

Gene Mutations and Cancer

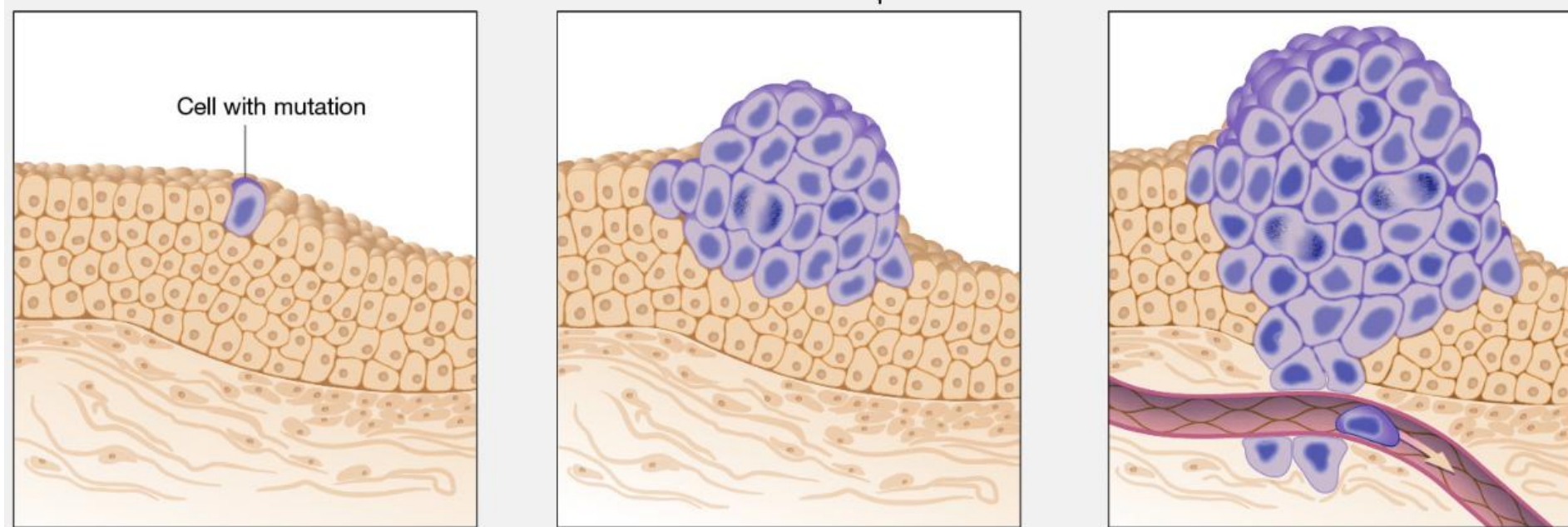
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Cancer is fundamentally a genetic disease

Cancer is clonal



Cancer is clonal

- **Acquired (Somatic) Mutations:**
- **Inherited (Germline) Mutations:**

Cancer is clonal

- **Acquired (Somatic) Mutations:**
 - TP53
 - KRAS
 - PTEN
 - RB1

Specific targetable somatic mutations

- **Acquired (Somatic) Mutations:**
 - EGFR: lung adenocarcinoma, osimertinib
 - ALK: lung adenocarcinoma, Lorlatinib
 - ROS1: lung adenocarcinoma, crizotinib

 - BRAF: melanoma, colorectal cancer, thyroid, cancer; BRAF/MEKK inhibitors
 - BRCA1/2: breast cancer, endometrial cancer, PARP inhibitors
 - MMR deficiency: MLH1, MSH2, MSH6, PMS2; immunotherapy

 - KIT: GIST
 - NTRK:

Specific germline mutations

- **Inherited (germline) Mutations:**
 - TP53: Li-Fraumeni syndrome
 - BRCA1/2: breast/ovarian cancer syndrome
 - MMR: Lynch syndrome
 - Hereditary polyposis colorectal cancer syndrome: APC

Tobacco exposure gene mutation signature

- **Single Base Substitution Signature 4 (SBS4)**
 - cytosine to adenine transversion

UV exposure gene mutation signature

- **Single Base Substitution Signature SBS7**
 - A high frequency of **C>T transition mutations** occurring at **dipyrimidine sites**.

