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

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The power of genetics: preventing and knowing cancer

Rosalind Franklin (1920-1958)

Gilda Radner 1946-1989

The Odd Couple
Lemmon 1925-99  Matthau 1921-98
Survivors, Previvors, Strivers

Applegate, Jolie, Lynch, Olopade, Narod
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?”
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
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...
There are cancer “secrets” in most families (Phuong L. Mai 2011) when people disclose their cancer histories, those histories are usually 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…
*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?

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.

Jack L 1925-1999
Walter M 1921-1998
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.
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…
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 cancer numbers 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

How do we find the hidden broken genes?

Gene variance plot of PPVs in 163 disease genes.

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

Lynch
Olopade
Christina A 1971-
Angelina J 1975-
Brad P 1963-

UT Southwestern Medical Center
Inspiration

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The anonymous patient volunteers

And of course….team genes....
Rosalind Franklin (1920-1958)

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