A CANCER IN THE FAMILY
Truthiness, Consent and Meaning in Our Genes

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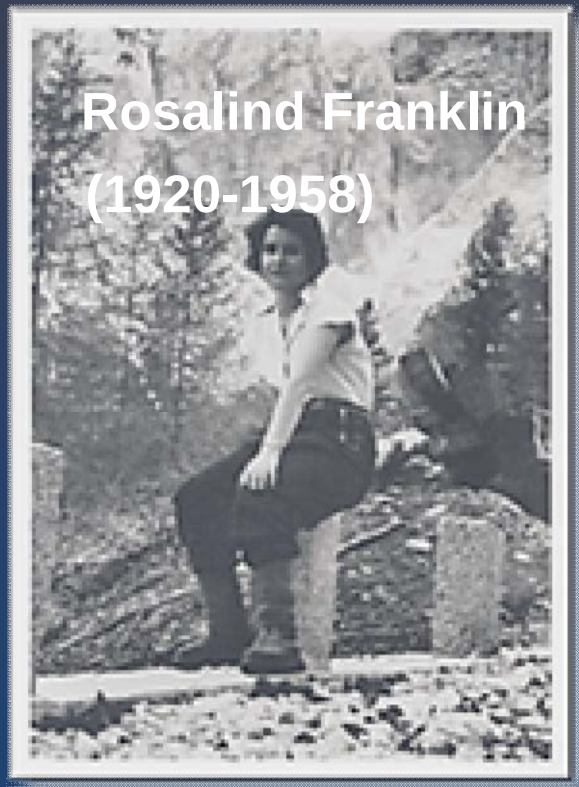
The power of genetics: preventing and knowing cancer



Gilda Radner
1946-1989

The Odd Couple
Lemmon Matthau
1925-99 1921-98

Survivors, Previvors, Strivers





Applegate, Jolie, Lynch, Olopade, Narod

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An Accurate Family History is the Essence of Cancer Genetics Research

“There have been no cancers in my family.”

“Everybody has cancer in my family.”

“I was adopted. Now what?”

“Was I adopted?”

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Difficult conversations about test results:
“no, you were not adopted”

Why not just sequence our genomes, find out our cancer risk and forego difficult conversations?

- Thankfully, $99, $199 or $249 DTC “genetics tests” (e.g. 23nMe) are outlawed from providing important health information – Why?

- We have 20,000 genes and many intervening sequences. We know a bit about 4,000 genes. We know nothing about the rest.

- The meanings of misspellings of our genes are only known if we know the health histories of those of us with those misspellings

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Why not just sequence your genome?

- **The meanings of misspellings of our genes are only known if we know the health histories of those with those misspellings**
- **This is why family history is so important.**
- **But are there problems with family history…**

Family History of Cancer: Skepticism Required

- There are cancer “secrets” in most families (Phuong L. Mai 2011) when people disclose their cancer histories, those histories are <u>usually</u> inaccurate.
- 1,000 Connecticut residents reported about cancers in their relatives and information compared to data in registries, Medicare databases, death certificates, and other health records.
- Up to 75 percent contained errors, with reports of lung cancer as least accurate. This could be due to misinformation, denial or secrecy… or even truthiness…

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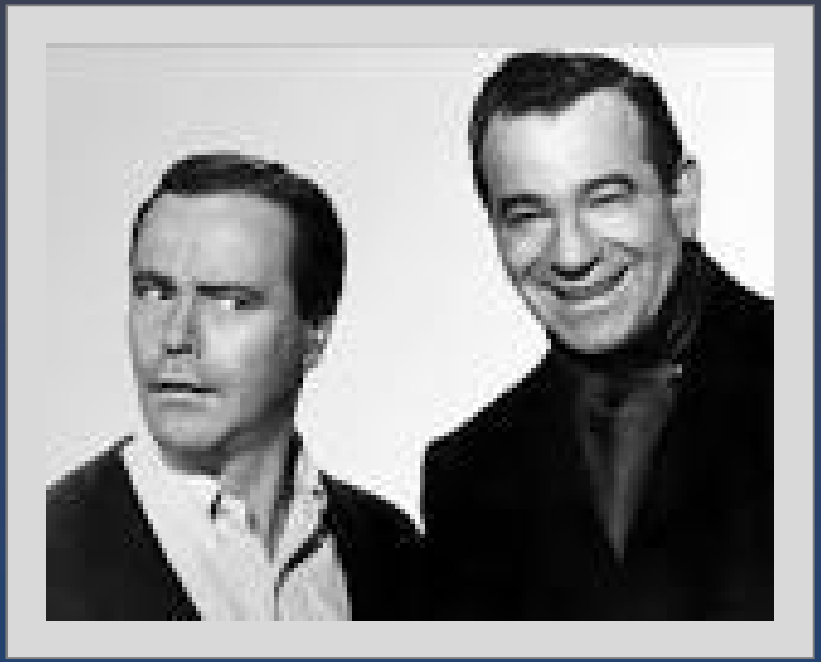
MMR genes, or Lynch genes, when broken lead to colon cancer in the family