“Clock-like” gene mutation signature

- **Signatures SBS1 and SBS5:** These specific patterns of DNA damage are found in almost every solid tumor type in older patients.
 - **SBS1:** Caused by the spontaneous deamination of 5-methylcytosine (a chemical change in the DNA "letter" C).
 - **SBS5:** A background mutation rate that accumulates constantly over time, regardless of how often cells divide.

Aging is the single greatest risk factor for
developing cancer

Why is aging a problem?

Why is aging a problem?

- ❖ Accumulation of somatic mutations
- ❖ Decline of DNA repair
- ❖ Changes in epigenetics
- ❖ Increased activity of transposons

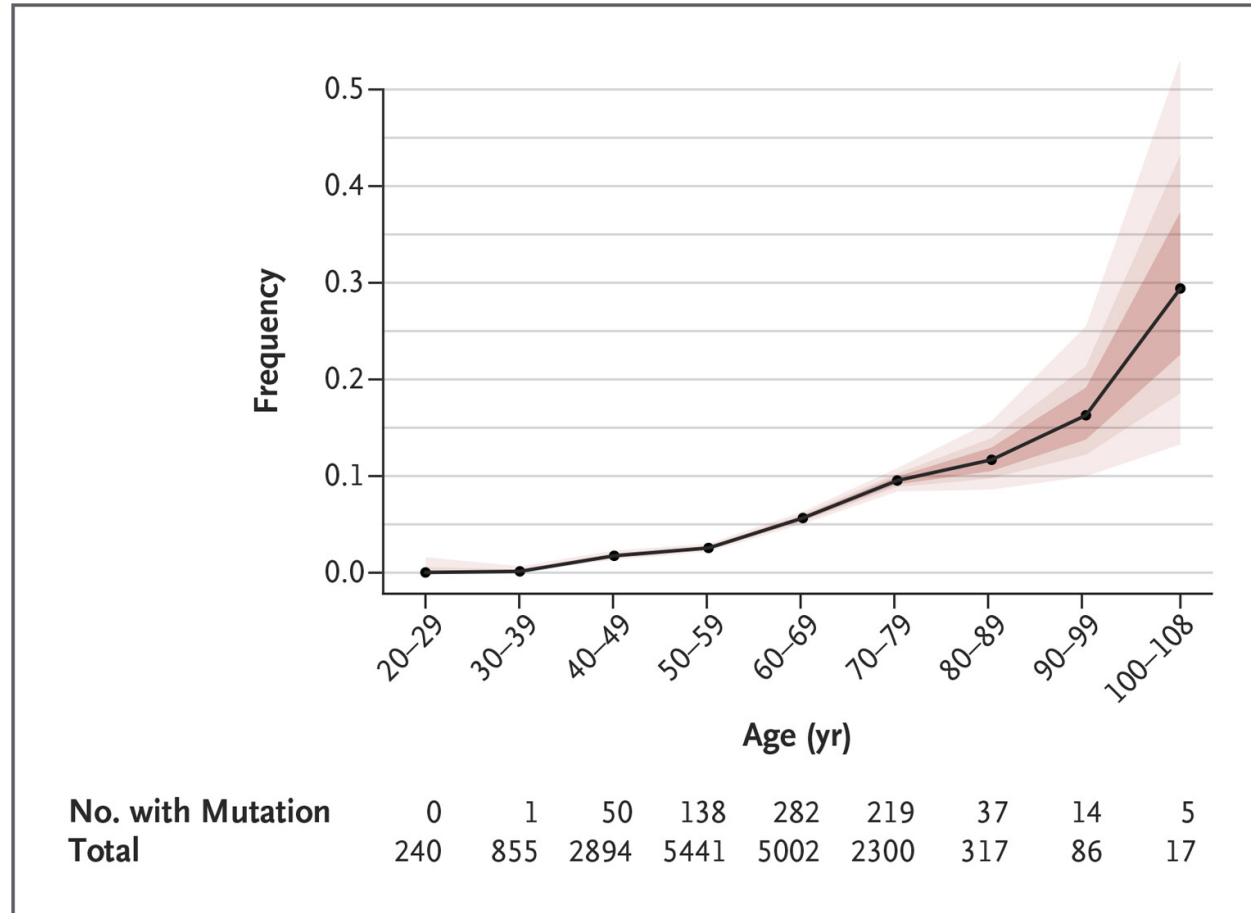
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Why is aging a problem?

