# Clinical Application of Multigene Panel Testing and Genetic Counseling for Hereditary/familial Breast Cancer Risk Assessment : Prospective Single Center Study

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# The Cost of Sequencing the Human

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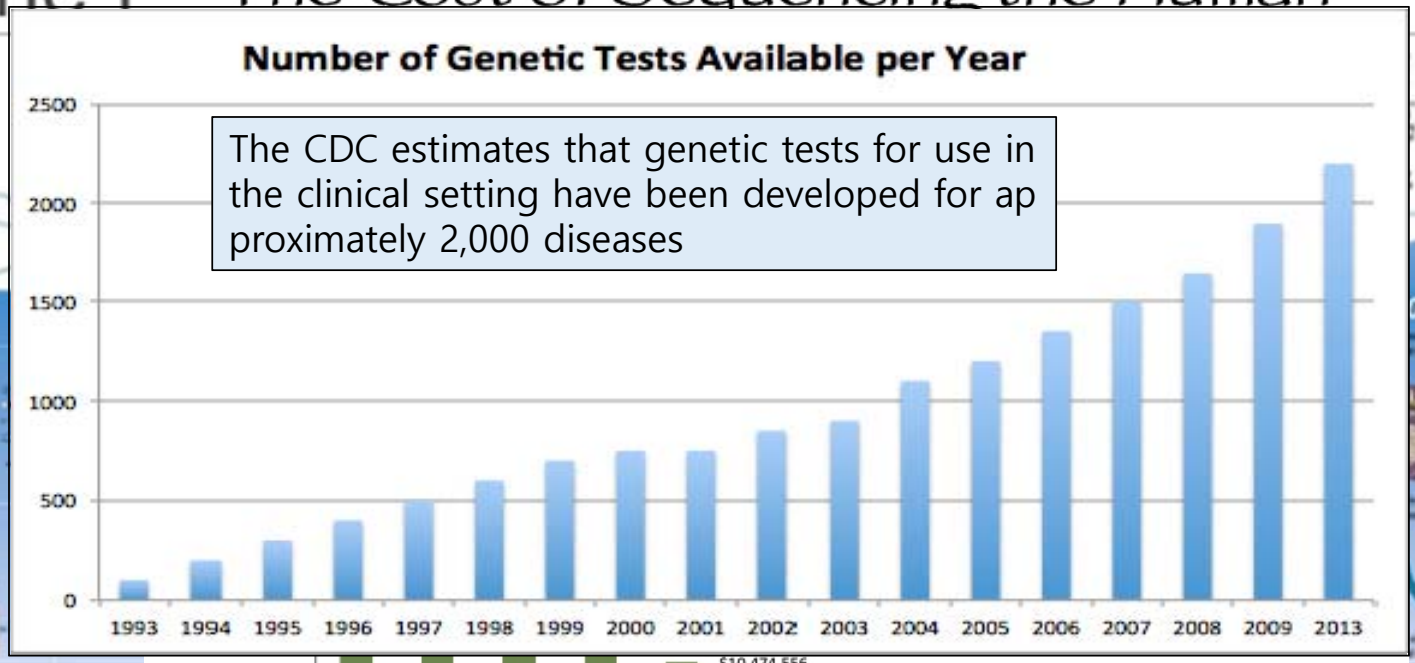


