# Genetic factors influencing individual risk of radiogenic cancer

## Workshop: Individual Response to Ionizing Radiation

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# Genetic Susceptibility to Radiation

- Rare syndromes with extreme radiosensitivity
- Ataxia-telangiectasia (AT)
  - Rare childhood neurodegenerative disease
  - Caused by mutations in *ATM* gene

Image courtesy Pollard and Gatti, 2009

- Cultured fibroblasts from patients three times as sensitive to radiation (Taylor et al., 1975)

# How Does this Affect the General Population?

Figure 1a Increasing Incidence with Radiation Dose

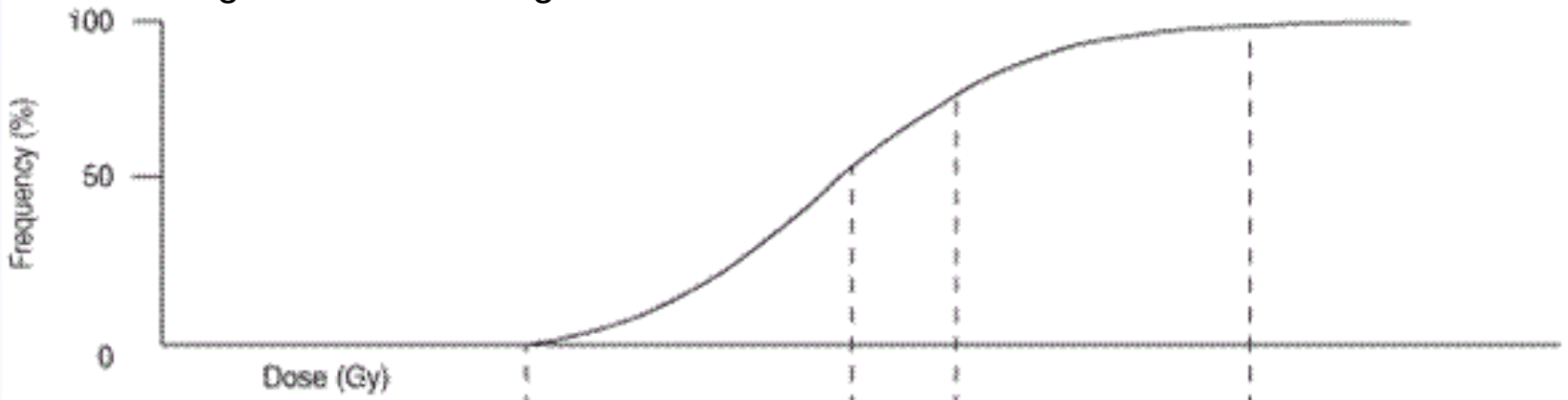
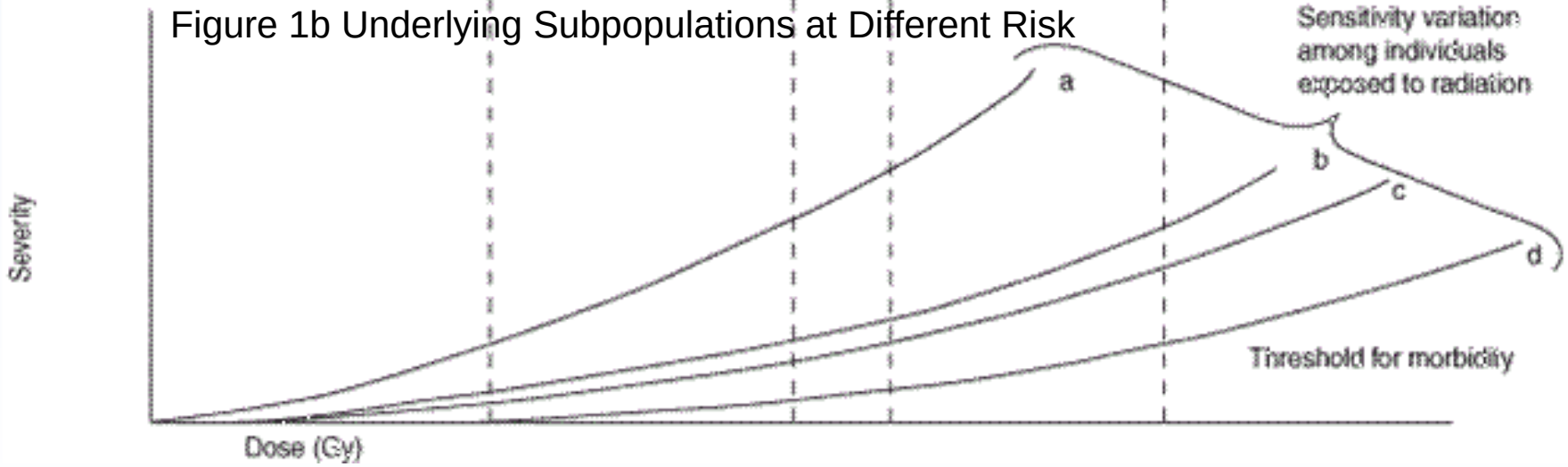


