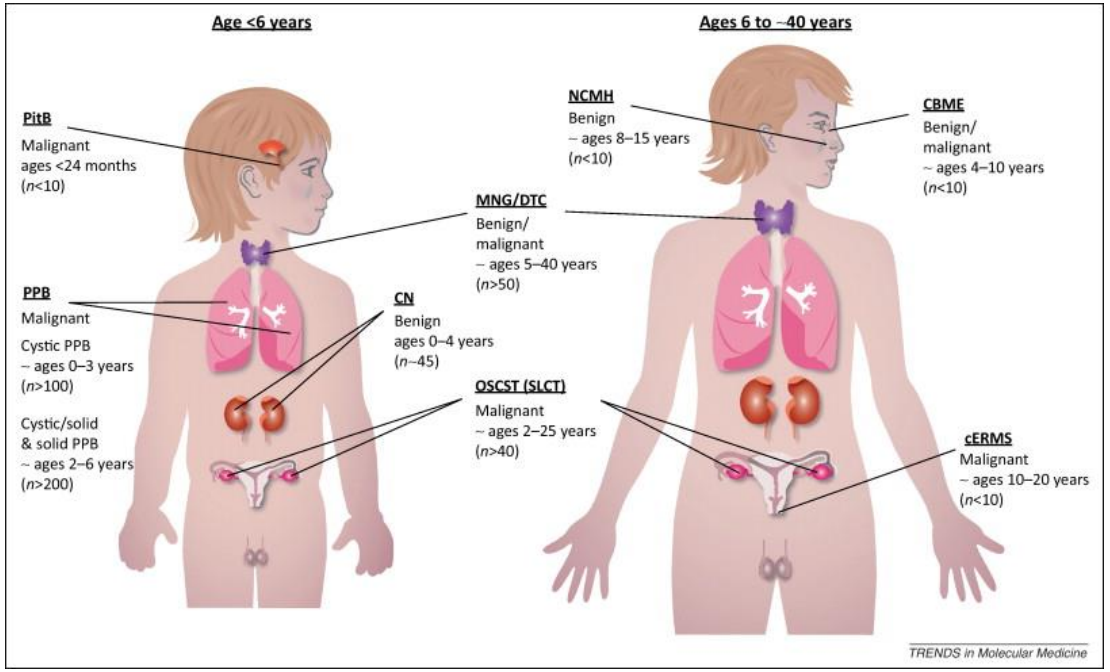


Lymphangiomyomatosis

DICER1

- Pleuropulmonary blastoma
- Cystic nephroma
- Pituitary blastoma
- Nasal chondromesenchymal harmartoma
- Multinodular goitre, differentiated thyroid cancer
- Embryonal rhabdomyosarcoma of the cervix
- Ovarian Sertoli-Leydig tumour
- Not well-defined surveillance





Genetic Testing

Genetic Myths

First Session, Forty-second Parliament,
64-65-66 Elizabeth II, 2015-2016-2017

STATUTES OF CANADA 2017

CCGF/CCEG

CHAPTER 3

An Act to prohibit and prevent genetic discrimination

ASSENTED TO

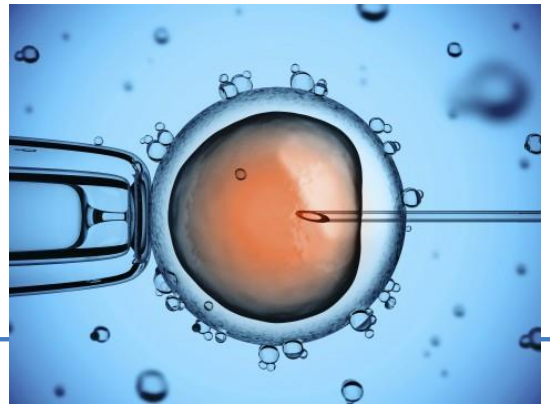
MAY 4, 2017

BILL S-201

Myth: Genetic patients will face discrimination

Myth: Patients pay for genetic testing: if eligible** (evolving) covered by OHIP
$1000/gene → $1/gene