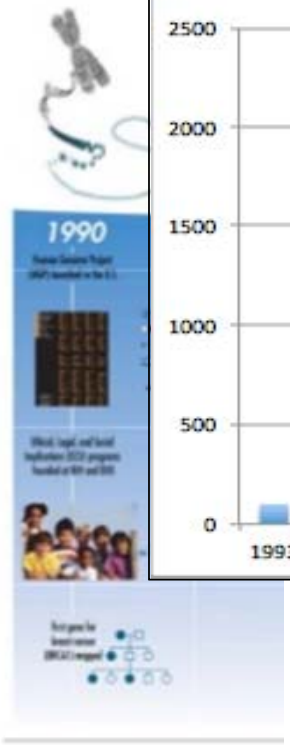



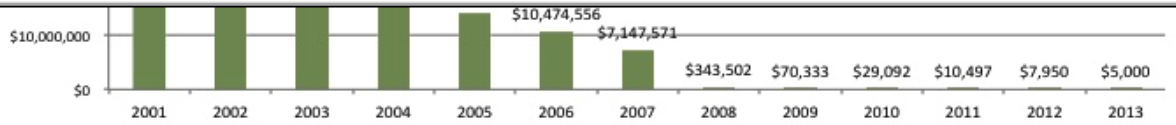


"Next-Next-" or "Third"-Generation Sequencing Technologies

# Introduction

- Next-G
- **Multig**
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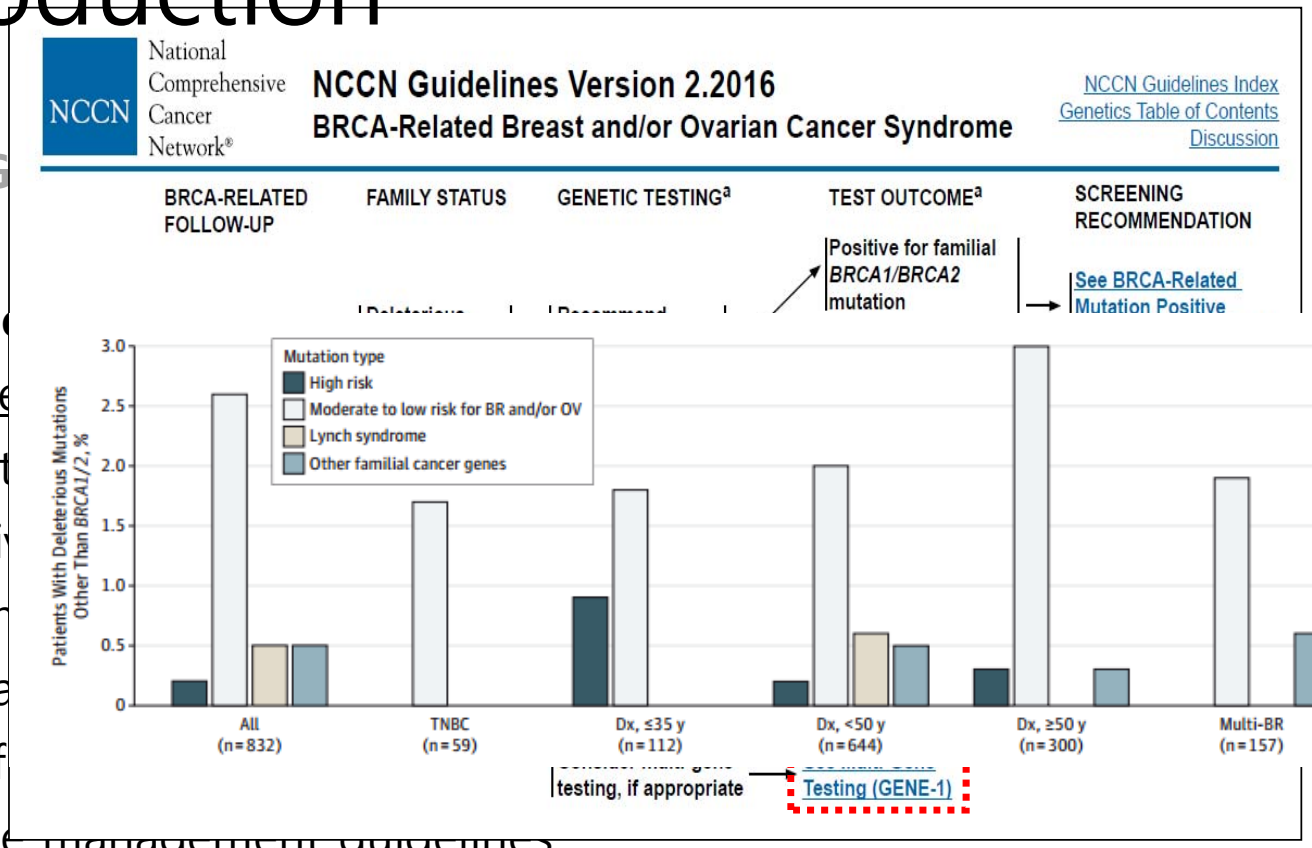