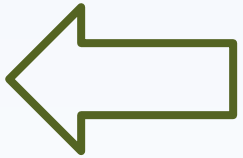

Figure 1b Underlying Subpopulations at Different Risk




Adapted from Hendry et al, 2006

Levels of Variation

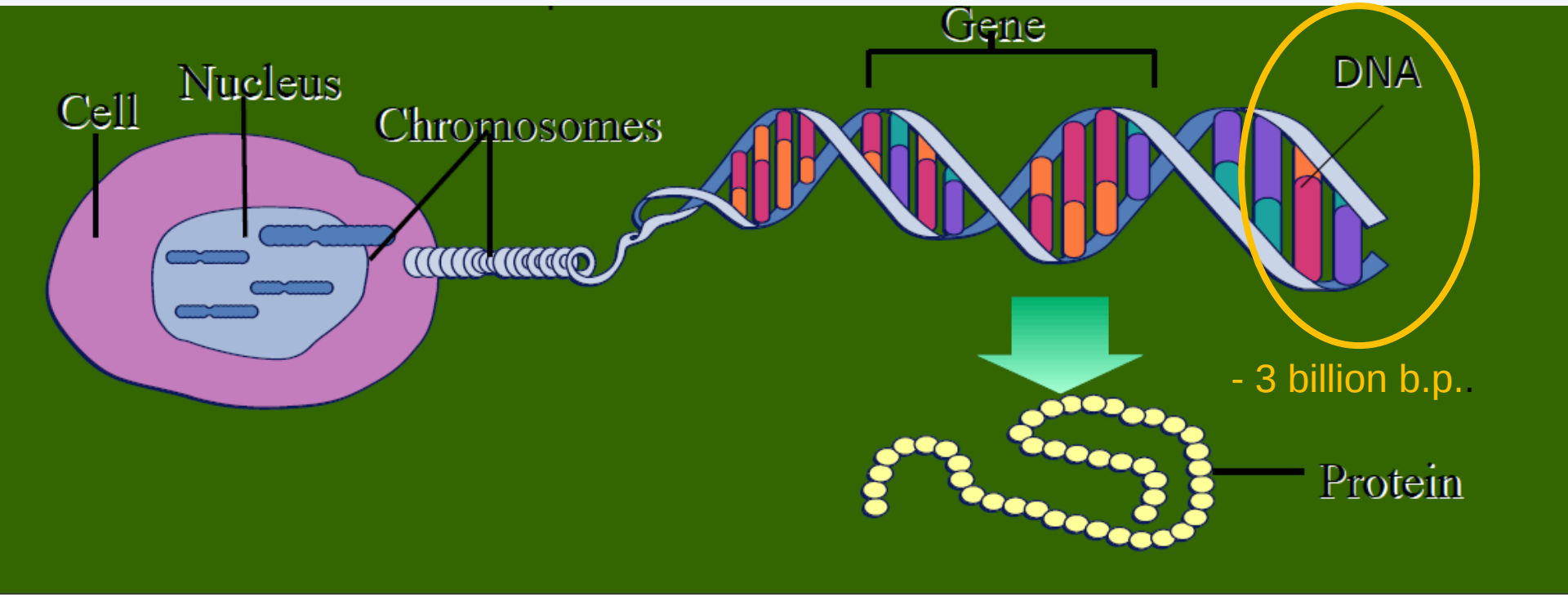
| | |
|---|---|
| Whole Organism | • Assays such as $LD_{50/30}$ |
| Clinical radiosensitivity | • Consequence of radiotherapy<br>• e.g. skin erythema, lung fibrosis |
| Susceptibility to Radiation Carcinogenesis | • Risk differences in populations<br>• Epidemiology studies |
| Tissue radiosensitivity | • By specific tissues/organs<br>• Epidemiology/clinical studies |
| Cellular radiosensitivity | • e.g. cell killing, chromosomal damage, DNA damage |