- ❖ Changes in epigenetics
 - ❖ **Global Hypomethylation**
 - ❖ **Local Hypermethylation**
 - ❖ **Epigenetic Clocks**

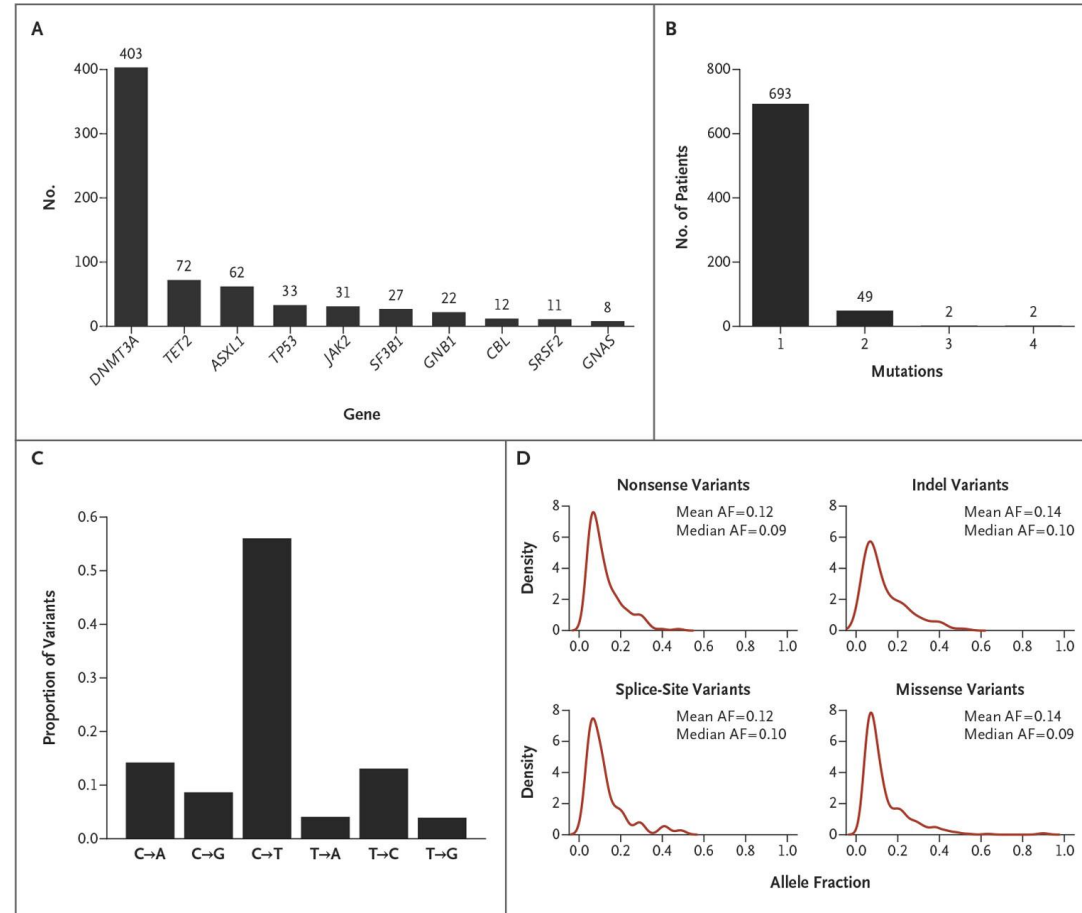
Why is aging a problem?



Age-Related Clonal
Hematopoiesis Associated
with Adverse Outcomes

Jaisal et al., NEJM 2014

Why is aging a problem?