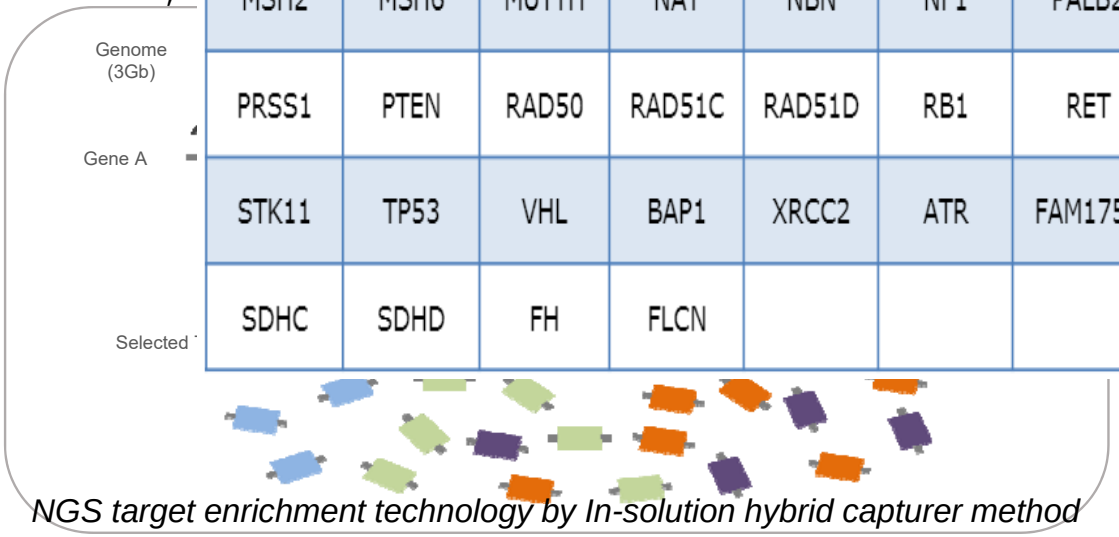

*NCCN guideline Version 1. 2017/Version2.2017*
*http://ascopubs.org/doi/pdf/10.1200/JCO.2013.53.6607*
*Andrea Desmond et al. 2015. JAMA oncology*

# Methods

Multi-gene sequencing for hereditary cancer risk Assessment in Breast C[illegible] Patients – Retrospective analysis

- Hereditary
  : Hereditary
  related
  : 64 genes
  PALB2, I

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ALK | APC | ATM | BARD1 | BLM | BMPR1A | BRCA1 | BRCA2 | BRIP1 | CDH1 |
| CDK4 | CDKN2A | CHEK2 | EPCAM | FANCA | FACB | FANCC | FANCD2 | FANCE | FANCF |
| FANCG | FANCI | FANCL | GSTP1 | KRAS | LIG4 | MEN1 | MET | MLH1 | MRE11A |
| MSH2 | MSH6 | MUTYH | NAT | NBN | NF1 | PALB2 | PALLD | PMS2 | PRKAR1A |
| PRSS1 | PTEN | RAD50 | RAD51C | RAD51D | RB1 | RET | SLX4 | SMAD4 | SPINK1 |
| STK11 | TP53 | VHL | BAP1 | XRCC2 | ATR | FAM175A | HOXB13 | RAD51 | SDHB |
| SDHC | SDHD | FH | FLCN | | | | | | |




