Here is Washington DC....Everything is political

So, let's begin the standard operating procedure:

Smearing your opponent and avoiding a serious discussion of ideas
Let’s Begin with Data from Cambridge (Analytica)

Who is Zak Kohane

Larry King

But doesn’t he look a lot like..............->

“Fair & Somewhat Balanced”
Back to Basic Facts

**Not: Fake Non-Genetic News**

- All diseases are complex- Human and non-Human.....
  - Modifiers- other genes and exposures
- Historically, Genetics handles time poorly, especially in our models....
- Family History....
  - Superb surrogate for genetic background (though shared exposure is key)
Genetic Susceptibility to Precision Medicine & Precision Prevention

Under Construction

Beware of Sources......
Arc of Genetics

Discovery  Validation  Clinical

Two Myths
- One Technology can do it all
- Single Studies tell the full story
Genetics and Context 2019- and Beyond
Pandora’s Box has been opened
Even Fox News can’t close it....

- Genetics and Absolute Risk
  - When is it useful for screening
  - When is it useful for Diagnosis/Treatment?
    - Individual vs Public Health
  - Common Diseases vs Rare & in between......

- Challenge is how to apply genetic knowledge to
  - Individual vs Populations
  - Specific Recommendation vs Stratification of Public Health Decision
  - Observational/Real Life vs RCTs

Current Paradigm: Can It Change?
Inverse Relationship Between Incidence and Risk Stratification
PRS for common challenges
Specific testing for rarer events
Precision medicine vs precision prevention

• “Individual vs States rights”
  • Individual harder right now but moving there.....
    • ACMG Genes
    • PRS for stratification for Heart disease (CHD & AF), Cancers, T1D

• Value of Family History
  • Cascade Testing- driven by testing and possibly family history

• Value of Risk Factors
  • Measured- lipids & PRS
  • Lifestyle

• Public Health Genomics is moving into prime time
Pharmacogenomics & Pharmacogenetics

• Early examples of using genetics
  • Malignant hyperthermia
  • FV-Leiden and risk
  • Cancer Therapy
    • Chemotherapy and Toxicity
• Paradox of Capitalism and Pharma
  • Precision breaks most models...
• **Toxicity** is as perhaps important as **Efficacy**
Evidence for Heritability of Cancer

1866  Broca observed heritability based on wife’s familial breast cancer

Interim  Twin/Family/Sibling studies...

1969  Li-Fraumeni observed familial clustering (TP53)

1971  Knudson postulated “two-hit” hypothesis for retinoblastoma

1991  Mapping of a familial breast cancer gene (BRCA1)
Breast Cancer Testing
Germline & Somatic

• Absolute Risk: 1 in 8 women in the US

• Genetic Predisposition- COMPLEX
  • 5-10% of population have ‘actionable’ mutation (BRCA1/2, etc)
  • PRS separates large fraction

• Modifiable Risk Factors
  • Target for higher PRS in Population

• Somatic Information-
  • Drives targeted and immunotherapy
  • Multiple Subtypes with distinct clinical courses
  • Mutational Signatures- (cancer genome patterns)
Can we identify additional loci by accounting for tumor heterogeneity?

Proportion of familial breast cancer relative risk explained*

Unexplained: ~36%

- BRCA1
- BRCA2
- CHEK2
- ATM
- PALB2
- TP53
- PTEN
- LKB1
- 27 loci
- 80 loci iCOGS (~5%)
- 72 loci Oncoarray (~5%)
- 27 loci pre-iCOGS (~9%)
- Estimated on chip (~22%)

In Europeans

Familial Relative Risk (FRR) = 2.0

Michailidou et al. Nature 2017
Milne et al. Nature Genetics 2017
PANEL TESTING – THE WILD WEST

ACMG 26
CPG ~125
Academic (somatic) 400-550
The Impact of Changes in Lifestyle May be Larger for Women at Higher Non-modifiable Risk

Distribution of modifiable risk by deciles of non-modifiable risk

- Heavy drinker, smoker, obese/HRT
- Never drinker or, smoker, no HRT use, healthy weight,

Can we utilize PRS for Stratification leading to Prevention & Intervention?

Maas et al JAMA Oncology 2016
Breast cancer risk stratification by different risk factors

US Non-Hispanic Whites
Ages 50 - 70 years

- Classical risk factors only (AUC=58.5)
- MD only (AUC=61.0)
- 313-SNP PRS only (AUC=63.1)
- All risk factors (AUC=68.3)

Number of women crossing a 3% risk threshold

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Number of Women Crossing 3% Risk Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>153,000</td>
</tr>
<tr>
<td>MD</td>
<td>3.5 M</td>
</tr>
<tr>
<td>313 SNP PRS</td>
<td>76,000</td>
</tr>
<tr>
<td>Integrated Model</td>
<td>46,500</td>
</tr>
<tr>
<td>Classical plus MD</td>
<td>17,000</td>
</tr>
<tr>
<td>Classical plus 313 SNP PRS</td>
<td>1,304,629</td>
</tr>
<tr>
<td>MD plus 313 SNP PRS</td>
<td>2,030,499</td>
</tr>
<tr>
<td>Integrated Model</td>
<td>500,167</td>
</tr>
</tbody>
</table>

Number of breast cancer cases within 5 years

- Classical: 500,167 cases, 58.5 AUC
- MD: 1,304,629 cases, 61.0 AUC
- 313 SNP PRS: 2,030,499 cases, 63.1 AUC
- Integrated Model: 3,501,245 cases, 68.3 AUC

Choudhury, Wilcox et al. Under Review
Mutational signature analysis has emerged as a powerful approach for investigating the processes that generate somatic mutations. Conceptually, this analysis is based on the observation that different mutational processes generate specific base-pair changes, typically in particular nucleotide contexts. For instance, ultraviolet radiation generally results in cytosine to thymine (C to T) changes, often with a C-adjacent pyrimidine (with the same name). 

However, recent genome-wide analyses have shown that the same pattern of mutations found in BRCA1/2-mutant tumors is also present in several other tumors. Here, we present a new computational tool called Signature Multivariate Analysis (SigMA), which can be used to accurately detect the mutational signature associated with HR-deficiency from targeted gene panels. Whereas previous methods require whole-genome or whole-exome data, our method detects the HR-deficiency signature even from low-mutation counts, by using a likelihood-based measure combined with machine-learning techniques. Cell lines that we identify in HR-deficient show a significantly longer overall survival with platinum-based chemotherapy, and our method substantially increases the number of patients that may be considered for treatments targeting HR deficiency.

Mutational Signature 3
Pediatric and Adult Experience
Identifying Germline Susceptibility to HRD
But immediately actionable for ‘PARP-inhibitor’
Genetics: Here to Stay...
Why we might move to national health care: The Schumer-McConnell Conundrum

Damn it- why are my premiums 3 times yours?
Answer:
Family History of Prostate Cancer, CHD & Alzheimers
How un-American....Didnt We Fight a Revolution to Remove Heredity??

Lucky me- I have a better family history