- Lynch syndrome name after Henry Lynch
  1966 Lynch described families
- *MLH1, MSH2, MSH6, PMS2*, *EpCAM* (Kolodner et al)
- If inherit a broken gene, 75% lifetime risk for colon ca
- Endometrial, ovarian, gastric AND bladder (Lemmon?)

What have *family history of cancer shares* done for us in the last 20 years?



Jack L
1925-1999

Walter M
1921-1998

Lemmon has two bio-children.
It would be good to know his family tree --he had both bladder and colon, it's suspicious

If his kids have Lynch S, they will be able to live longer and healthier.

If they don't have LS, do they have another mutation? A good research question.

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BRCA1/2 are only two of many genes that when broken lead to cancer in the family

- *BRCA1* was discovered in 1994 (Futreal et al, Miki et al)
- *BRCA2* In 1995 (Wooster et al)
- In the 1990s there was no clinical value to the knowledge
- Now it helps us prevent cancer from happening

What has information sharing done for us in the last 20 years?

**“I grew up in front of a TV.
I guess I’ll grow old Inside one”
-Gilda R**

Christina and Angelina will grow old inside one -as they had their “exquisite breasts” replaced.

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Why not just sequence your genome and avoid the tough conversations?

- **Why are family conversations still so important?**

  A 20 vs. 80 percent risk spread is key in our choices of life-changing surgeries or screening or family searches…

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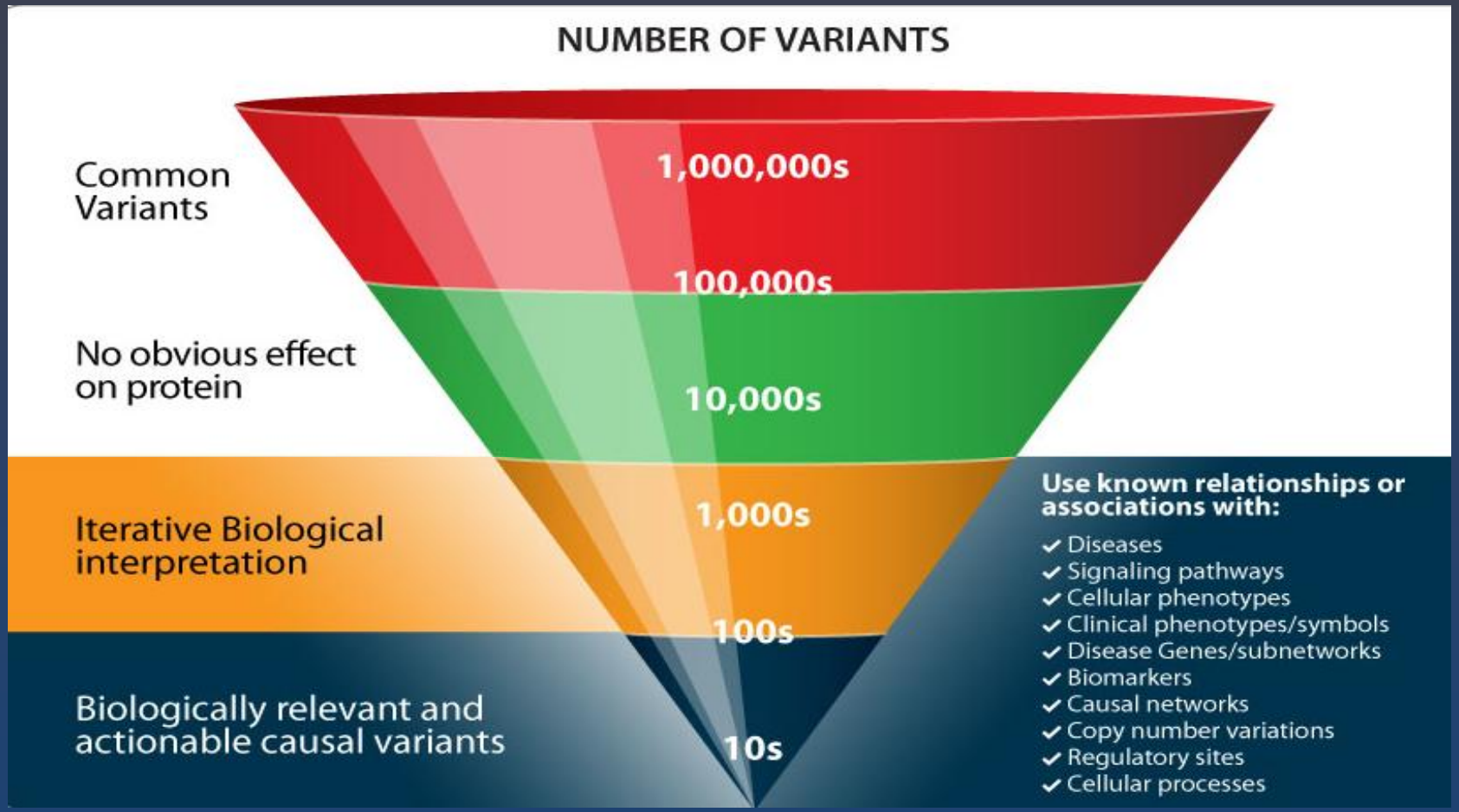
Not everybody with a *cancer gene* mutation gets cancer. Why?