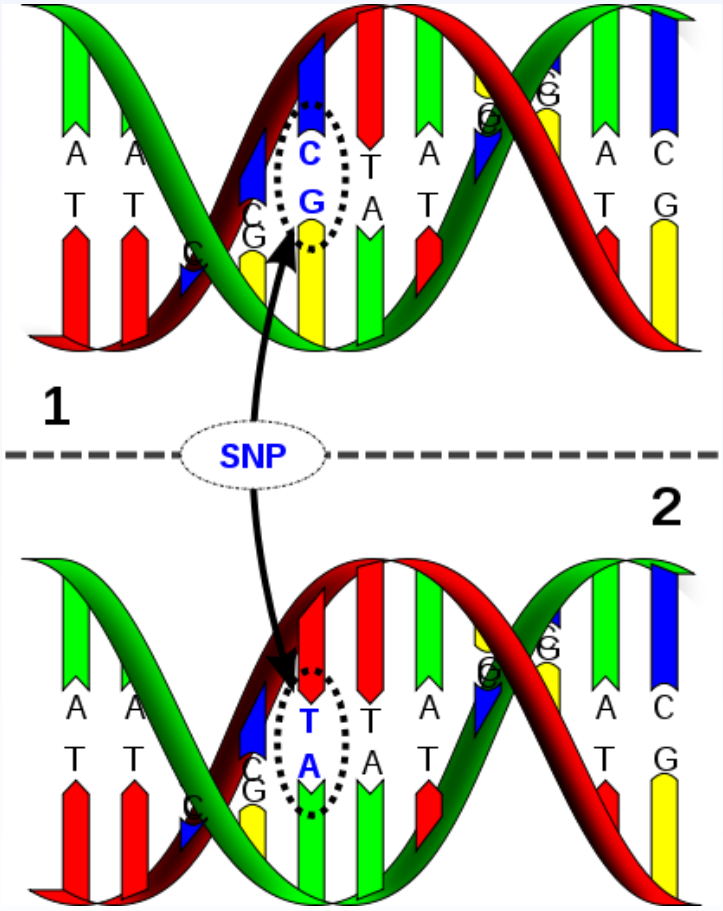
Adapted from Human Radiosensitivity: Report of AGIR, 2013