Myth: My children Will carry my genes

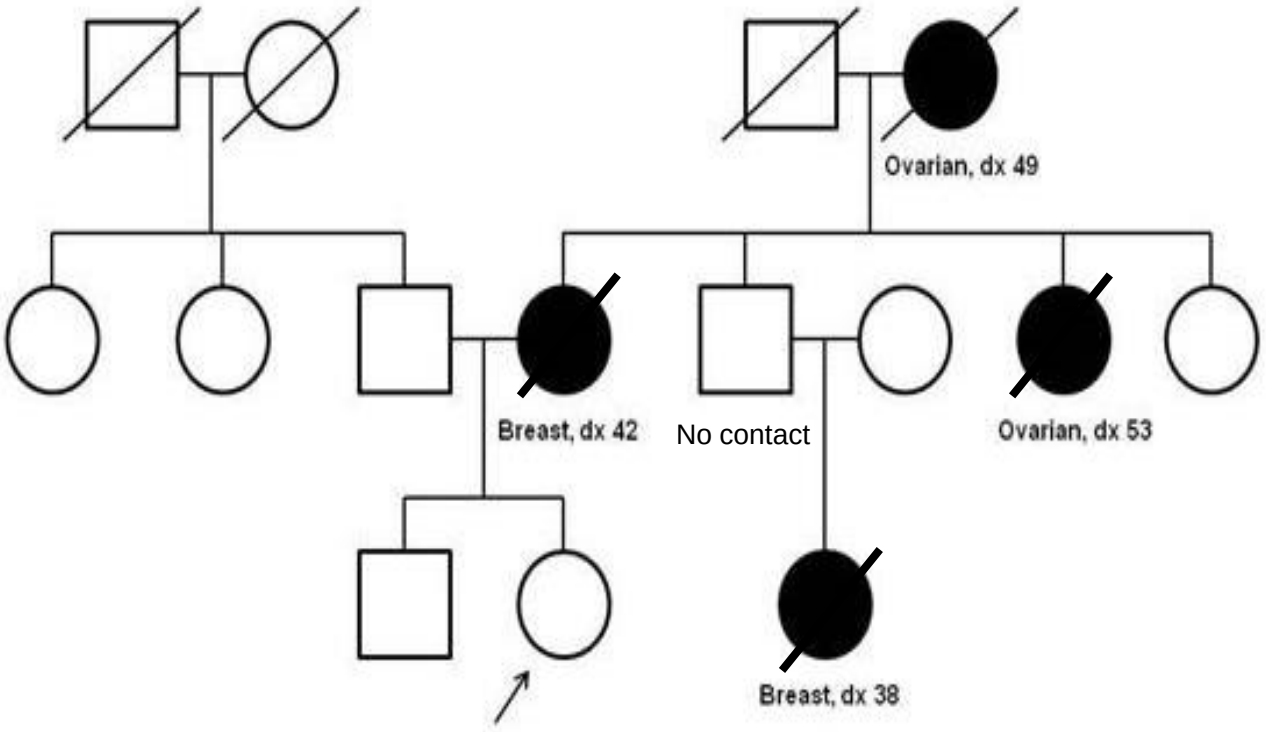


Myth: Genetics is a taboo; awareness is increasing

UHN Princess Margaret Cancer Centre

Who to test?

- Patients affected with cancer are the most appropriate individuals to test to interpret the genetic results
- If no family members, available, some high risk families can have testing on unaffected individuals if probability of mutation based on computer models >10%, but many limitations of this
- Need to consider DNA banking on all individuals with cancer as new genes are discovered (panel testing)



Genetic testing Results

Positive

- Mutation is found
- “have the gene”
- Seen in other individuals with disorder
- Surveillance decisions can be made

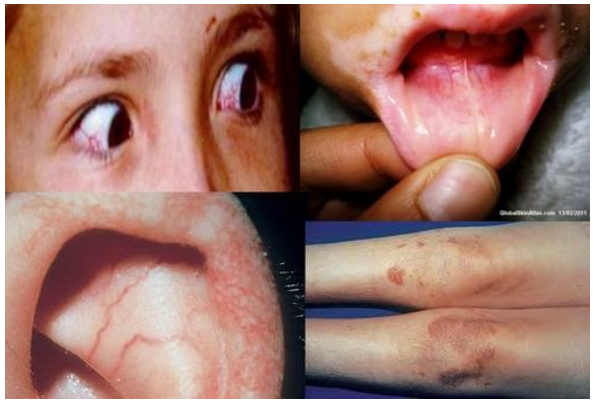
Maybe

- Genetic change is found
- Not seen in other individuals with disorder
- Significance uncertain
- “Variant of uncertain significance”
- Seen 30% during panel testing
- Management decisions NOT made
- Revisit the clinic

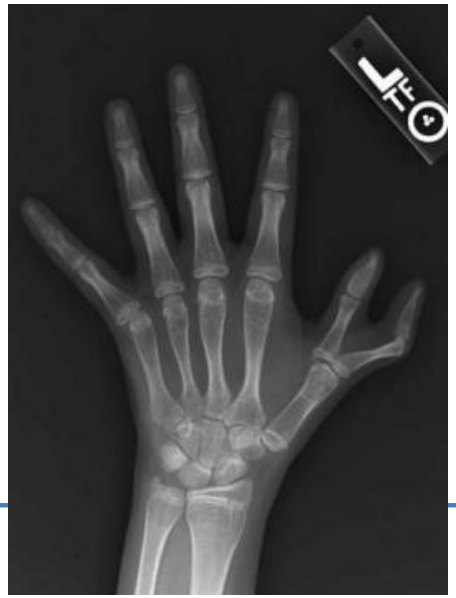
Negative

- No genetic change is found
- Limitation of the technology
- May have another gene involved
- Revisit the clinic, other gene testing