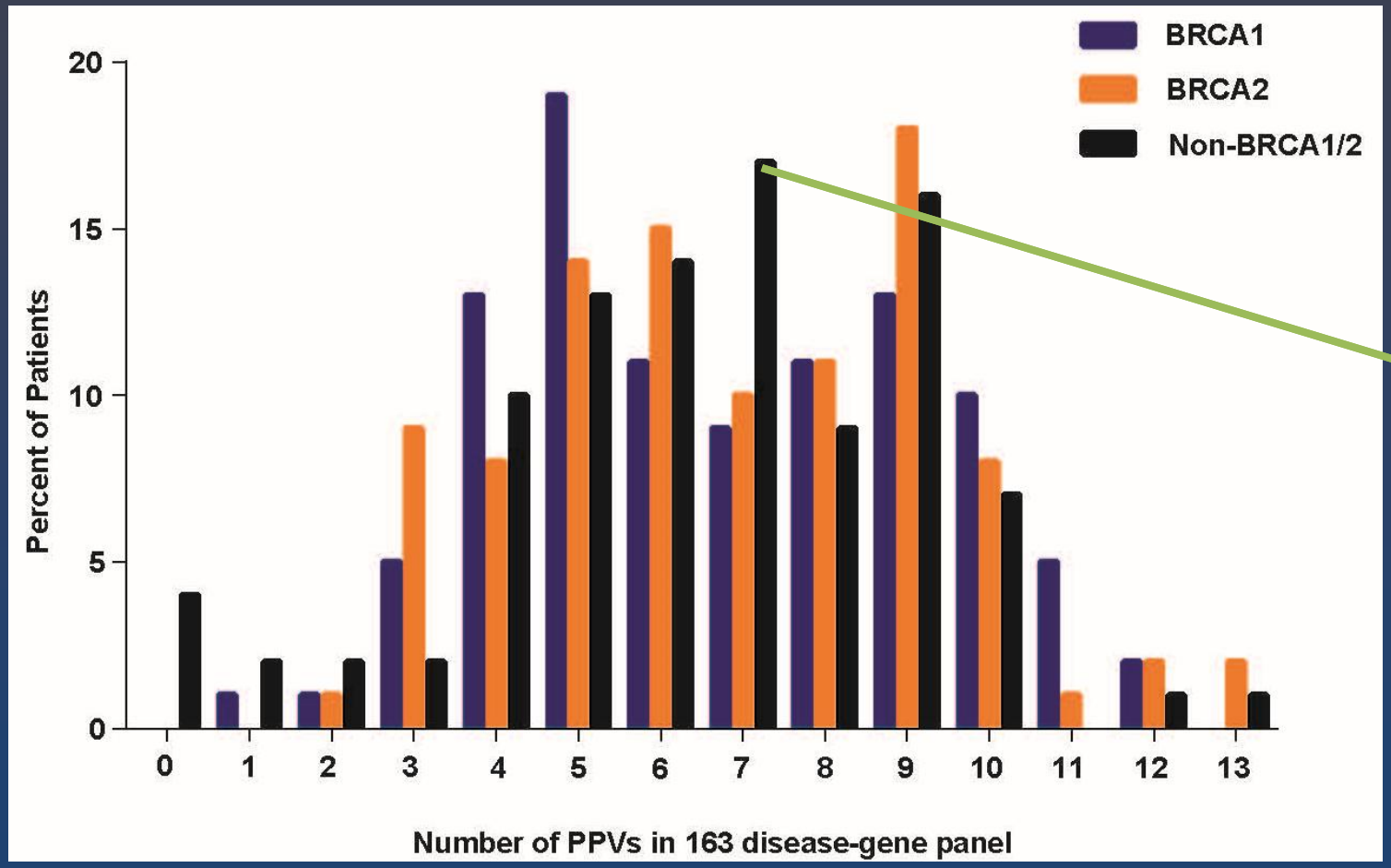
-Environment: aspirin, radiation, alcohol and exercise (Erma Bombeck philosophy of exercise: the real reason to jog is to hear heavy breathing again)

