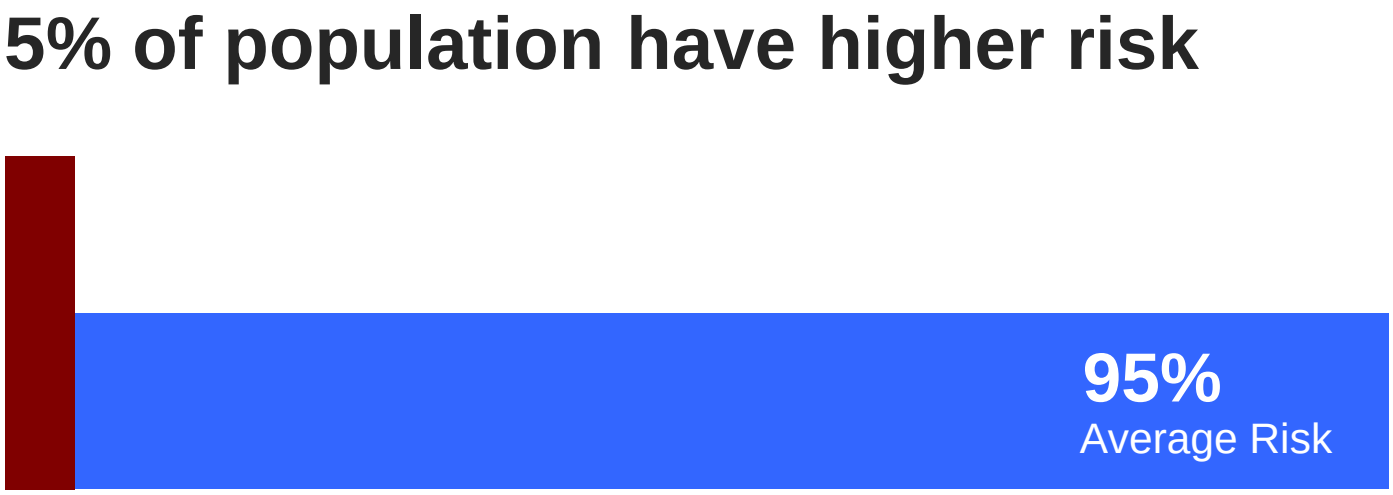
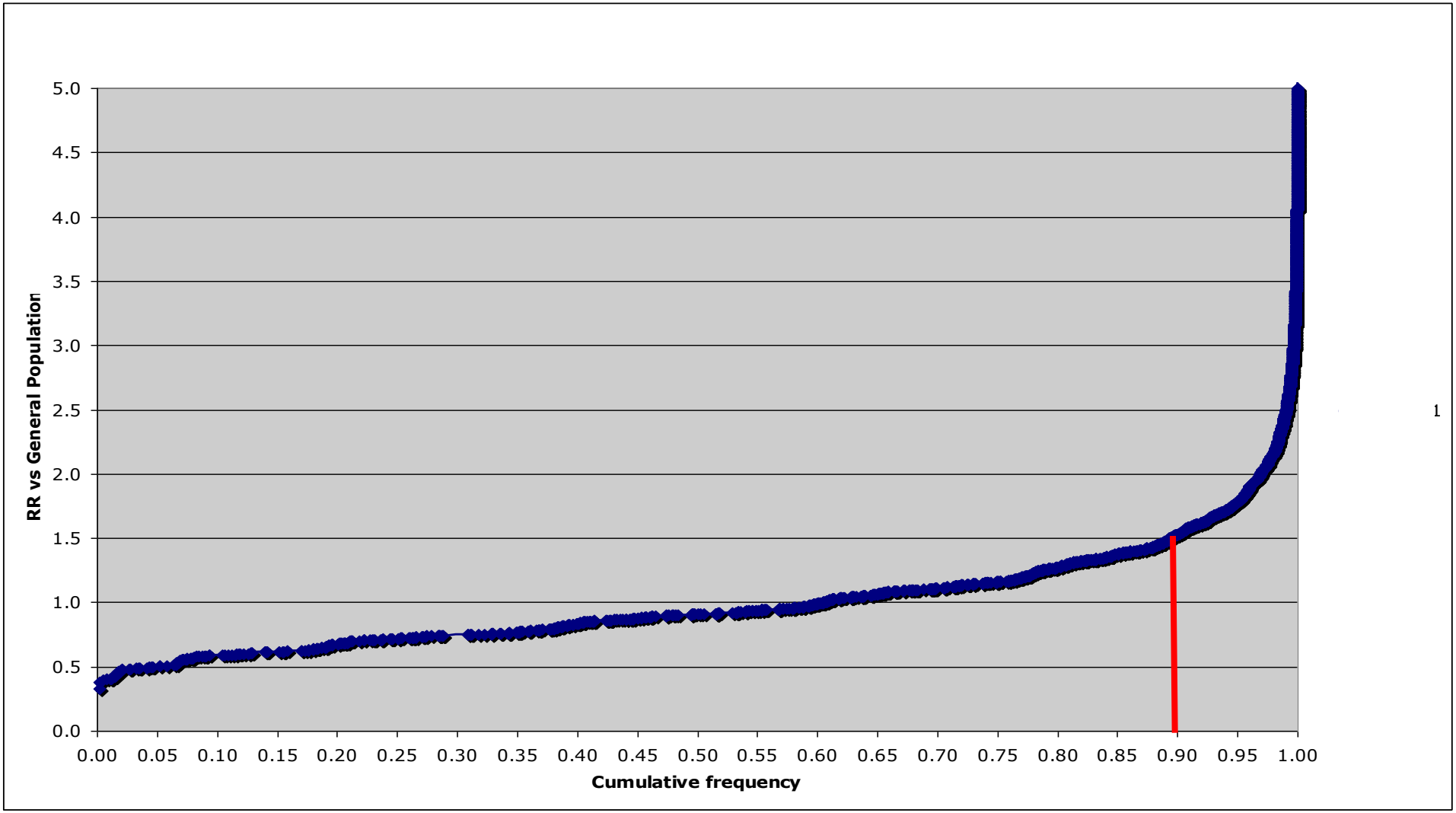
The only risk factor for prostate cancer in whites is family history of early prostate cancer

