Here is Washington DC….Everything is Political

So, lets begin the standard operating procedure:

Smearing your opponent and avoiding a serious discussion of ideas

Let’s Begin with Data from Cambridge (Analytica)

HARVARD MEDICAL SCHOOL

Who is Zak Kohane

But doesn’t he look a lot like…….->

Larry King

FOX NEWS

“Fair & *Somewhat* Balanced”

Back to Basic Facts

Not: Fake Non-Genetic News

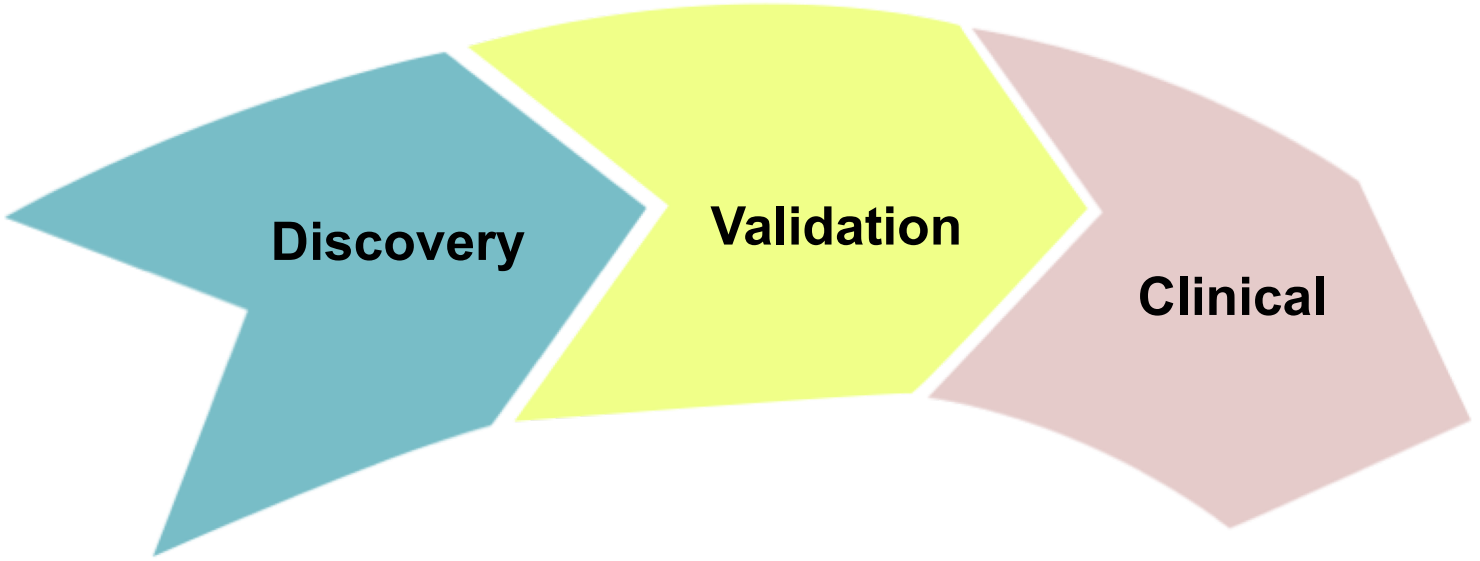
- All diseases are complex- Human and non-Human…..
  - Modifiers- other genes and exposures
- Historically, Genetics handles time poorly, especially in our models….
- Family History….
  - Superb surrogate for genetic background (though shared exposure is key)

Genetic Susceptibility to Precision Medicine & Precision Prevention

Under Construction

Beware of Sources…….

Arc of Genetics



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?