-Family: The youngest age and breast ca #s in the family can predict if others in the family will develop colon or breast cancer (30 v. 60 percent chance influences management choices).

Germlines of 176 *BRCA* mutant and 82 non-BRCA mystery patients



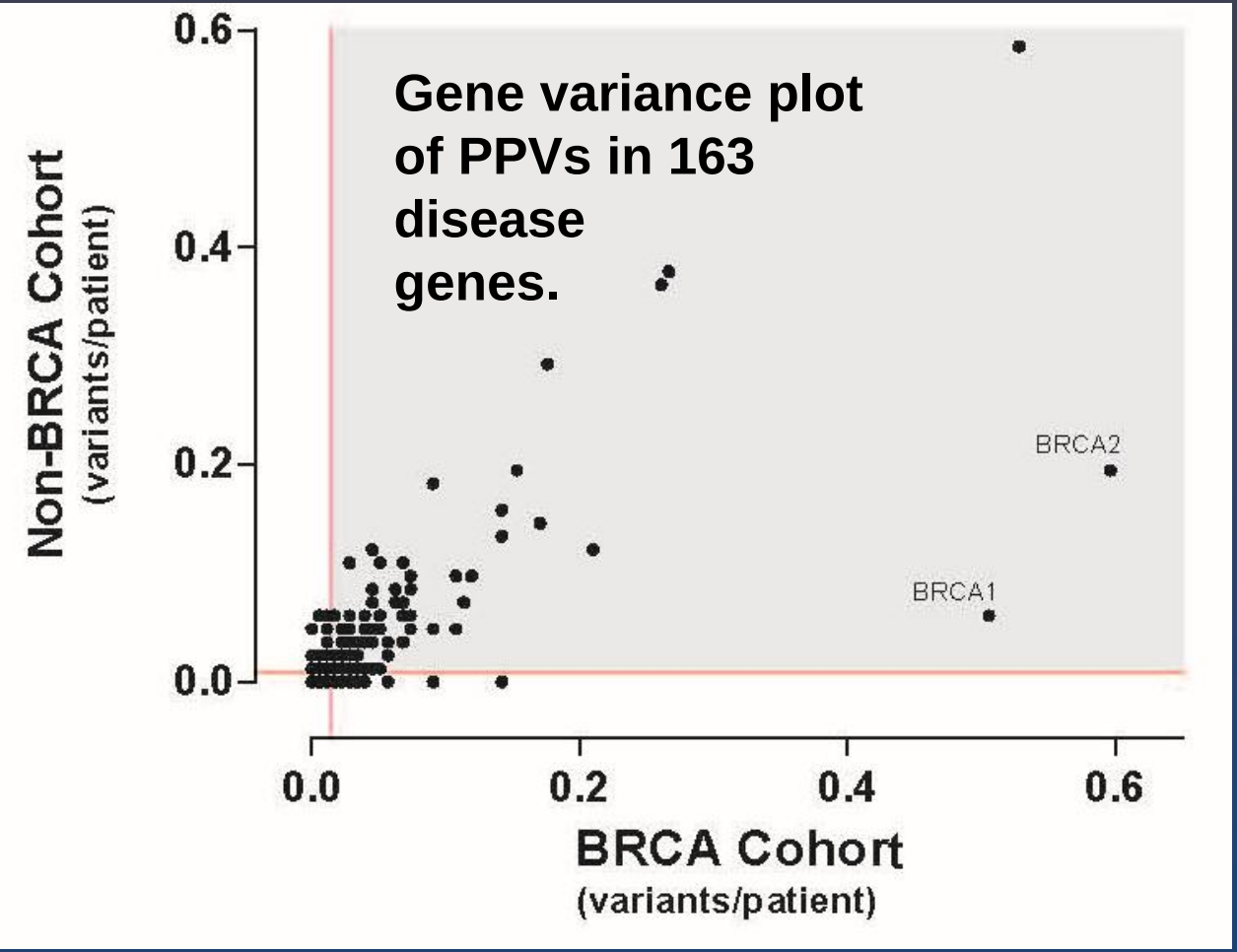
A flood of sequence variations in disease genes