# Types of Genetic Variation

- Chromosomes, genes, RNA, DNA



# Single Nucleotide Polymorphisms (SNPs)

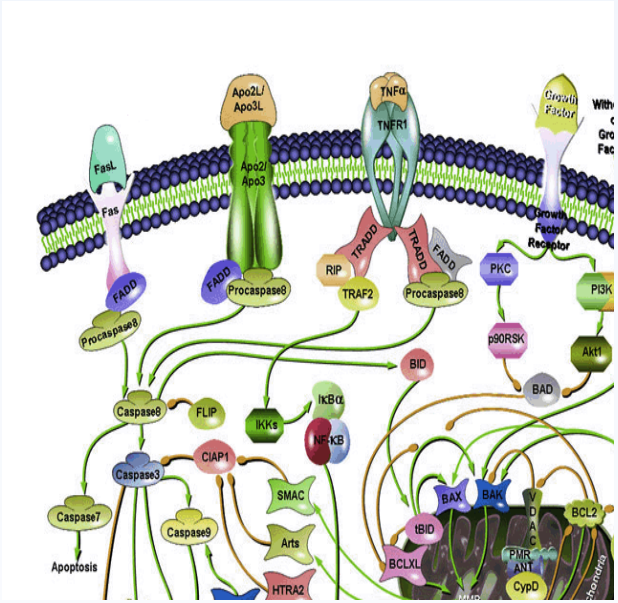



- Most common genetic variation
- Each individual has two alleles
  - CC (common referent)
  - CT (heterozygote)
  - TT (homozygous variant)
- Much of the variation appears meaningless
- Some variation increases risk of outcome (e.g. cancer, circulatory disease).

# Approaches to Study Genetic Variation - 1

- **Early candidate gene approach**
- **Pre-defined SNPs in Pathways of Interest**

  DNA repair, Cell-cycle control, Apoptosis, Immune-related, Oxidative Response




Focus on genes thought to be involved in radiation toxicity

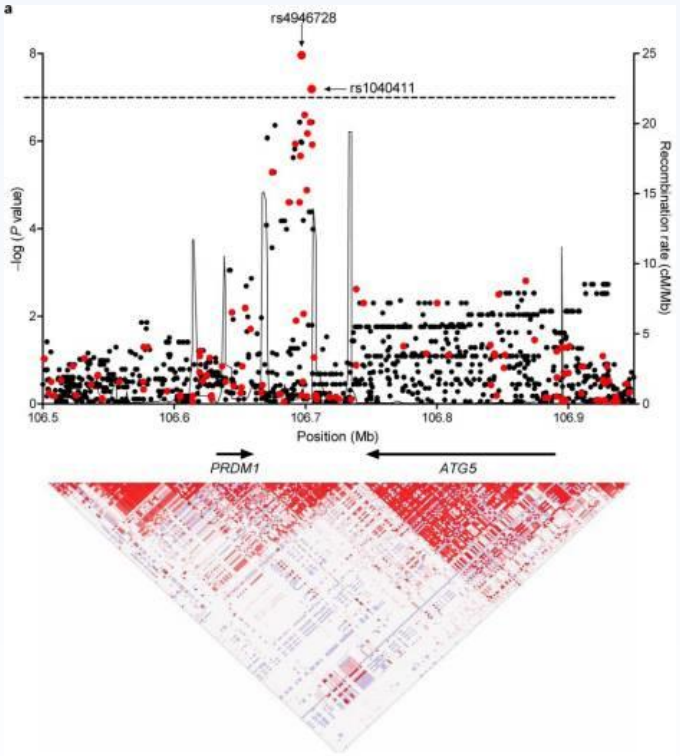
A few signals, but not consistent

Limited knowledge of underlying biology; ability to query genome

# Approaches to Study Genetic Variation - 2

## Genome-Wide Association Studies (GWAS); Whole Exome/Genome Sequencing (WES/WGS)

- Agnostic – no assumptions about underlying biology
- GWAS approach has identified 1000s of risk loci in germline DNA for various disease endpoints (1297 for cardiovascular disease)
- GWAS typically 600,000 to 5 million markers across genome
- WGS every base in the genome (<30 hrs from sample to report)