<u>Inverse Relationship Between Incidence and Risk Stratification</u>

PRS for common challenges

Specific testing for rarer events

Precision medicine vs precision prevention

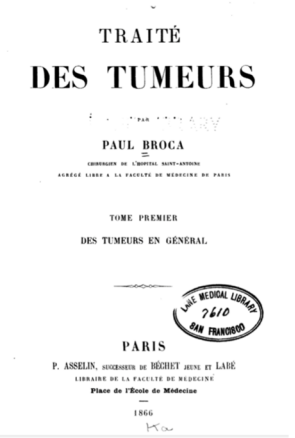
- “Individual vs States rights”
- Individual harder right now but moving there…..
  - ACMG Genes
  - PRS for stratification for Heart disease (CHD & AF), Cancers, T1D
- Value of Family History
  - Cascade Testing- driven by testing and possibly family history
- Value of Risk Factors
  - Measured- lipids & 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

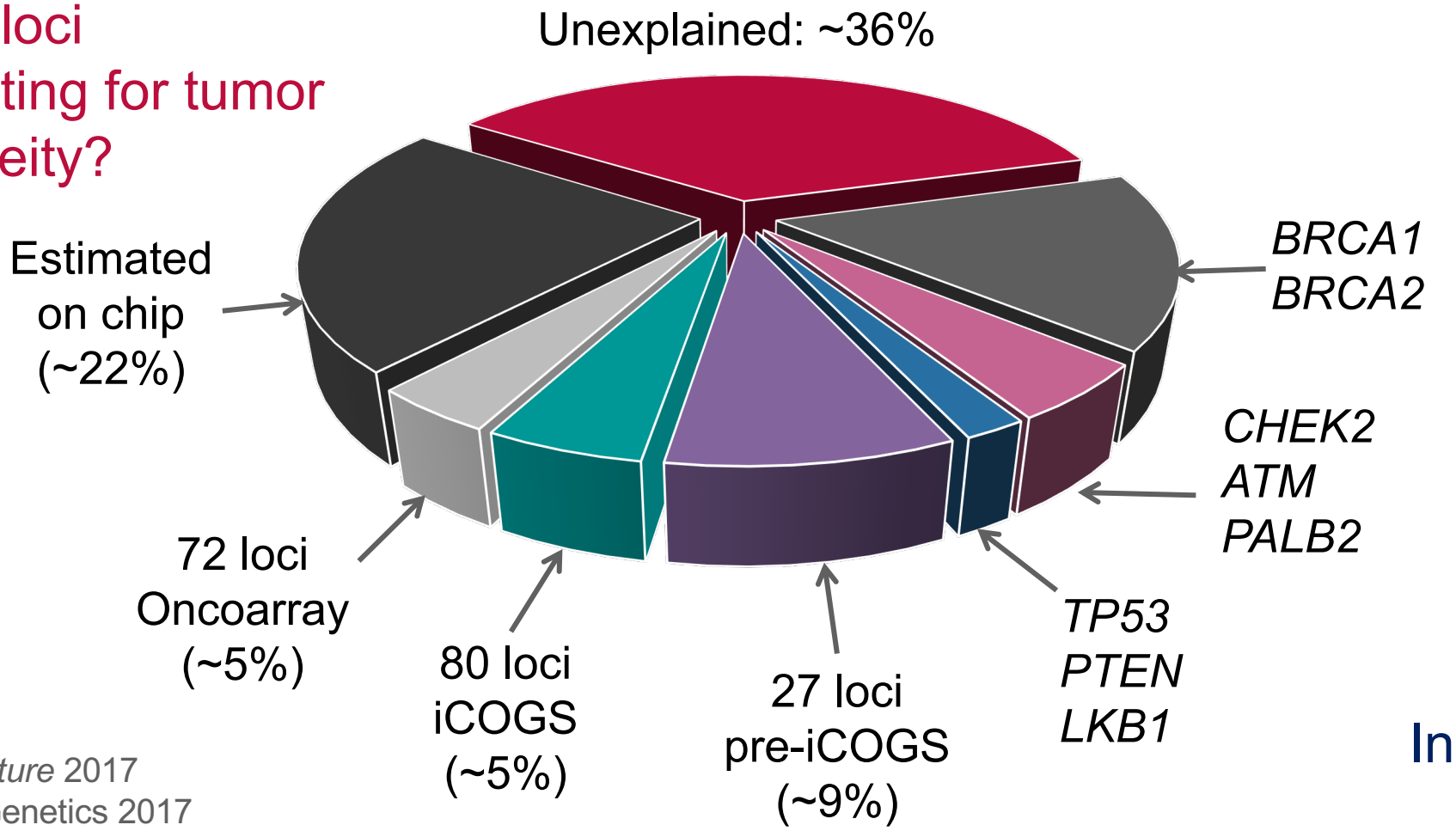
1991 Mapping of a familial breast cancer gene (*BRCA1)*

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)

Proportion of familial breast cancer relative risk explained*

Can we identify additional loci by accounting for tumor heterogeneity?