7/163 x 20,000 = 858 PP variants In coding regions alone! 400 never seen before.

Foley et al EBM 2015

TFI to TMI: too many ideas



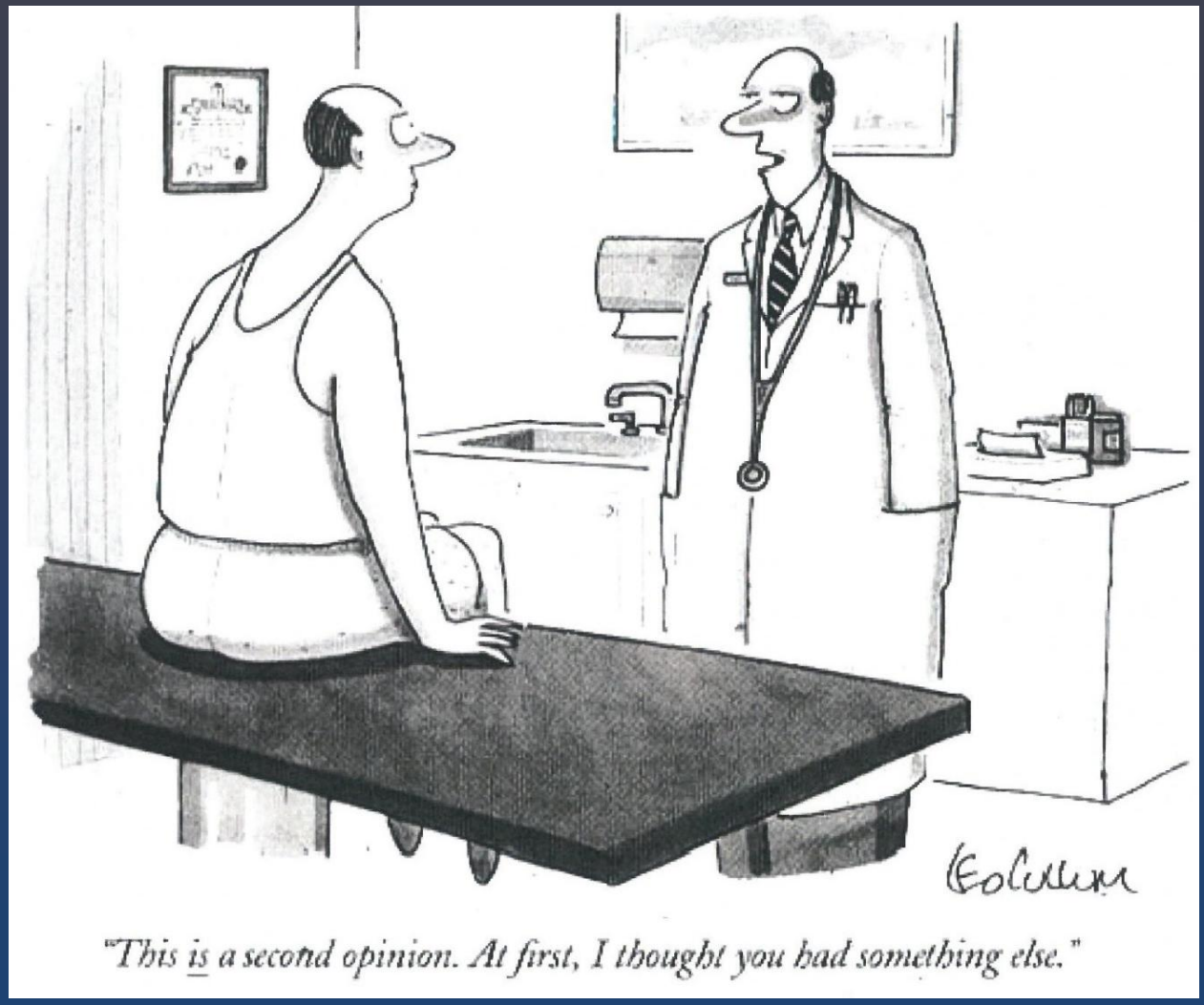
Shaded are PPVs in at least 2% of the BRCA control cohort. Being in the grey area means a VUS (can't interpret).

