GENETIC TESTING FOR BREAST CANCER RISK

TAKE-HOME MESSAGES:

1) TEST MORE INDIVIDUALS
2) USE EXPANDED PANEL
3) VUS (VARIANT OF UNCERTAIN SIGNIFICANCE) - NO CAUSE FOR ALARM.

BRCA+ carriers identified & informed:

- Over 220,000* Unaffected carriers (U.S.):

  5-6% identified and informed

- Over 35,000 Breast Cancer patients have deleterious BRCA mutations:

  30% identified and informed

Drohan B, Roche CA, Cusack JC Jr, Hughes KS. Ann Surg Oncol. 2012;19:1732–7.

A Positive Test for a Known Family Mutation

- **Directs Appropriate Resource Utilization**
  - "High Risk" Surveillance (MRI, WBUS…)
  - Chemoprevention
  - Preventative surgery
    - BSO (mastectomy in selected cases)
- about Targeting Resources (Not mastectomy)

*Breast Cancer Res Treat 2010 Jan; 119(2):409-14. doi: 10.1007/s10549-009-0611-y

Negative Test with Known Familial Mutation

- Ordinary Population-level Risk*
  - (Previously controversial)
- Stop wasting resources, reduce distress

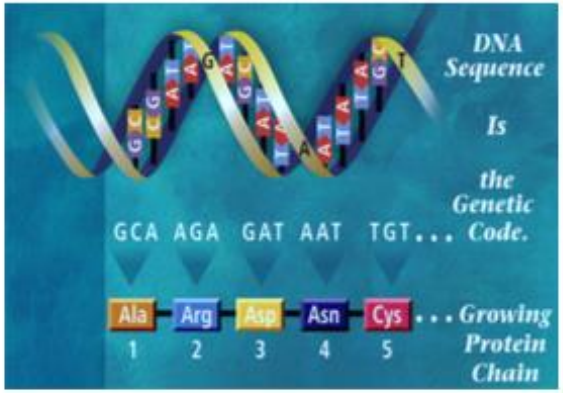
Ordinary screening vs "high risk" screening

  - Corrects the biopsy threshold
  - Ordinary screening vs fear-based mastectomies

*Breast Cancer Res Treat 2010 Jan;119(2):409-14. doi: 10.1007/s10549-009-0611-y

Pathogenic/Deleterious Mutations

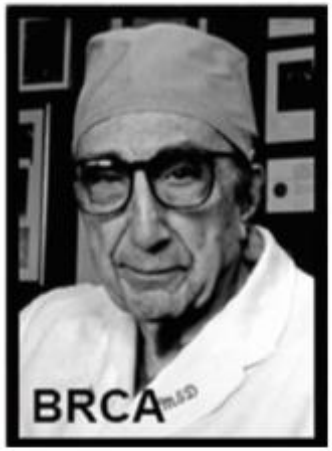
- **Thousands of BRCA mutations with *unambiguous severe effects* on cancer risk identified**
  - Nearly all **truncate or delete their host gene**
  - **In addition**: About a dozen amino acid substitutions proven to cause loss of BRCA function
    - **Great majority** of AA substitutions: - benign



IS THERE A BRCA 3 ?

- HIGH RISK FAMILIES WHO TESTED NEGATIVE FOR BRCA 1 & 2
- WITH RAPID "NEXT GENERATION" SEQUENCING OF DNA, IT TURNS OUT THERE ARE MANY POTENTIAL MUTATIONS THAT ARE RESPONSIBLE.
- SIGNAL TRANSDUCTION PATHWAYS