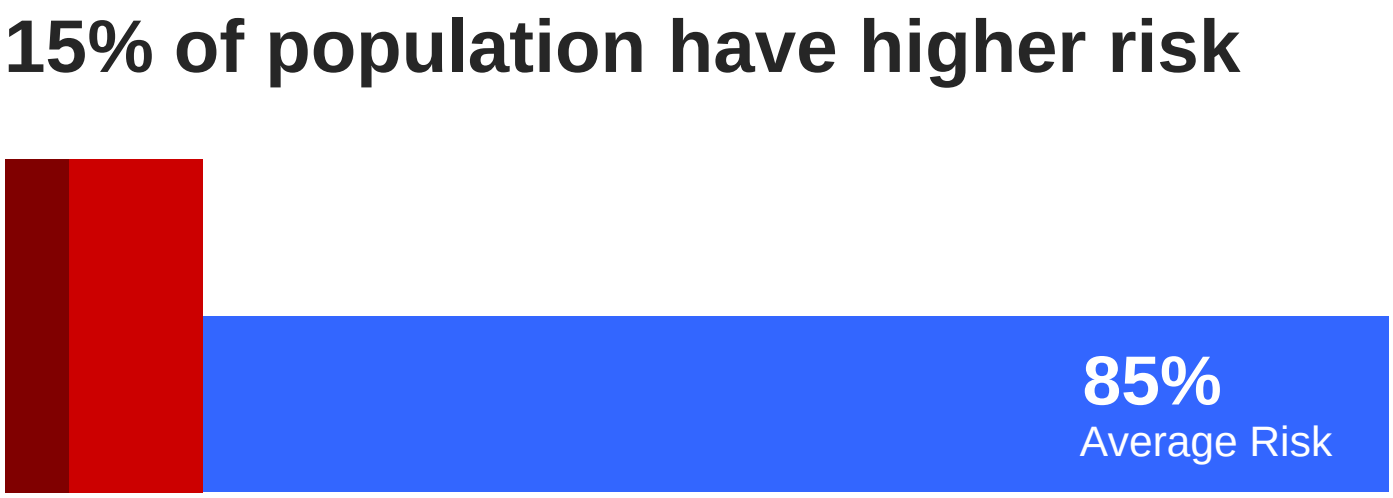
Need to discover the genetic risk that goes beyond the nuclear family