*NGS target enrichment technology by In-solution hybrid capturer method*

**Sequencing**

effective genetic screening method of variant profiling

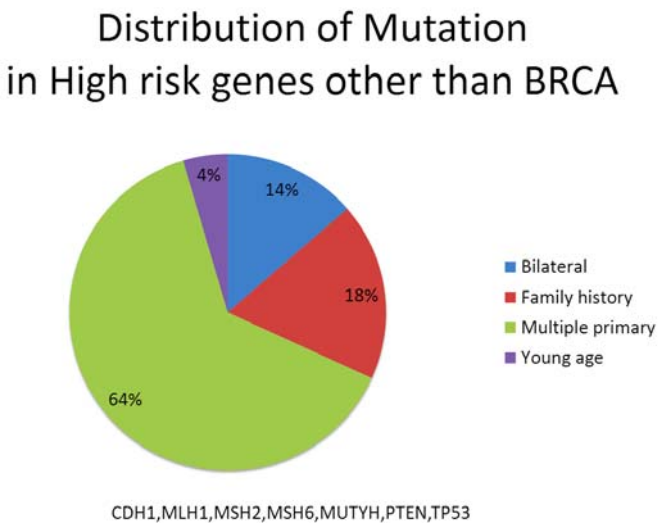
- Detectable variant types: SNV, InDel, CNV, Rearrangement

# Methods

## Multi-gene sequencing for hereditary cancer risk Assessment in Breast Cancer Patients - Retrospective analysis

- 252 breast cancer patients with high risk for hereditary cancer syndrome
- 18 pathogenic/likely pathogenic mutations in 77 patients(ACMG guideline: Pathogenic/Likely pathogenic/Benign/Likely bening/VUS)
- High risk gene for hereditary cancer : BRCA1/2, CDH1, MLH1, MSH2, MSH6,

| Characteristics | No. of Patients |
|---|---|
| Total number of patients | 252 |
| Mean age of breast cancer diagnosis, year | 49.6 |
| Personal cancer history | |
| Breast and another primary cancer | 179 |
| Breast cancer family history ≥ 2 relatives | 35 |
| Bilateral breast cancer and age ≤ 40 | 27 |
| Young breast cancer age ≤ 25 | 11 |



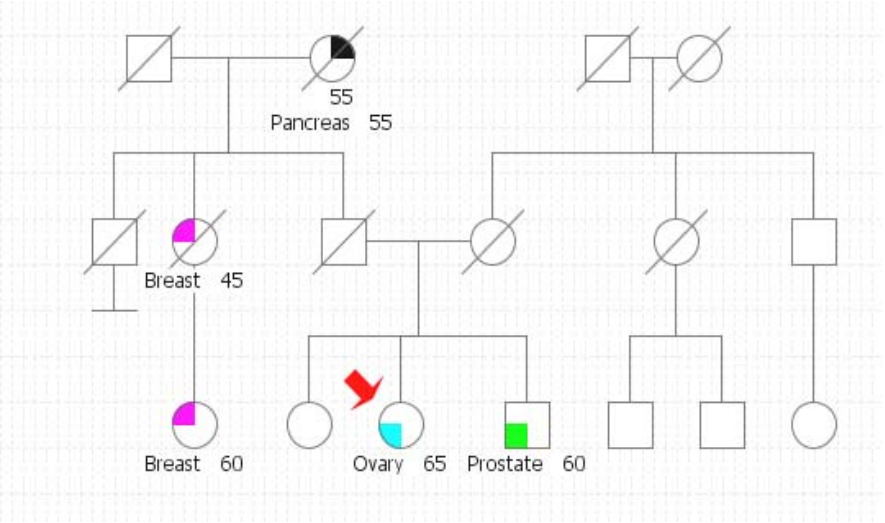

*Hee-Chul Shin, Wonshik Han, Tae-Kyung Yoo*

# Methods

- Clinical Application of Multigene Panel Testing and Genetic Counseling for Hereditary/familial Breast Cancer Risk Assessment : Prospective Single Center Study

  ◆ Process in the clinic

  - Patients with high risk for hereditary breast cancer
  - Pedigree
  - BRCA test
  - Informed consent for Multi-Gene panel testing
  - Counselling about genetic test




⇒***After 3~5(8~10) weeks***,

- Informed the results both of BRCA1/2 & multigene panel testing
- Explain the cancer risk and advantage/disadvantage of cancer-specific screening and/or risk-reducing procedure in deleterious mutation-proven patients.
- Recommend genetic testing for their family member

# Results

- Clinical Application of Multigene Panel Testing and Genetic Counseling for Hereditary/familial Breast Cancer Risk Assessment : Prospective Single Center Study