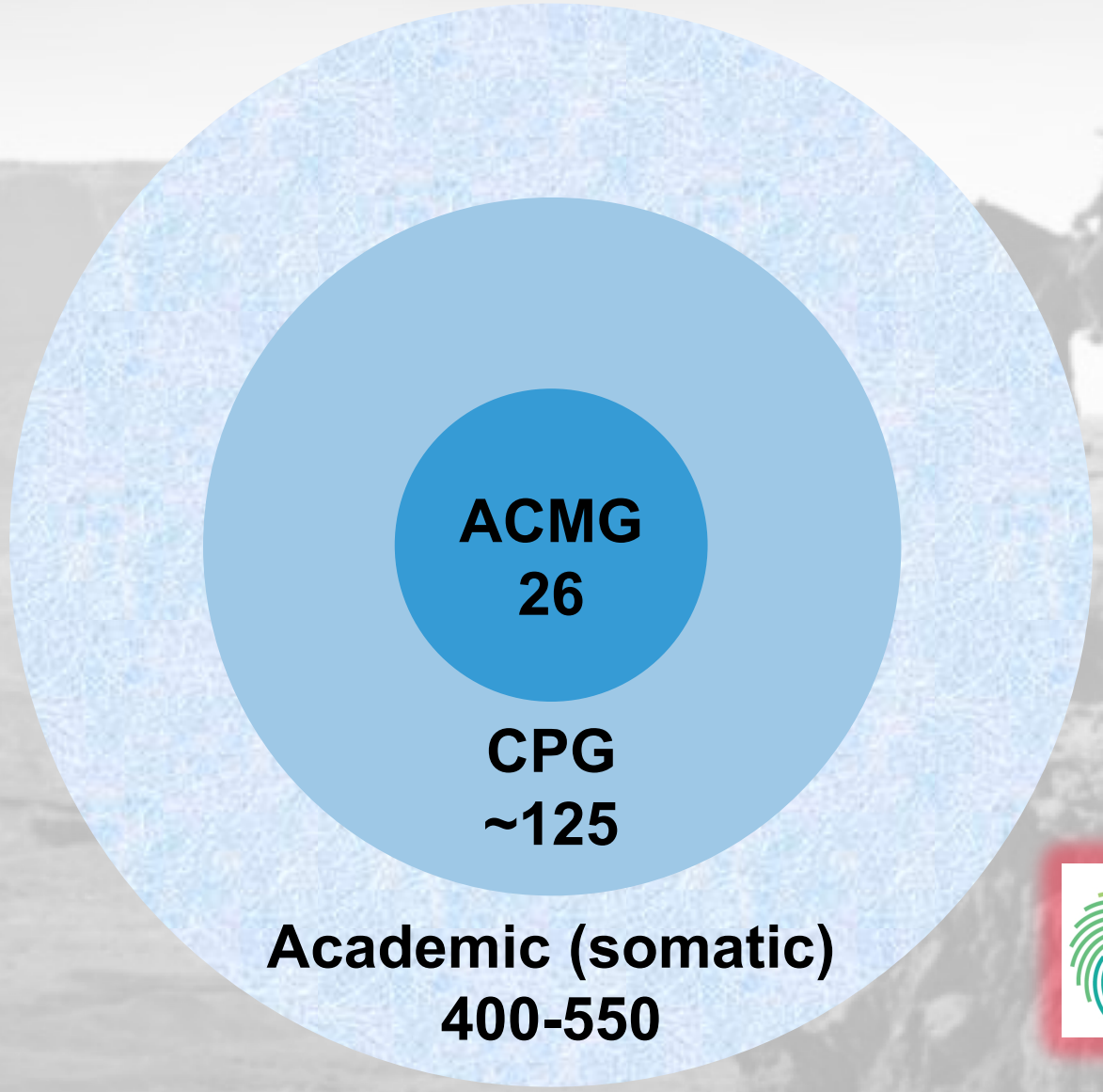


In Europeans

Michailidou et al. *Nature* 2017
Milne et al. Nature Genetics 2017

Familial Relative Risk (FRR) = 2.0