Best et al, Nature Med 2011

# GWAS of Radiation-related Cancer

1. **Second cancers following HL dx <18yrs, treated with RT (Best et al, Nature Med 2011)**

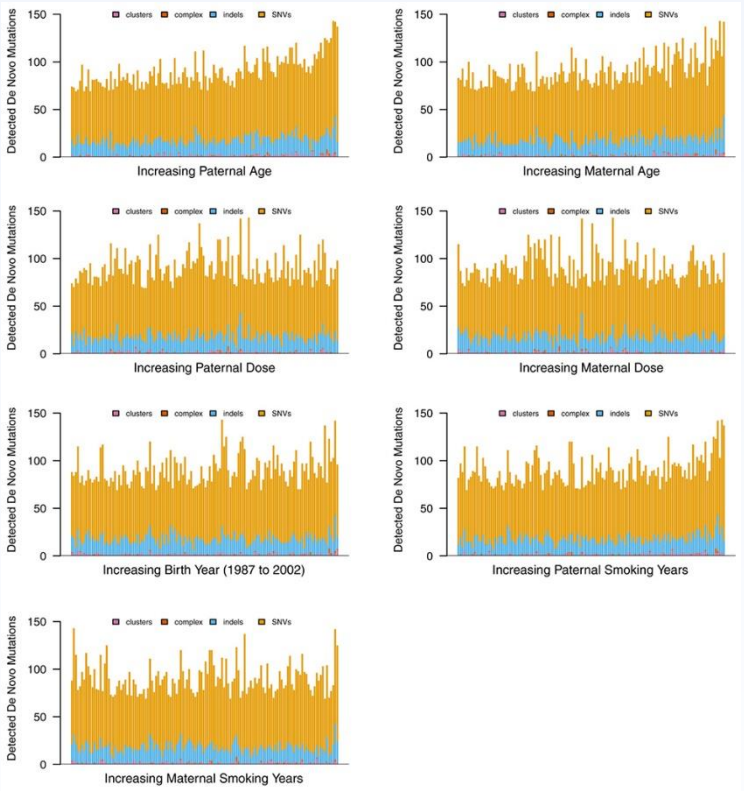
- Genotyped on Affymetrix 6.0 (approx. 700K directly genotyped)
- 6q21 rs4946728, PRDM1
  - Discovery:100 SMN cases, 89 SMN-free controls
  - Independent replication: 62 SMN, 71 controls

2. **Breast cancer in female childhood cancer survivors dx <18yrs (Morton et al, JNCI 2017)**

- Two studies: CCSS + St. Jude Life (approx. 17m variants after imputation)
- Genotyped on Affymetrix 6.0 1q41 rs4342822, near PROX1
  - >10Gy to breast HR=1.92 (1.49-2.44)
  - <10Gy to breast HR=1.04 (0.75-1.45)

# Whole Genome Sequencing of Trios

- Compare number of de novo mutations (DNMs) for 130 children compared to parents (“trios”) exposed to IR post-Chernobyl
- Pre-conception gonadal dose (mGy)
  - Pat. 0-4080 (365 mean, 29 med)
  - Mat 0-550 (19 mean, 2.1 med)
- No elevation in DNM regardless of cumulative paternal or maternal dose
  - Incr. DNM with paternal age