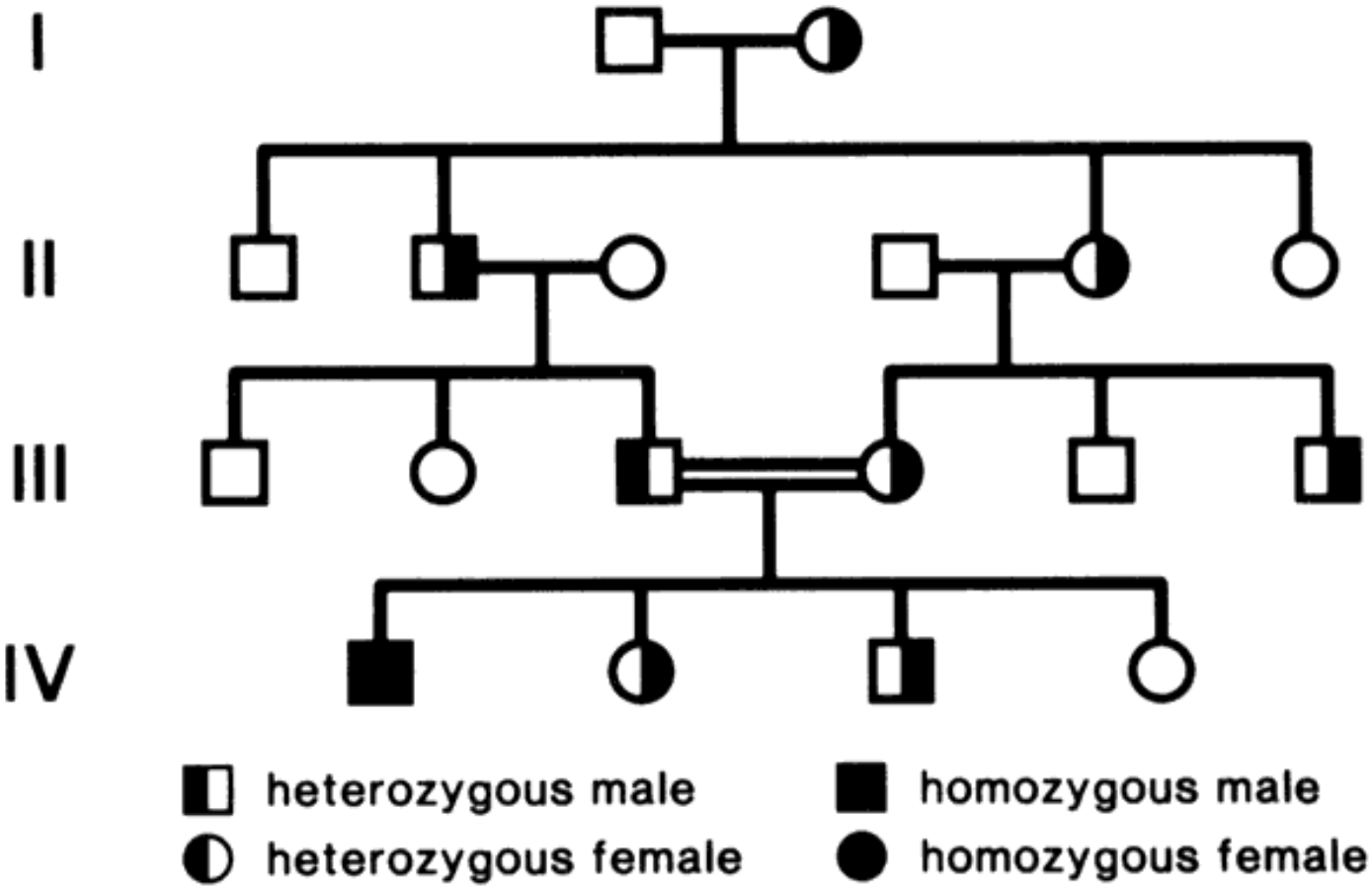
Autosomal dominant and autosomal recessive