PANEL TESTING – THE WILD WEST



myriad®
WHEN DECISIONS MATTER

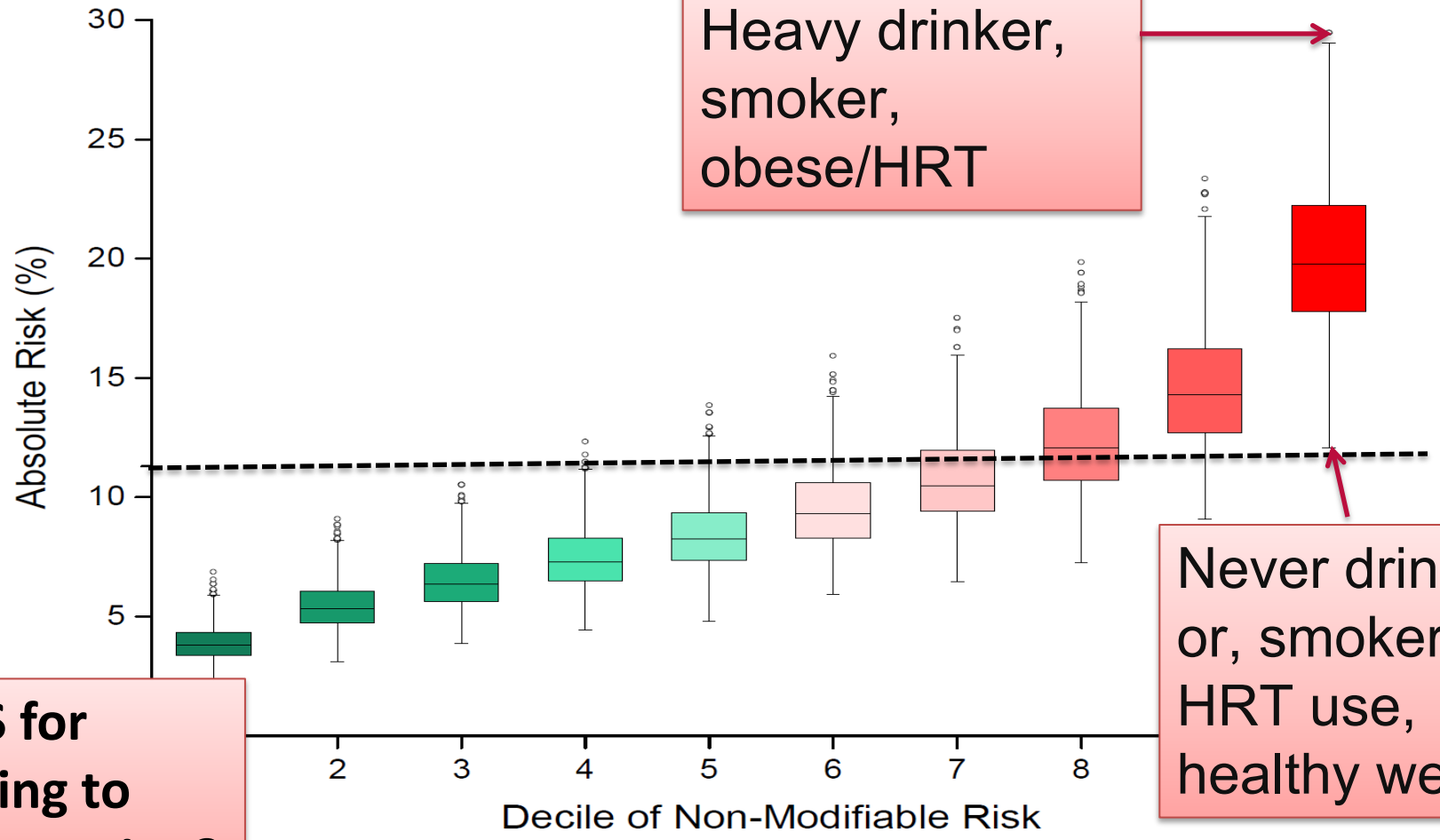
color

GeneDx
an OPKO Health Company

INVITAE