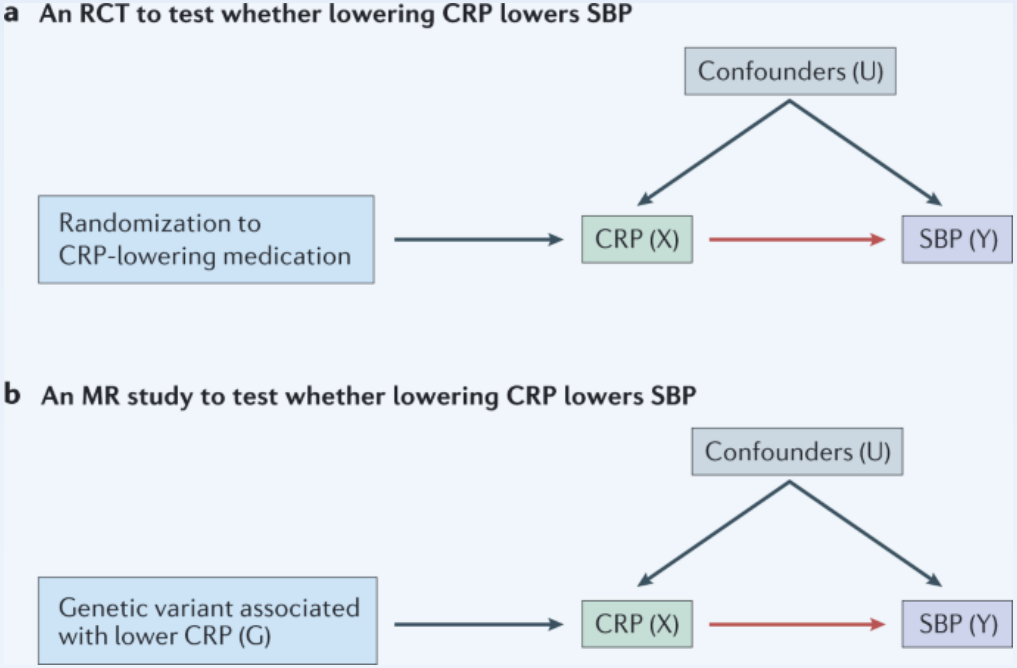

Yeager et al, Nature Science 2021

# Approaches to Study Genetic Variation - 3

## Instrumental Variable Analysis: Mendelian Randomization

- First suggested in 1986 (Lancet, Martjin Katan)
- Use genetic variation to understand how modifiable exposures cause disease outcome
- Instrumental variable related to exposure but not disease, other than through causal pathway

Example: Estimating the Effect of C-reactive protein (CRP) on Systolic Blood Pressure (SBP)




Sanderson et al, Nature Rev 2022

# St. Jude Lifetime Cohort Study: Stroke

- WGS of 686 childhood cancer survivors (EUR ancestry) treated with cranial radiotherapy (CRT)
- Outcome n=116 clinically-dx stroke
- Strong association between 5p13.33 rs112896372 and stroke
  - Overall HR=2.55, p=1.4 x $10^{-8}$
  - Potential modification by radiation dose, but low power

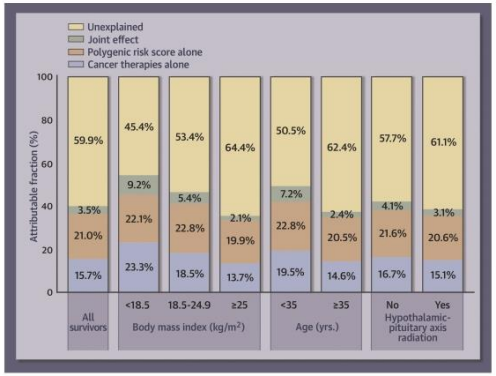
| CRT Dose | n | $HR_{rs112896372\text{-}stroke}$ (95% CI) | P-value |
|---|---|---|---|
| ≤20 Gy | 191 | 2.14 (1.01–4.53) | 0.047 |
| 20–25 Gy | 218 | 2.40 (1.45–3.97) | $6.5\times10^{-4}$ |
| 25–50 Gy | 124 | 3.68 (1.82–7.46) | $2.9\times10^{-4}$ |
| >50 Gy | 153 | 2.28 (1.27–4.09) | $5.7\times10^{-3}$ |