How do we find the hidden broken genes?

1. There are additional mutations in cancer-associated genes in BRCA-mutants – could explain why family history remains key.

2. Found new mutations in mystery non-BRCA patients – ERCC3, FANCC

Continue the genetic analysis



"This is a second opinion. At first, I thought you had something else."

The roots of our family trees are found in *accurate* health histories

Finding the truth in truthiness

→ prevention

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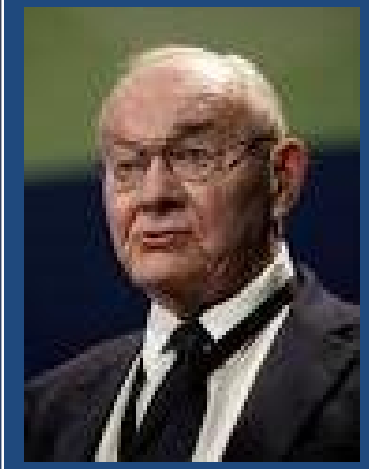
Strivers, Survivors, Previvors



Lynch

Olopade

Christina A
1971-

Angelina J
1975-

Brad P
1963-

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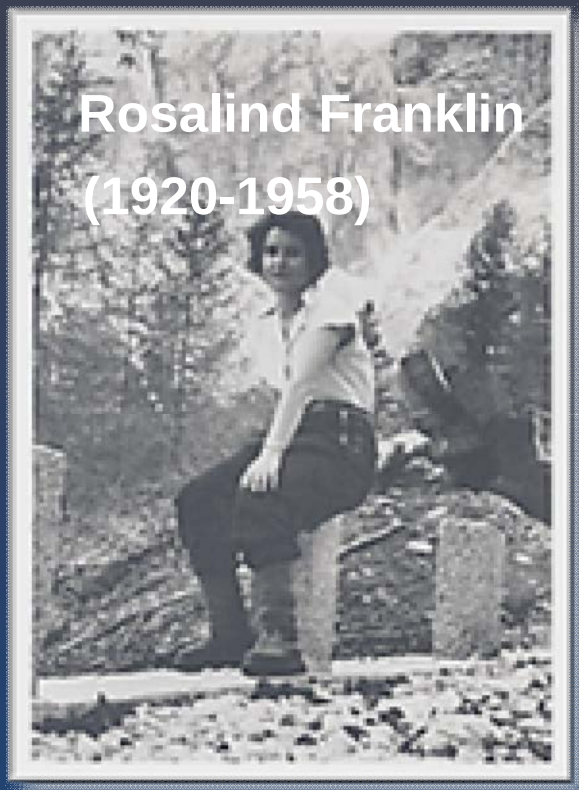
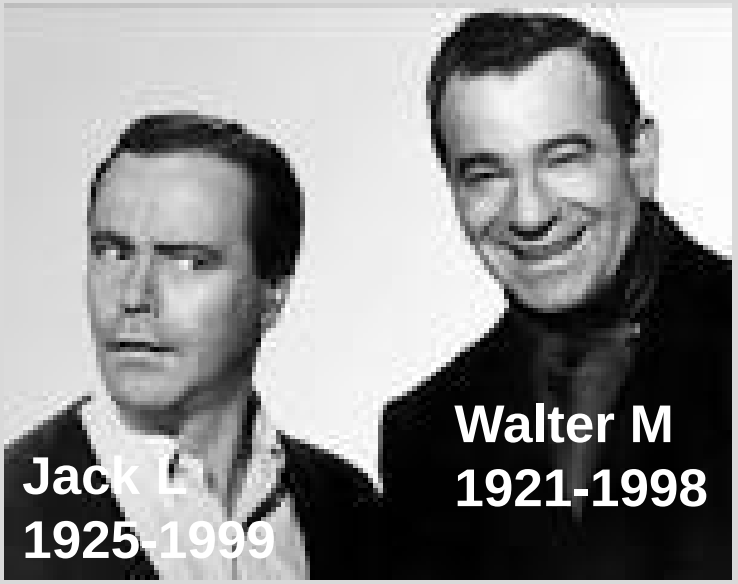
Inspiration