◆**Patients**

Breast cancer patients with high risk for hereditary cancer syndrome

who meet one of the following criteria

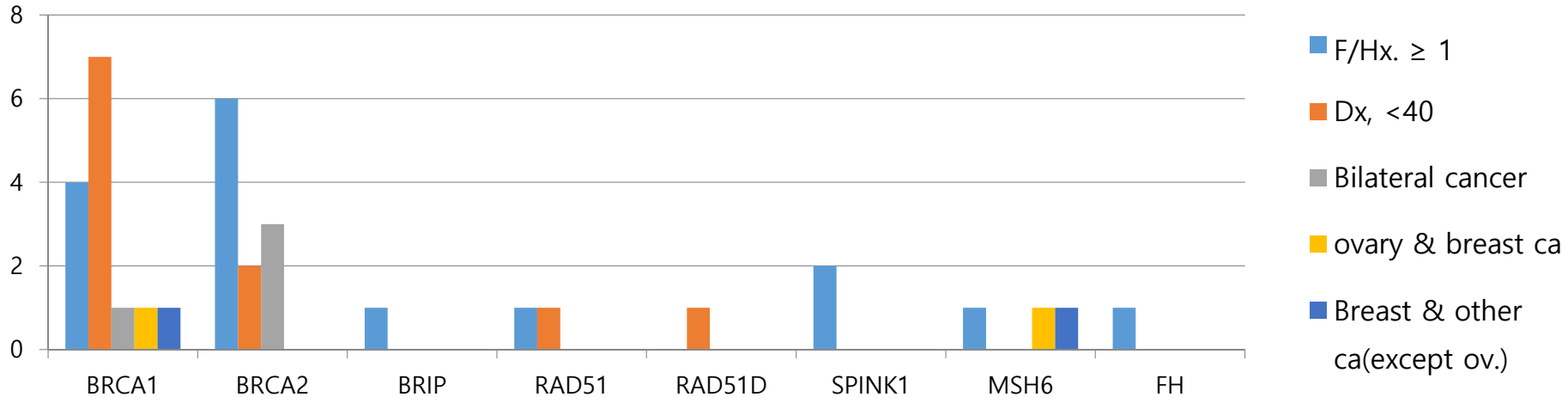
| Characteristics | No. of Patients |
|---|---|
| Total number of patients | 104 |
| Mean age of breast cancer diagnosis, year | 47.3 |
| Personal cancer history | |
| **Breast cancer family history ≥ 1 relatives (≥2)** | **66(18)** |
| **Young breast cancer age ≤ 40 (≤ 30)** | **37(6)** |
| **Bilateral breast cancer** | **17** |
| **Breast and ovary cancer** | **8** |
| **Breast and another primary cancer(exc. Ov)** | **6** |
| **Ovary cancer w/o breast cancer** | **5** |

# Results

## ◆Results

✓ P/LP Mutation Prevalence Among Patients With Breast Cancer

- Among 104, 26(25%) patients with P/LP mutations
- BRCA1(10), BRCA2(7), BRIP1(1), RAD51(1), RAD51D(2), SPINK1(2), FH(1), MSH6(2)
- 12 frameshift, SNV(4 stopgain, 10 nonsynonymous)
- All mutations in BRCA1/2 were validated using another manner(Sanger seq.) in same patients



# Results

◆ **Pathogenic mutation more frequent**

- F/Hx. ≥ 1 relatives, both of 2 factors, TNBC in BRCA1/2 +

◆ **Pathogenic mutation in other genes except BRCA1/2**

- 9 patients(8.7%)
- BRIP1(1), RAD51(1), RAD51D(2), SPINK1(2), FH(1), MSH6(2)

◆ **Risk reducing procedure**

- Prophylactic mastectomy or oophorectomy in 6 patients(23%)
- Most of them received cancer specific screening : in 19 patients(73%)