Sapkota et al, Clin Can Res 2019

# Other CVD outcomes in Cancer Survivors

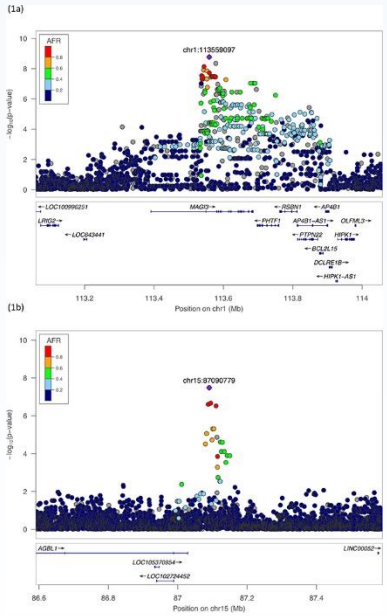
- Blood pressure polygenic risk score (PRS) and <u>hypertension</u> risk in childhood cancer survivors (EUR ancestry) from CCSS and SJL cohorts
- PRS from 895 established BP loci
- Association between BP PRS and HT
  - Potential modification by radiation to hypothalamic-pituitary axis

**CENTRAL ILLUSTRATION: Adjusted Attributable Fraction for Hypertension by Specific Cancer Therapies Considered as Risk Factors Using the Children's Oncology Group Guidelines and the PRS Among Survivors**



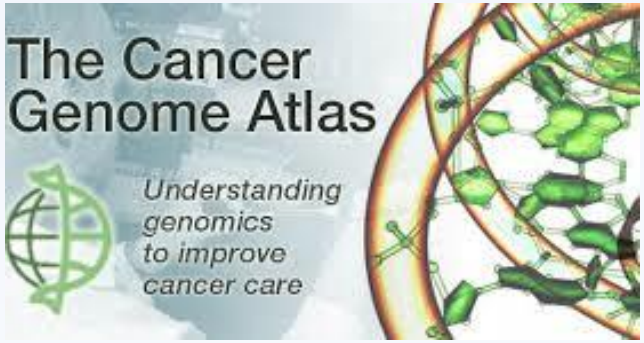

Sapkota, Y. et al. J Am Coll Cardiol CardioOnc. 2021;3(1):76-84.

- Ejection fraction and <u>cardiomyopathy</u>
- WGS of 246 childhood cancer survivors (AFR ancestry) treated with heart radiation and/or anthracycline. Replication in 1,645 EUR
- 1p13.2 rs6689879
  - Reduction in EF per allele $5.9\%_{AFR}$; $0.4\%_{EUR}$
  - Cardiomyopathy
    $OR_{AFR}$= 5.24 (Gr2-4), $p=7*10^{-5}$
    $OR_{EUR}$=1.25 (Gr2-4), p=0.7
  - Possible modification with radiation




Sapkota et al, Clin Can Res 2021

# Parallel Investigations: Germline vs. Tissue


2008

33 tumor types

>11,000 exome seq


2020

38 tumor types

> 2600 WGS

# Tumor Sequencing: Information Gained

- Tumor classification
  - Within tumors (e.g. 4 subtypes GBM)
  - Across tumors
    - Common tumor-driving mutations (*BAP1, FBXW7, TP53*) correlated with poor survival across several cancer types
- Mutational Signatures
  - UV, platinum-based compounds
- Molecular timing of cancer evolution
- Large structural variation

# Challenges: Genetic Susceptibility to Radiation

- **Setting**
  - High versus low dose radiation
- **Outcome**
  - Cancer; subtypes
  - Intermediate outcomes
- **Analytical challenges**
  - Power
  - Volume of data, methods need to be developed
- **Replication**

# The Way Forward…

- **Continue to explore genetic susceptibility**
  - Germline + tumor
  - Whole genome sequencing of special populations
  - Integration of platforms: methylation, RNA, proteins

- **But also characterize traditional risk factors**
  - Age, sex, smoking
  - BMI, infection, co-morbidities, environmental factors
  - Clinical data [ARGO-ICGC]

- **New methods**
  - Artificial Intelligence