- One mutation results in hereditary breast/ovarian cancer
- Two mutations result in pediatric disorders
- Ataxia telangiectasia (*ATM*)
  - Ataxia, scleral telangiectasia, immunodeficiency
- Fanconi Anemia (*BRCA2, PALB2, BRIP1, RAD51C*)
  - Café au lait macules, radial ray defects, bone marrow failure, congenital anomalies
- Nijmengen Breakage syndrome (*NBN*)
  - Microcephaly, IUGR, developmental delay, immunodeficiency

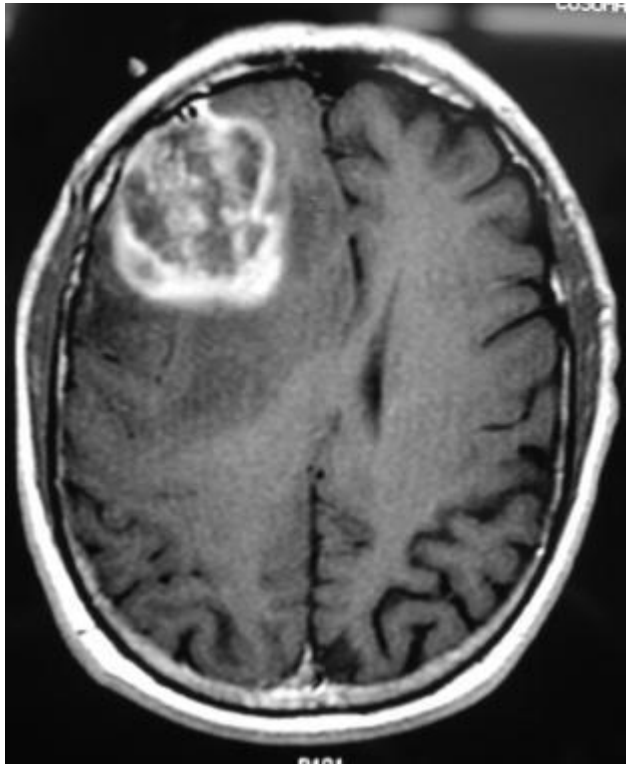


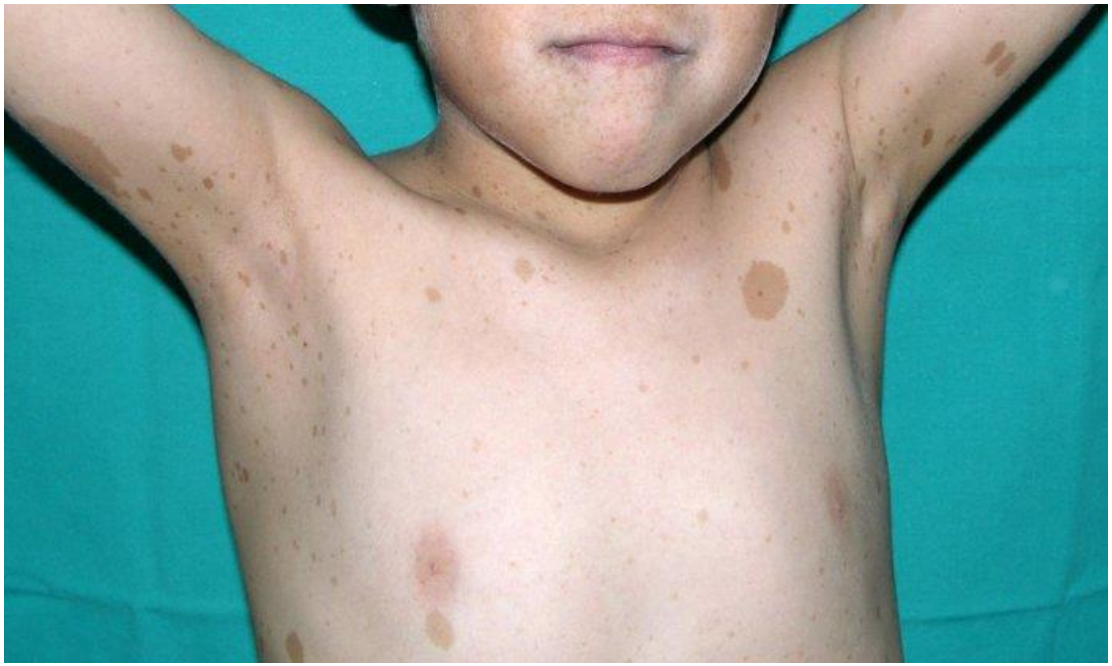
Two Lynch syndrome parents have a child…