# Results

◆ ***Testing Results by Gene Category and Personal History***

| Characteristics of patients | All deleterious mutation (Individuals of patients) | Result by Gene Category, No. of Mutations | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | BRCA1 | BRCA2 | BRIP | RAD51 | RAD51D | SPINK1 | MSH6 | FH |
| **F/Hx. ≥ 1** | 11 | 3 | 3 | 1 | | | 2 | 1 | 1 |
| **Dx, <40** | 4 | 3 | | | | 1 | | | |
| **F/Hx. ≥ 1 & Dx, <40** | 4 | 2 | 1 | | 1 | | | | |
| **F/Hx. ≥ 1 & Bilateral ca.** | 2 | | 2 | | | | | | |
| **Dx, <40 & Bilateral ca** | 2 | 1 | 1 | | | | | | |
| **ov./breast ca** | 1 | 1 | | | | | | | |
| **Dx, <40 & Breast/other ca** | 1 | 1 | | | | | | | |
| **ov./breast ca & Breast/other ca** | 1 | | | | | | | 1 | |

| Gene | Patient (n=26) | Characteristics<br>1. F/Hx. ≥ 1 2. Dx,<40 3. bilateral ca<br>4. breast/ov ca. 5. breast/other ca. | Screening/Risk reducing procedure recommendation |
|---|---|---|---|
| BRCA1 | #1 | 1(>2),2(36) | yes -> CPM*+/GY screening |
| BRCA1 | #23 | 2(27),3 | yes -> GY screening |
| BRCA1 | #31 | 2(38), TNBC | yes-> CPM+/GY screening |
| BRCA1 | #56 | 1(>2) | yes -> CPM+/RRSO+ |
| BRCA1 | #78 | 1(>2),2(36), TNBC | yes -> plan : CPM(not yet), GY screening(nulliparity) |
| BRCA1 | #88 | 1(>2 breast),6(only ov.ca) | yes -> breast screening |
| BRCA1 | #101 | 2, TNBC | No -> stageIV, advance |
| BRCA1 | #104 | 2(30),5,TNBC | N/A |
| BRCA1 | #80 | 4, TNBC | No -> Routine f/u(s/p BSO, BCS) |
| BRCA1 | #103 | 2(31), TNBC | N/A |
| BRCA2 | #9 | 1,3 | yes -> GY screening |
| BRCA2 | #23 | 2(27),3 | yes-> GY screening |
| BRCA2 | #24 | 1,3 | yes -> GY screening |
| BRCA2 | #33 | 1 | yes -> RRSO+ |
| BRCA2 | #58 | 1(>2, 7) 2(34) | yes -> CPM+/GY screening |
| BRCA2 | #67 | 1(>2) | yes-> GY screening |
| BRCA2 | #90 | 1(>2), TNBC | yes -> BSO(ov. Cyst+) |
| **BRIP 1** | **#87** | 1, Her2 type | No -> (s/p BSO d/t other cause) |
| **RAD51** | **#20** | 1,2(34) | yes -> GY screening |
| **RAD51D** | **#64** | 2(34) | Yes -> GY screening |
| **SPINK1** | **#15** | 1(breast) | No |
| **SPINK1** | **#99** | 1(breast) | N/A |
| **FH*** ** | **#41** | 2(mother-ov, father- prostate), Her2 type | N/A |
| **MSH6** | **#44** | 4, 5(PTC, ov, MD) | O -> CFS screening rec. |
| **MSH6** | **#92** | 1 | N/A |

- *CPM contrlateral prophylactic mastectomy**RRSO Risk Reducing Salphingoophorectomy *** FH(Fumarate hytdratase) –hereditary leiomyosarcoma & renal cell carcinom*

# Results

◆ Recommendation for the patients with deleterious mutation in hereditary cancer related genes except BRC1/2

| Gene | Patient (n=7) | Characteristics<br>1. F/Hx. ≥ 1 2. Dx,<40 3. bilateral ca<br>4. breast/ov ca. 5. breast/other ca. | Screening/Risk reducing procedure recommendation |
|---|---|---|---|
| **BRIP 1** | #87 | 1, her2 | No -> (s/p BSO d/t other cause)<br>Rec sequencing & GY screening to female family members |
| **RAD51** | #20 | 1,2(34) | yes -> GY screening<br>Rec sequencing & GY screening to female family members |
| **RAD51D** | #64 | 2(34) | Yes -> GY screening<br>Rec sequencing & GY screening to female family members |
| **FH** | #41 | 1(mother-ov, father-prostate) | N/A* |
| **MSH6** | #44 | 4, 5(PTC, ov) | O -> CFS screening rec.<br>Rec sequencing & CFS screening to family members |
| **MSH6** | #92 | 1 | N/A |