The anonymous patient volunteers

And of course….team genes….

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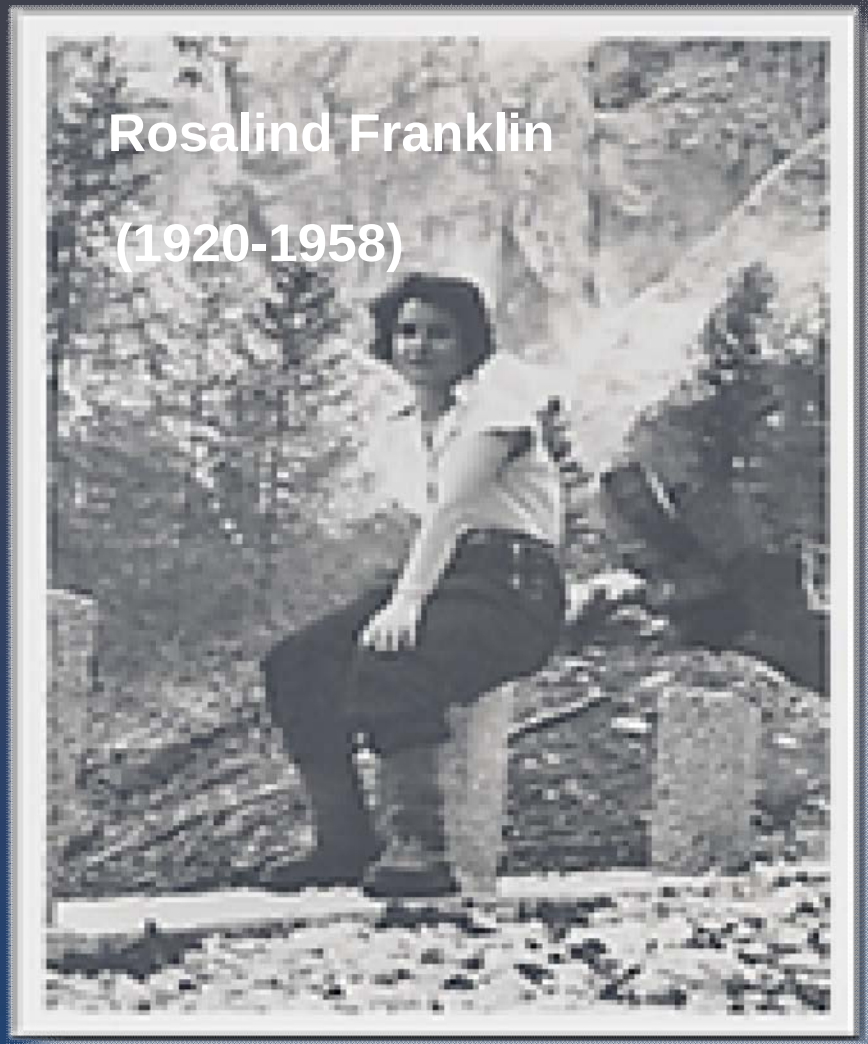

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