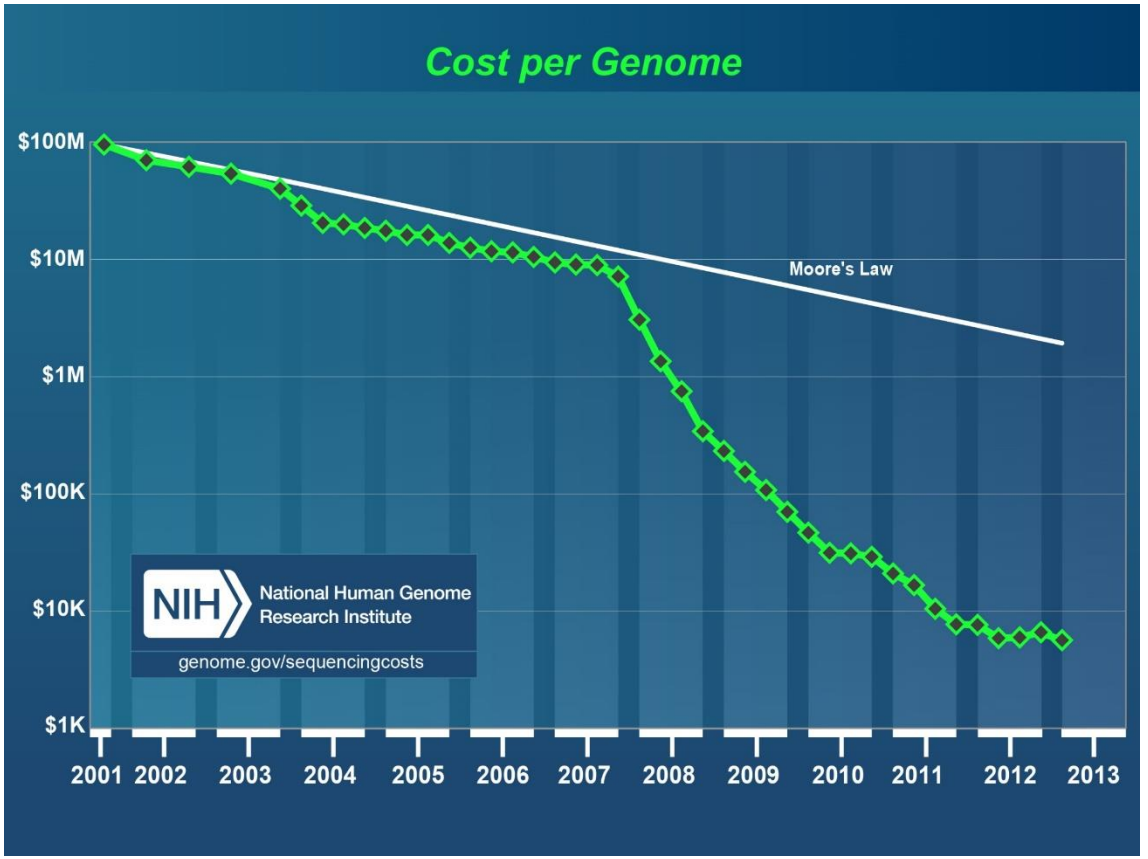
consanguineous

At risk of biallelic mismatch repair, severe hereditary cancer disorder (brain, hematologic malignancy, look like they have neurofibromatosis)






nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
THE FUTURE IS BRIGHT
Reflections on the first ten years of the human genomics age
GENOMICS
THE END OF THE BEGINNING
Eric Lander on the impact of the human genome sequence
METHODS
MORE BASES PER DOLLAR
Elaine Mardis on the march of sequencing technology
HEALTH
FROM LAB TO CLINIC
A road map to genomic medicine
NATURE.COM/NATURE


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013

Ethical challenges in sequencing 30, 000 genes vs one gene

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

- Medically actionable genetic findings
- Should be returned to patient in a clinical exome
- Cardiac disease (hypertrophic cardiomyopathy, hereditary arrhythmia)
- Metabolic disorders (familial hypercholesterolemia, Wilsons disease)