** N/A : She did not visit to counsel about gene panel result*

# Conclusion

- **Suggestion**

➢ **Indication to recommend multi-gene panel testing**

**- The patients with breast cancer who meet one of the following criteria**

✓ Family history of cancer in relatives

✓ Diagnosed in young age

✓ Bilateral cancer and developed one of that in young age

✓ Diagnosed cancer in multiple organ

# Conclusion

- **Suggestion**

➢ **Guidelines to recommend prophylactic process**

✓Cancer specific screening : Breast MRI/MMG, GY Screening, CFS/GFS

✓Risk Reducing Procedure : have enough time in discussion with the patients

✓Recommend genetic testing for their family members

National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2016**
**Genetic/Familial High-Risk Assessment: Breast and Ovarian**

NCCN Guidelines Index
Genetics Table of Contents
Discussion

**BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]**

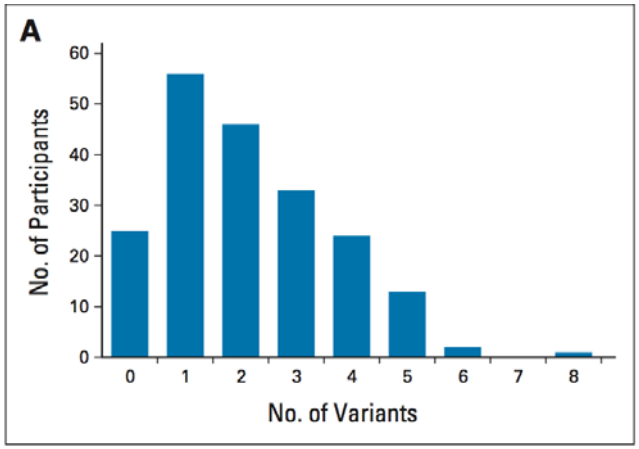
| | Recommend Breast MRI[d] (>20% risk of breast cancer[e]) | Discuss Option of RRM | Recommend/Consider RRSO |
|---|---|---|---|
| Intervention warranted based on gene and/or risk level | *ATM*<br>*BRCA1*<br>*BRCA2*<br>*CDH1*<br>*CHEK2*<br>*PALB2*<br>*PTEN*<br>*STK11*<br>*TP53* | *BRCA1*<br>*BRCA2*<br>*CDH1*<br>*PTEN*<br>*TP53*<br>*PALB2* | *BRCA1*<br>*BRCA2*<br>Lynch syndrome[f]<br>*BRIP1*<br>*RAD51C*<br>*RAD51D* |
| Insufficient evidence for intervention[b,c] | *BRIP1* | *ATM*<br>*CHEK2*<br>*STK11* | *PALB2* |

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy

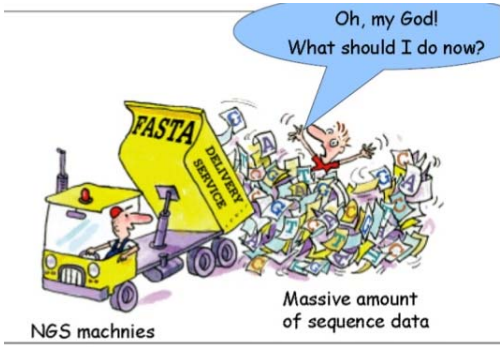
# Limitation & Challenging

◆ **Variants with Uncertain Significance**

- 3.8 VUS on average (about 400 in 104 patients)
- Difficulty in counseling in real clinical field




*Allison W. Kurian et al. J Clin Onc 2013*


◆ Lack of long term f/u data in Patients with deleterious mutation
- Incidence of Malignancy and Survival

◆Not definite survival benefit
of risk reducing procedure and cancer-specific screening

◆ Furthermore

**In the future, it will be the social problem related insurance system**

# Acknowledgement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