8 validated genetic markers defines Prostate Cancer risk ranging from 0.4 to 5 fold



Risk in the population when using Family History (5%) and Prostate Cancer Test (10%)



Risk & Family History

5%

High Risk

Family History Alone

95%

Average Risk

15% High Risk account for 30% of prostate cancers

Prostate Cancer Genetic Risk Test

&

Family History

Case Study in the use of deCODE Prostate Cancer

- 48 year old white male in good apparent health,
  - father diagnosed with localized prostate cancer at age 68
  - ACS guidelines recommend screening with PSA beginning at age 50 unless family history of early prostate cancer < 65

- deCODE Prostate Cancer results:
  - Relative risk = 1.88 fold compared to general population risk for white males.
  - Calculated lifetime risk = 1.88 X 16% = 30%
  - Modestly higher risk for aggressive vs. non-aggressive disease

Case Study in the use of deCODE Prostate Cancer

- High risk prompted early PSA test by primary care
  - PSA – high normal at 2.0ng/ml
- High risk prompted urologist to perform TRUS-guided biopsy
  - Positive in 3 out of 12 core biopsies – 15% volume
  - Gleason score of 6 (3/3) – intermediate grade
- Negative workup for metastasis
- Radical prostatectomy with nerve sparing for likely cure
- Final pathology on resected prostate showed Gleason 7 (high-grade) in both lobes

Ongoing Prostate Cancer Utility Studies supported by deCODE – Going from N=1 to N=6,000

- Does the genetic risk test increase specificity of PSA, free PSA, proPSA?
  - Show that higher risk patients have fewer negative first and second biopsies at any level of PSA
    - Northwestern (Catalona) – recruit 4000 patients with negative biopsies to match the 1500 patients with positive biopsies already collected
    - Iceland biopsy database- 5000 patients

- Do markers correlate with aggressiveness at diagnosis or long-term? Need 10 to 15 year observational cohorts

Levels of Evidence for Clinical Utility

- Risk is independent of conventional risk factors in large epidemiologic studies – fits onto the front in risk-driven guidelines or complements current risk scales - (multiply Gail 5yr risk, multiply Framingham 10yr risk for MI)
- Change in patient behavior
- Change in physician behavior
- Increased specificity and sensitivity when combined with conventional risk factors including biomarkers and imaging
- Significant reclassification of patients in large prospective cohorts when markers added to conventional risk factors
- Better outcome in cohort tested vs cohort not tested when followed over 5 to 20 years

Ongoing/planned Clinical Utility Studies

- Prostate Cancer
  - Does genetic testing increase specificity/sensitivity of PSA based on biopsy outcome (positive vs negative) – 2 sites (10,000 patients)

- Breast Cancer
  - Does genetic testing increase specificity of breast imaging based on biopsy outcome? (3000 patients?)
  - Does genetic testing add to Gail score? NSABP studies (30,000 patients?)
  - Does genetic likelihood of ER positive tumors predict responders vs failures of tamoxifen/raloxifene prevention? NSABP
  - Does testing change pt behavior?

- Atrial fibrillation 4q25 markers
  - Does testing for AF variants in acute stroke and subsequent extra cardiac monitoring for 4 weeks increase sensitivity for diagnosis of AF-related strokes (1000 patients)
  - Do patients with higher genetic risk for AF after cardiac surgery respond to amiodarone prevention of AF – 2 sites including GW – 400 pts)

- Type 2 diabetes
  - Do prediabetics told they have 50 to 70% chance of converting to diabetes within 3 to 4 years lose more weight than patients told they have 30 to 35% risk? (Duke U – Joy, Ginsberg) – 1000 patients
  - Drug response vs genetic risk factors – 2 sites – 2000 patients
  - ACTNOW study