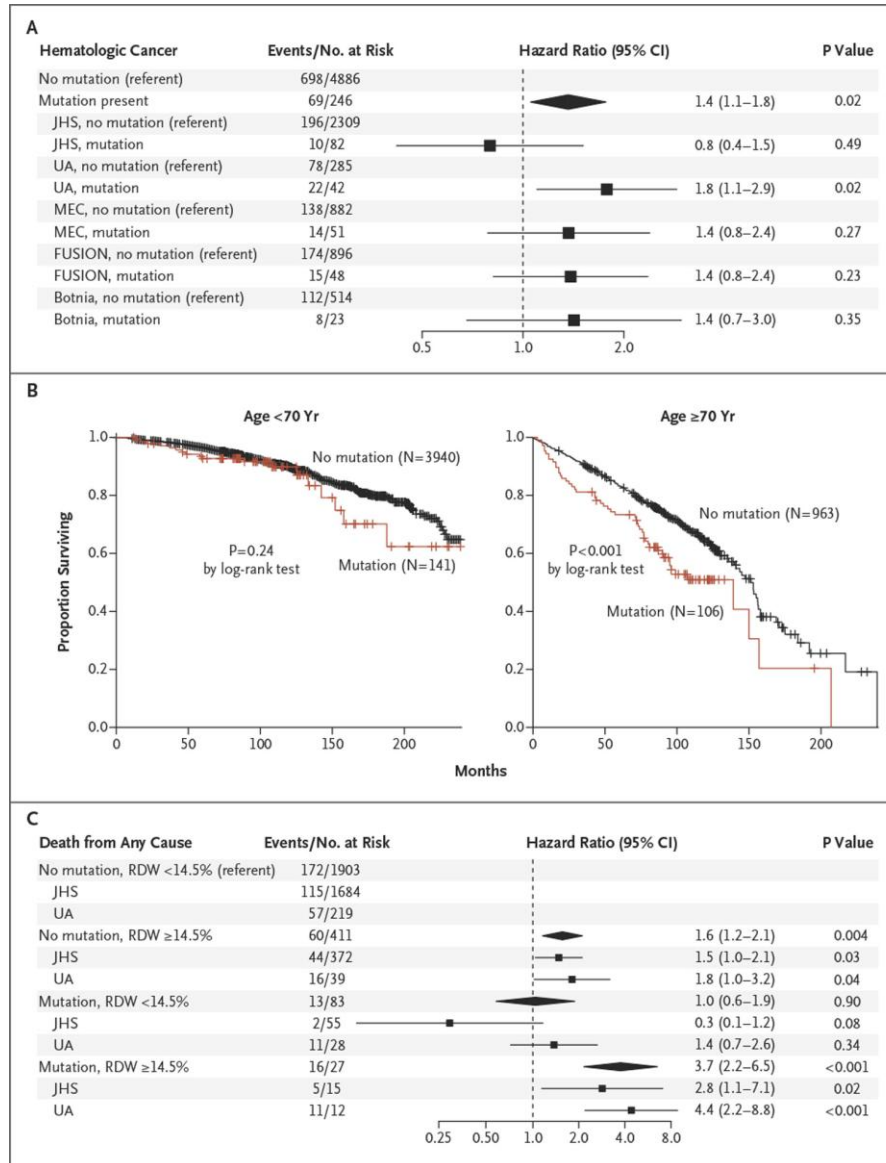
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Why is aging a problem?

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

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1. 基因突变引起癌症的机制？
2. 有哪些不良习惯容易引起基因突变？
3. 如何预防基因突变？
4. 基因治疗的临床应用例子，临床实验的例子。科研的瓶颈
5. 基因都是四个碱基组成的，为什么有些基因容易突变，为什么有些基因突变了容易引起癌症？为什么某些人容易出现某些基因突变？
6. 林奇综合证的诊断，与肿瘤发生的关系和治疗相关性
7. 卵巢癌brac胚系和体系突变与预后和治疗的关系
8. 筛查肿瘤可以查血基因突变预防吗