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

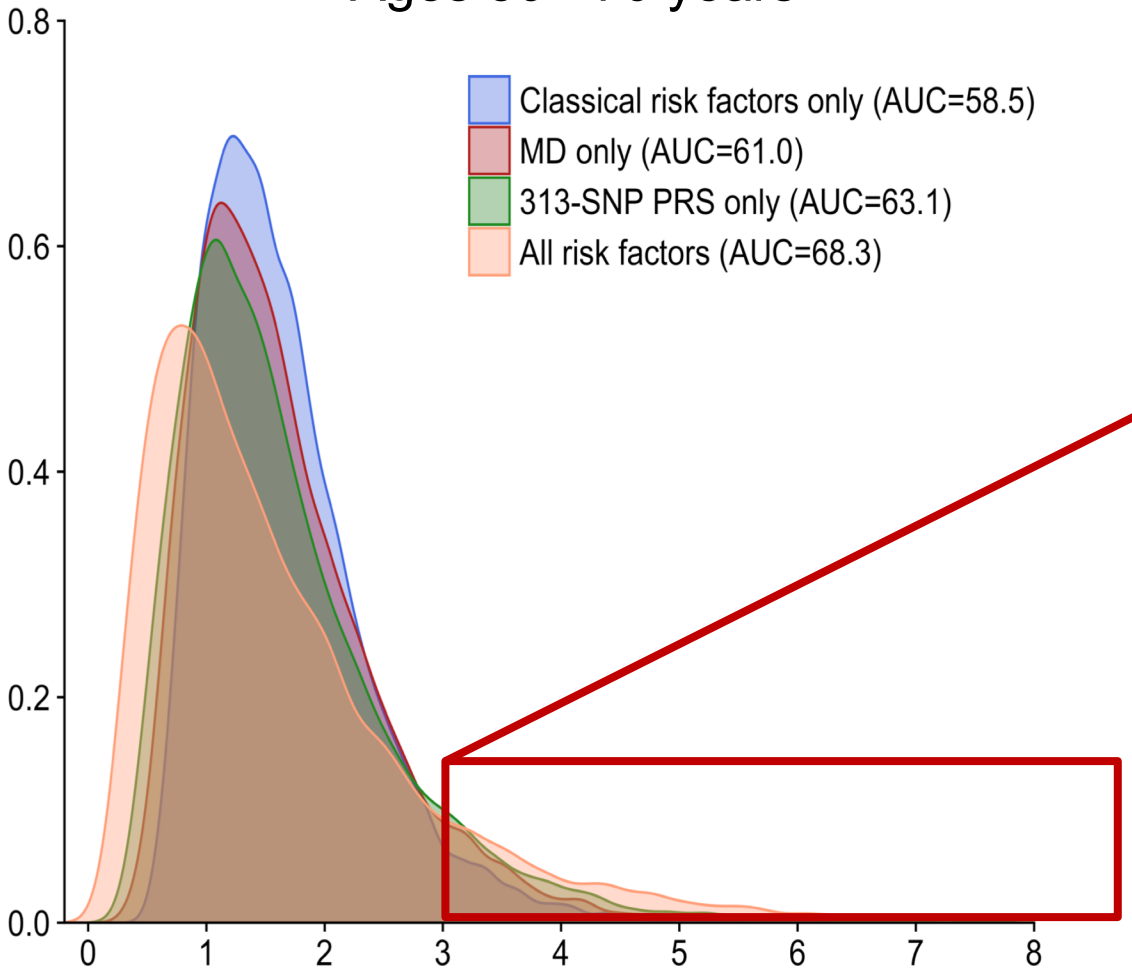


Can we utilize PRS for Stratification leading to Prevention & Intervention?