Most breast cancer-related genes are:
DNA repair genes



RAD51

CHEK2

BRCA2

ATM

PALB2

BRCA1

MRG15

DNA

DSB

Hayakawa T et al. J Cell Sci 2010;123:1124-1130

Journal of Cell Science
jcs.biologists.org

Pathogenic Mutations in Panel testing: Almost 50% "other than" BRCA Genes

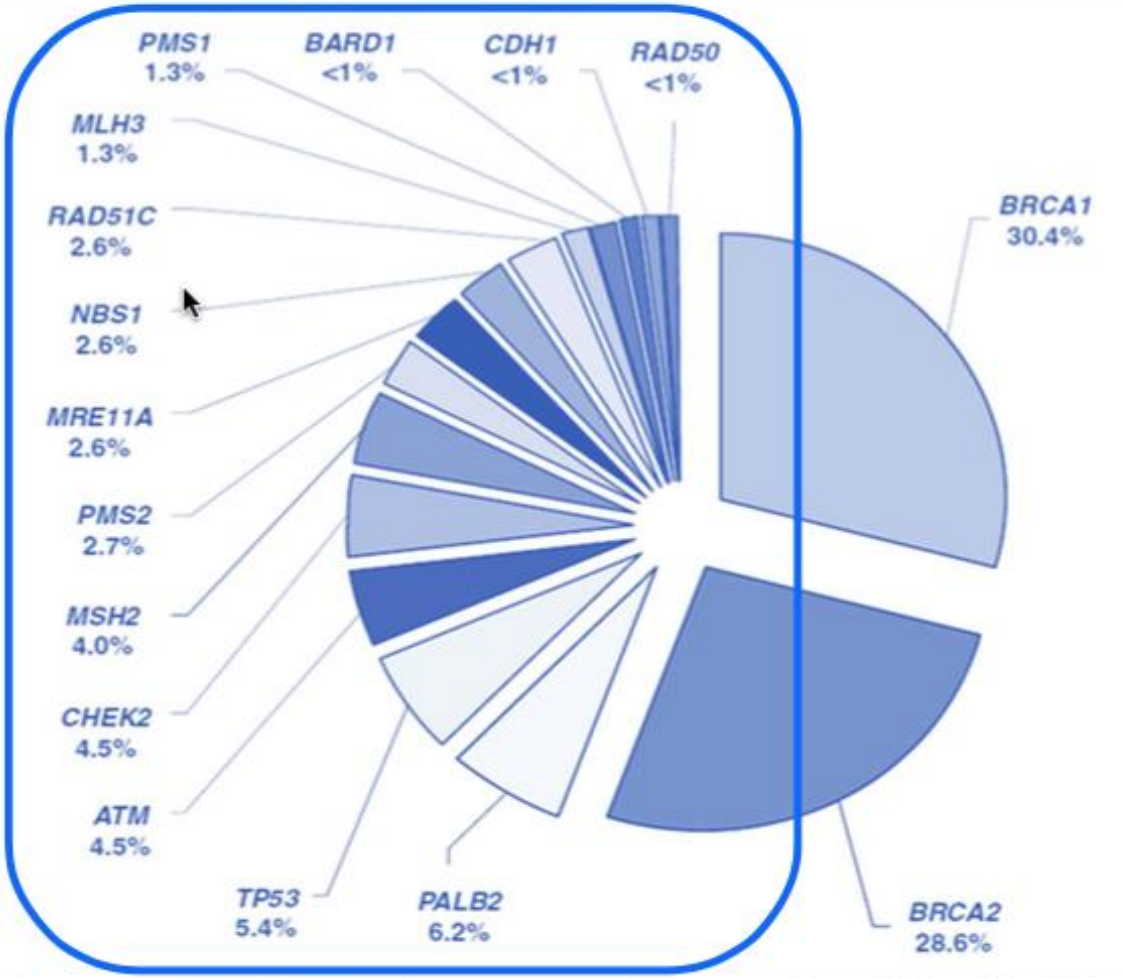


Figure 1 Relative distribution of variants detected with NGS in 708 HBOC

Castéra L, et al. *Eur J Hum Genet*. 2014 Feb 19. [Epub ahead of print]

Genetic Variant Classification

Classification	Probability Pathogenic
Pathogenic	>99%
Likely Pathogenic	95-99%
VUS	5 - <95%
Likely Not Pathogenic	1- <5%
Not Pathogenic	<1%

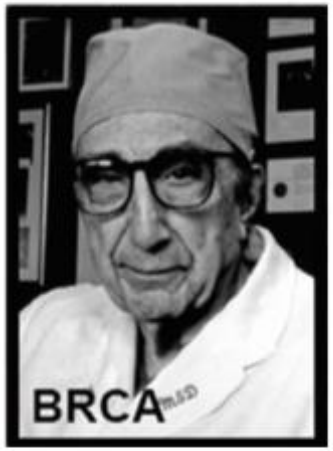
Average healthy person:

- about 10 million SNPs (single nucleotide polymorphisms)

VUS – VARIANT OF UNCERTAIN SIGNIFICANCE

- HIGHLY UNLIKELY TO INCREASE CANCER RISK
- IT'S LIKE A DIFFERENT SPELLING OF A WORD.
- IN THIS COUNTRY WE SPELL THE WORD "COLOR" DIFFERENTLY FROM BRITAIN, WHERE THEY SPELL IT "COLOUR"
- IT'S STILL THE SAME WORD WITH THE SAME SOUND AND THE SAME MEANING. IN SIMILAR FASHION, A VUS STILL PRODUCES THE SAME PROTEIN WITH THE SAME FUNCTION