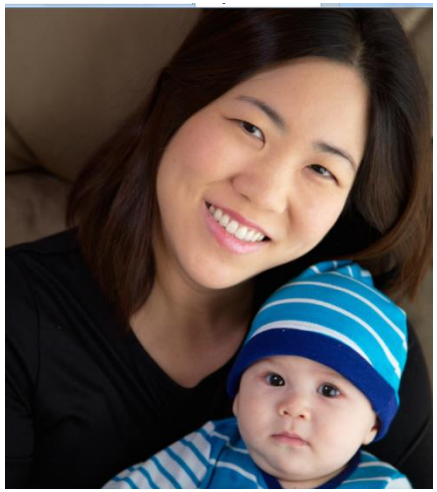
Circulating DNA from fetuses to tumours

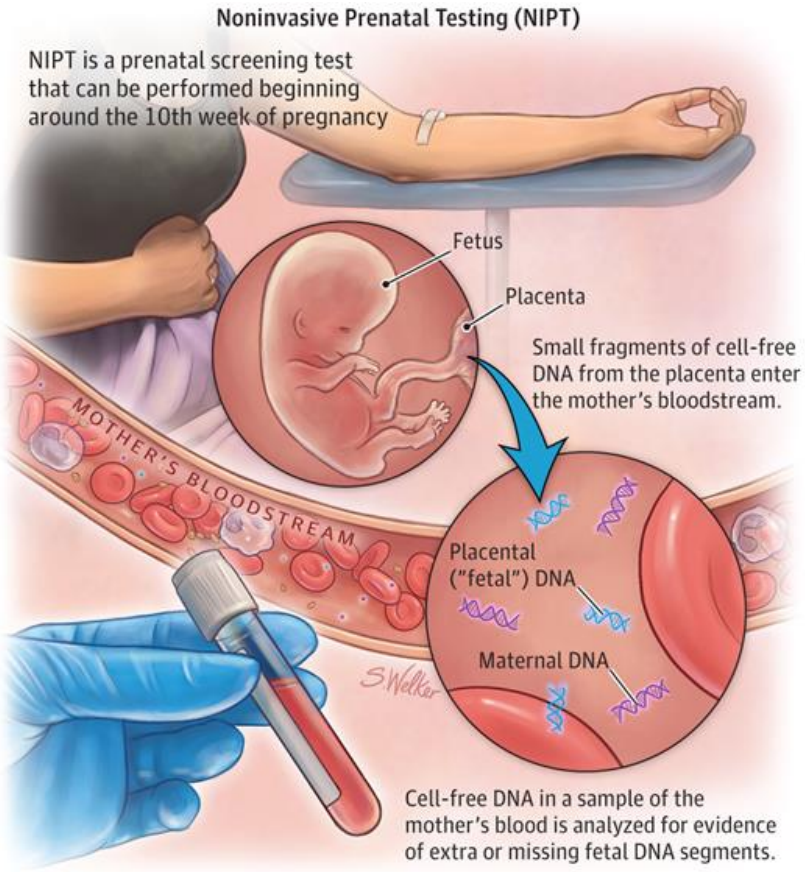
Preliminary Communication

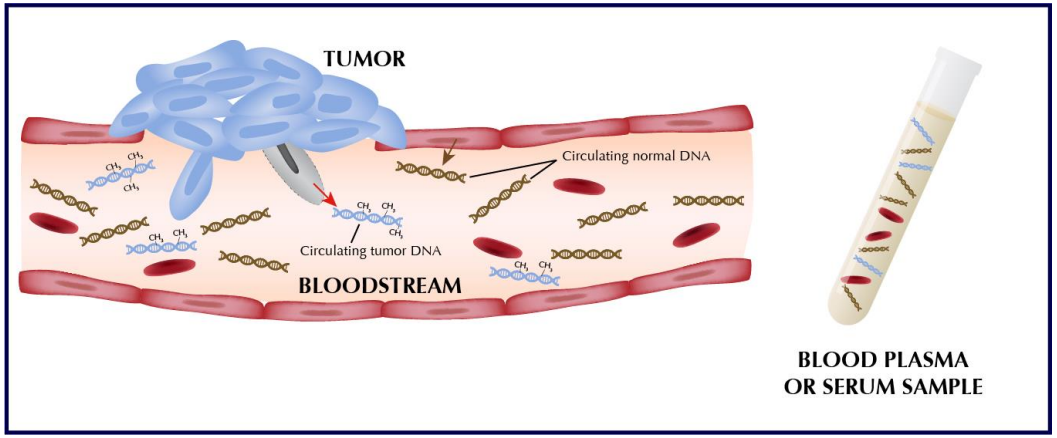
Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies

Diana W. Bianchi, MD; Darya Chudova, PhD; Amy J. Sehnert, MD; Sucheta Bhatt, MD; Kathryn Murray, MS; Tracy L. Prosen, MD; Judy E. Garber, MD; Louise Wilkins-Haug, MD, PhD; Neeta L. Vora, MD; Stephen Warsof, MD; James Goldberg, MD; Tina Ziainia, MD; Meredith Halks-Miller, MD