Maas et al *JAMA Oncology* 2016

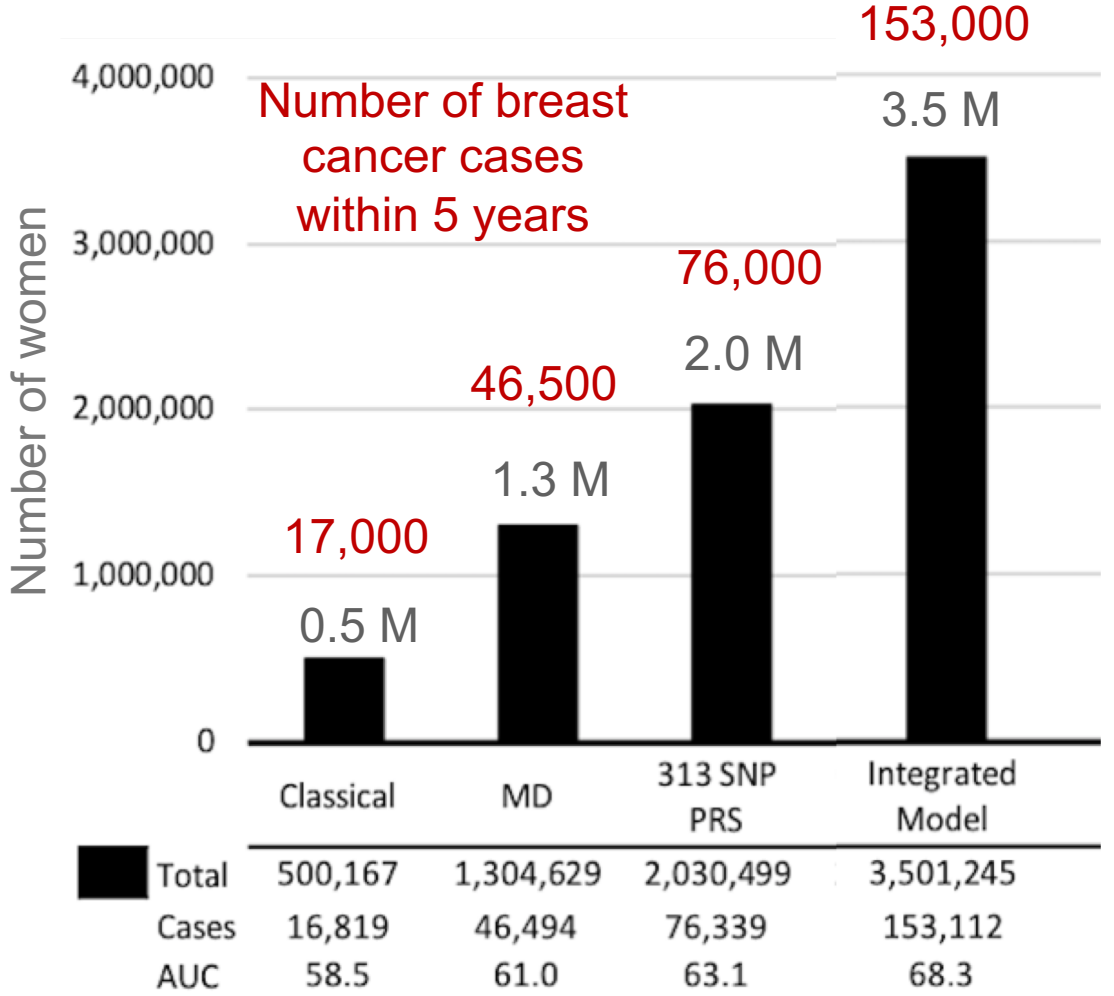
Breast cancer risk stratification by different risk factors

US Non-Hispanic Whites
Ages 50 - 70 years



5-year absolute risk of breast cancer (%)

Number of women crossing a 3% risk threshold



Choudhury, Wilcox et al. Under Review

ONCOtype DX

Somatic profile of breast cancer profile

“To treat or not to treat….
That is *no* longer a question”

But where is the transition…..