Most breast cancer-related genes are:
DNA repair genes



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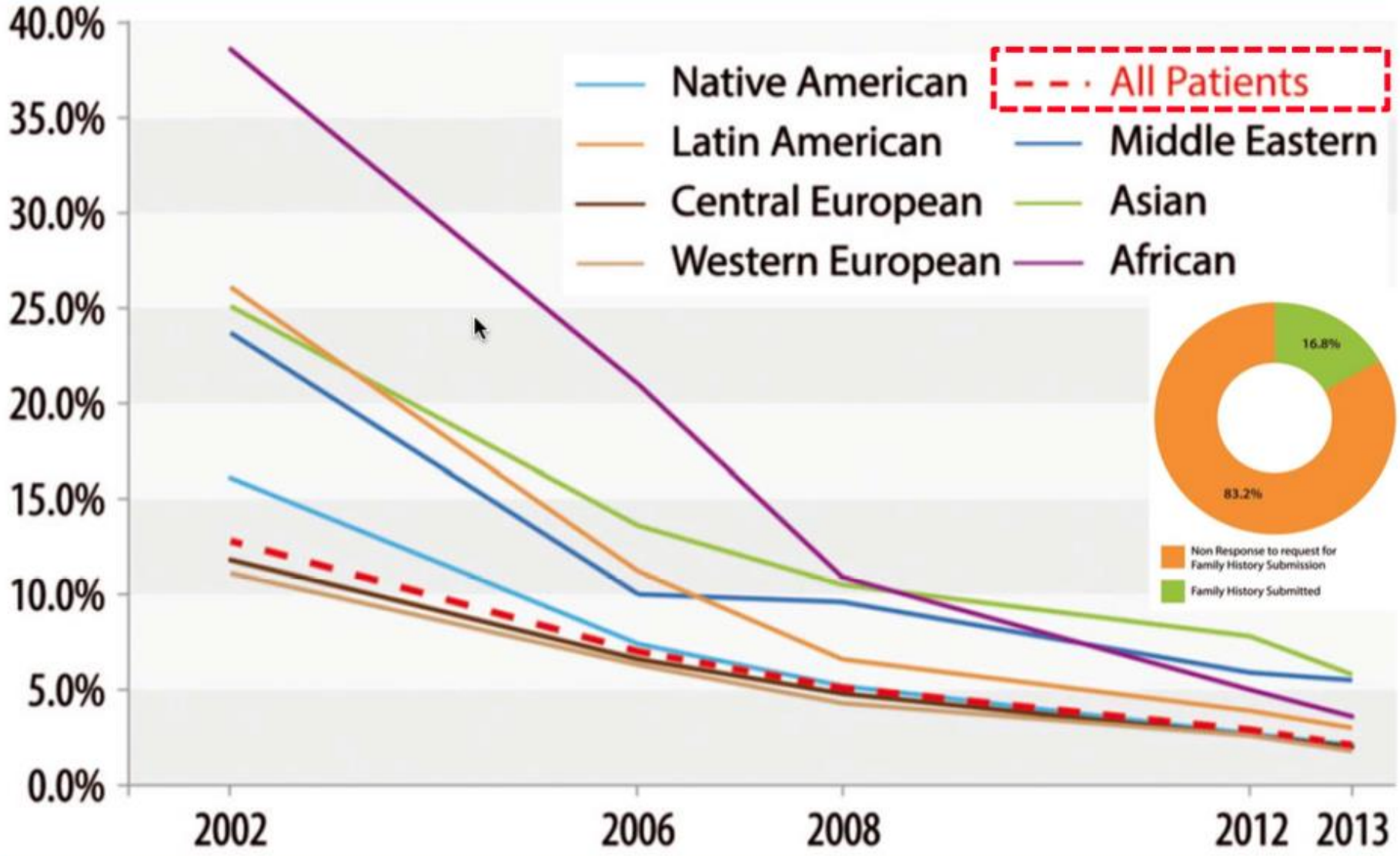
Decline in BRCA VUS Rate (Myriad)



Eggington J.M., et al., Clin Genet 2014: 86: 229–237 doi: 10.1111/cge.12315

WHO SHOULD BE TESTED?

- NCCN – NATIONAL COMPREHENSIVE CANCER NETWORK – ONLINE GUIDELINES UPDATED REGULARLY – A NETWORK OF CANCER CENTERS

WHO SHOULD BE TESTED?

WOMEN WITH BREAST CANCER & "RED FLAG"

- <=45Y AT DIAGNOSIS
- <=50Y AT DIAGNOSIS PLUS: a) 2ND PRIMARY BREAST CANCER, b) RELATIVE WITH BREAST, PANCREATIC, OR PROSTATE CANCER
- <=60 AT DIAGNOSIS, WITH TRIPLE NEGATIVE BREAST CANCER
- ANY AGE AT DIAGNOSIS PLUS: a) ONE CLOSE RELATIVE WITH BREAST CA <50 OR OVARIAN CANCER OR MALE BREAST CANCER b) TWO CLOSE RELATIVES WITH BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER.

WHO SHOULD BE TESTED?

THOSE WITH OTHER CANCERS

- INDIVIDUAL WITH OVARIAN CANCER OR MALE BREAST CANCER
- INDIVIDUAL WITH HIGH-RISK PROSTATE CANCER AND CLOSE FH OF BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER
- INDIVIDUAL WITH PANCREATIC CANCER AND CLOSE FH OF BREAST, OVARIAN, PANCREATIC, OR PROSTATE CANCER
- INDIVIDUAL WITH PANCREATIC CANCER AND ASHKENAZI JEWISH ANCESTRY

WHO SHOULD BE TESTED?

CANCER-FREE BUT WORRISOME FAMILY:

- INDIVIDUAL FROM A FAMILY WITH A KNOWN BRCA MUTATION
- FIRST-DEGREE OR SECOND-DEGREE RELATIVE MEETING ANY OF THE CRITERIA ON PREVIOUS SLIDE
- THIRD-DEGEE RELATIVE WITH BREAST +/OR OVARIAN CANCER AND 2 CLOSE RELATIVES WITH BREAST OR OVARIAN CANCER

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