Editorial page 131



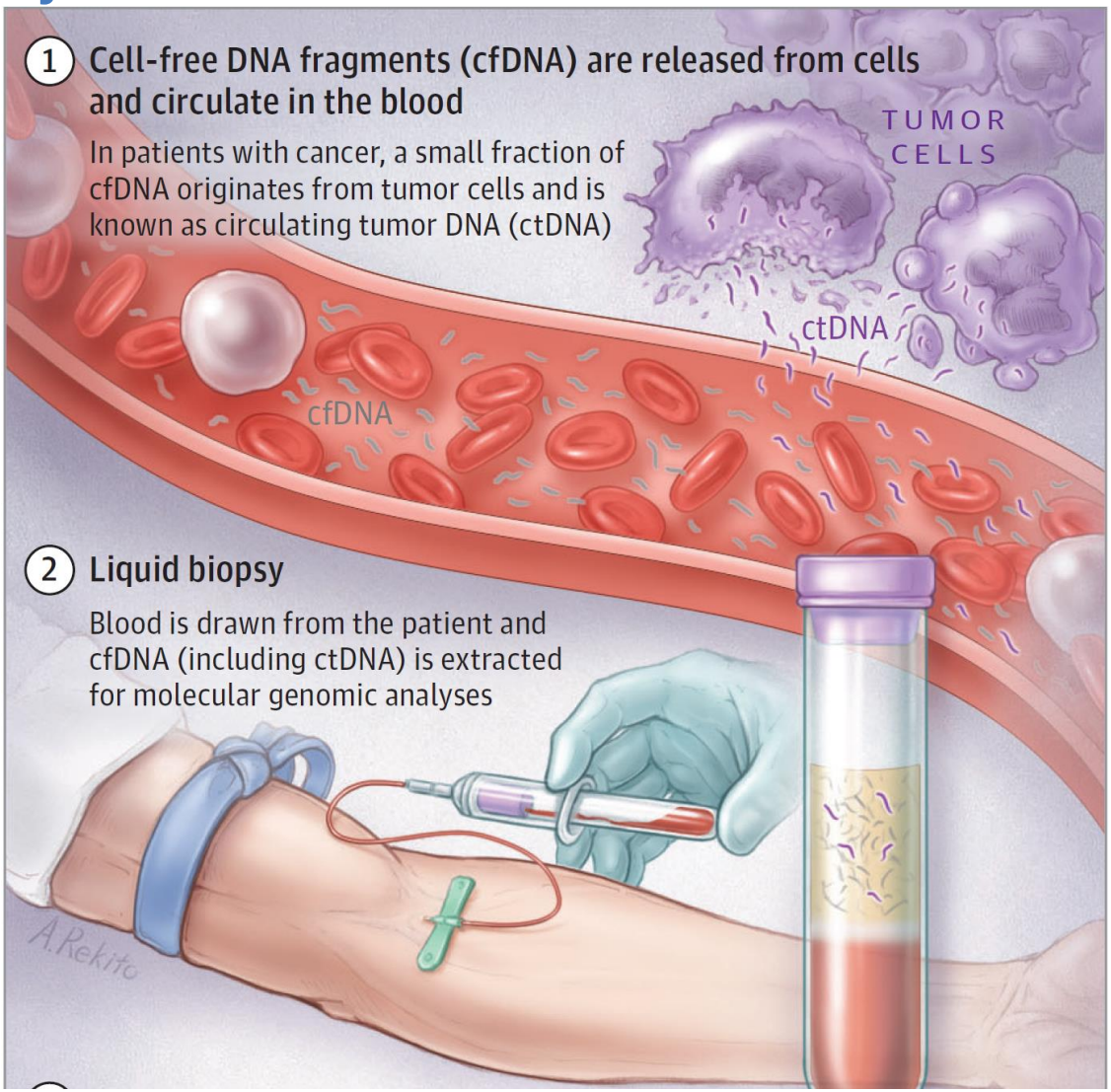




UHN Princess Margaret Cancer Centre

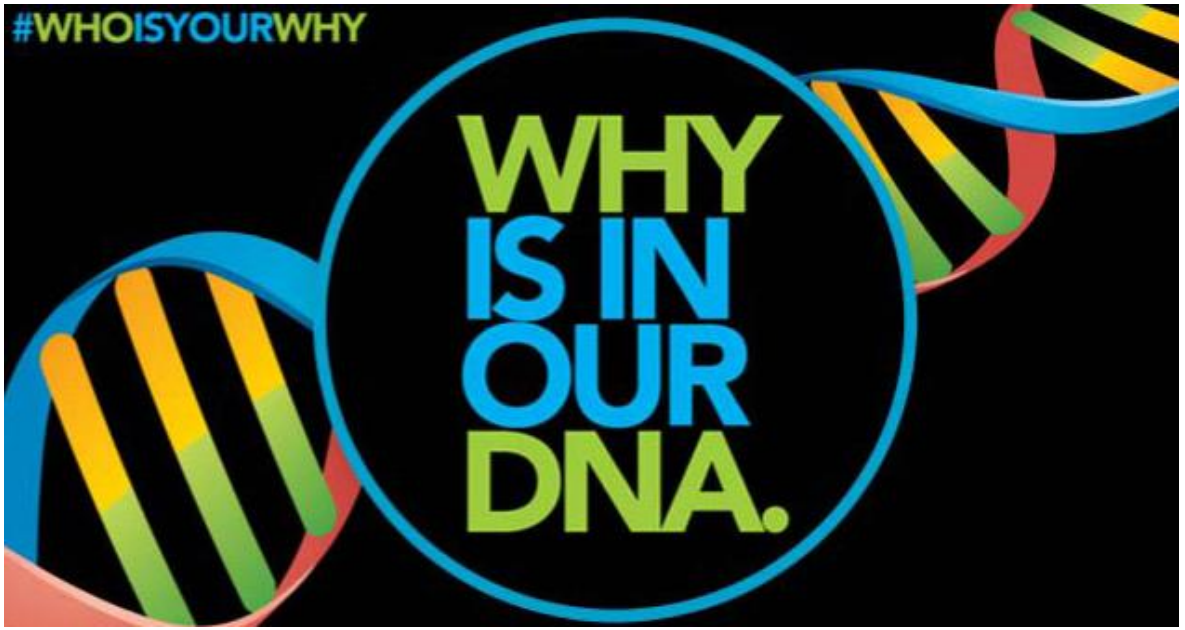
Concepts in tumour DNA analysis

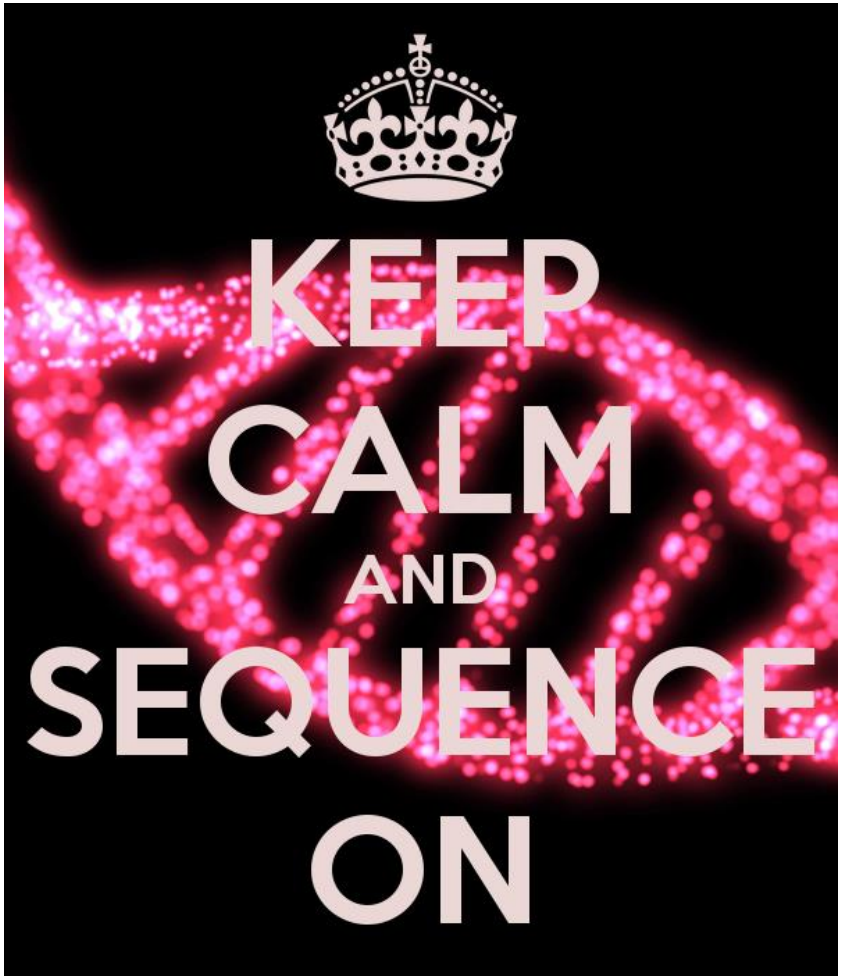
- Cancer is caused by genetic changes in cells
  - Germline: born with first hit
  - Somatic: tumour-specific events
  - Tumour: includes both somatic and germline events
- Germline is analyzed by isolating peripheral blood lymphocytes (buffy coat)
- Somatic/tumour mutations analyzed by tumour (biopsy)
- Tumour cells shed DNA into the plasma



Summary

- Genetic terminology and concepts
- Hereditary cancers
  - When to consider
  - Genetics assessment
- Pathology and genes
- Genetic testing
- Genetic counselling





raymond.kim@uhn.ca