TECHNICAL REPORT
https://doi.org/10.1038/s41588-019-0390-2
nature genetics

Detecting the mutational signature of homologous recombination deficiency in clinical samples

Doga C. Gulhan[1], Jake June-Koo Lee[1], Giorgio E. M. Melloni[1], Isidro Cortés-Ciriano[1,2] and Peter J. Park[1*]

Mutations in *BRCA1* and/or *BRCA2* (*BRCA1/2*) are the most common indication of deficiency in the homologous recombination (HR) DNA repair pathway. 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 as HR deficient show a significant response to poly (ADP-ribose) polymerase (PARP) inhibitors; patients with ovarian cancer whom we found to be HR deficient show a significantly longer overall survival with platinum regimens. By enabling panel-based identification of mutational signatures, our method substantially increases the number of patients that may be considered for treatments targeting HR deficiency.

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[1]. For instance, ultraviolet radiation generally results in C-to-T changes, often with a C flanked by a C or T on the 5′ side. In its popular form[2,3], this analysis computes a vector of 96 triplets (six substitution subtypes, C>A, C>G, C>T, T>A, T>C and T>G, each flanked by one of the four types on the 5′ and 3′ sides) for a set of genomes and deconvolves the observed mutational spectra into independent components. Application of this concept to thousands of tumor samples with exome or whole-genome sequencing (WGS) has led to a catalog of nearly 40 mutational signatures operative in cancer[2,4]. Some of these signatures have been matched to specific mutational processes, both endogenous (for example, replication clock, apolipoprotein B mRNA editing catalytic polypeptide-like (APOBEC) cytosine deaminases, defects in the DNA repair machinery) and exogenous (for example, smoking carcinogens, ultraviolet radiation)[5–12], although the majority still remain uncharacterized.

In breast cancer, a landmark study of 560 whole genomes[13] and subsequent studies[14,15] showed that one of these signatures—'Signature 3' (Sig3)—corresponds to a deficiency in the HR machinery (Supplementary Fig. 1). This signature is observed in tumors with complete *BRCA1/2* inactivation, which can occur by germline and somatic point mutations combined with loss of heterozygosity, hypermethylation of *BRCA1* promoters or loss-of-function mutations of *PALB2* and *RAD51D*[16]. Experimentally, Sig3 was observed in *BRCA*$^{-/-}$ isogenic cell lines, providing direct evidence of its association with HR deficiency[14].

Importantly, there is increasing evidence that Sig3 is not limited to those with a germline mutation in *BRCA1*/2 or other known HR-related genes[13,15,17]. This is clinically relevant because those without a mutation in a known HR gene but who present Sig3 may benefit from treatments that target selective vulnerabilities of HR-deficient cancers. A recent study using breast cancer organoids, for example, has shown that a high burden of Sig3 mutations is associated with a better response to poly(ADP-ribose) polymerase (PARP) inhibitors[18]. Inhibitors of PARP enzymes cause multiple double-strand breaks; tumor cells that cannot repair the breaks because of HR deficiency do not survive.

In this study, we propose a new method for detecting Sig3 from sequencing data of an individual. Although previous methods have addressed the identification of HR deficiency through mutational signatures[14,15], they were limited to exome or whole-genome data, thus hampering use in clinical practice. For the most common genetic testing platform in oncology clinics—targeted sequencing panels—the number of mutations identifiable is far too small for standard signature analysis. A recent panel-based study of 10,000 cancer patients, for example, could perform signature analysis for only 6% of the samples with the highest mutational burden[19]. Our computational tool, Signature Multivariate Analysis (SigMA), uses a likelihood-based approach that can detect signatures, including Sig3, from low mutation counts. Thus, application of this method has the potential to vastly expand the number of patients that could benefit from treatments available for HR-deficient tumors.

Results

Limitations of current methods. Existing methods for signature analysis follow one of two approaches. One approach is to discover signatures from all available genomes by applying an unguided decomposition algorithm, such as non-negative matrix factorization (NMF)[3,20,21]. The other approach is to find an optimal combination of predefined signatures for a given sample, for example, by using non-negative least squares (NNLS)[20,22]. The commonality in the two approaches is the decomposition step where the mutational spectra of tumors are described as a linear combination of signatures. In the first case, the signatures are discovered simultaneously with their coefficients, which we also refer to as 'exposures'; in the

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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