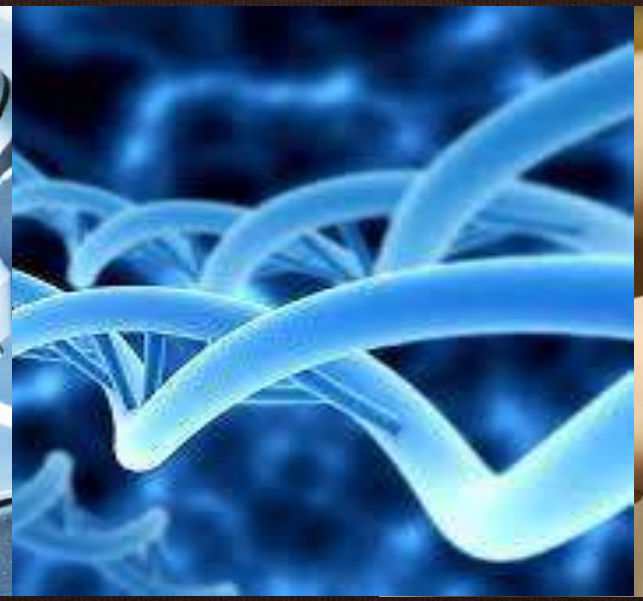
Mahidol University
Faculty of Medicine
Siriraj Hospital

Siriraj
Genomics

Cancer Precision Medicine

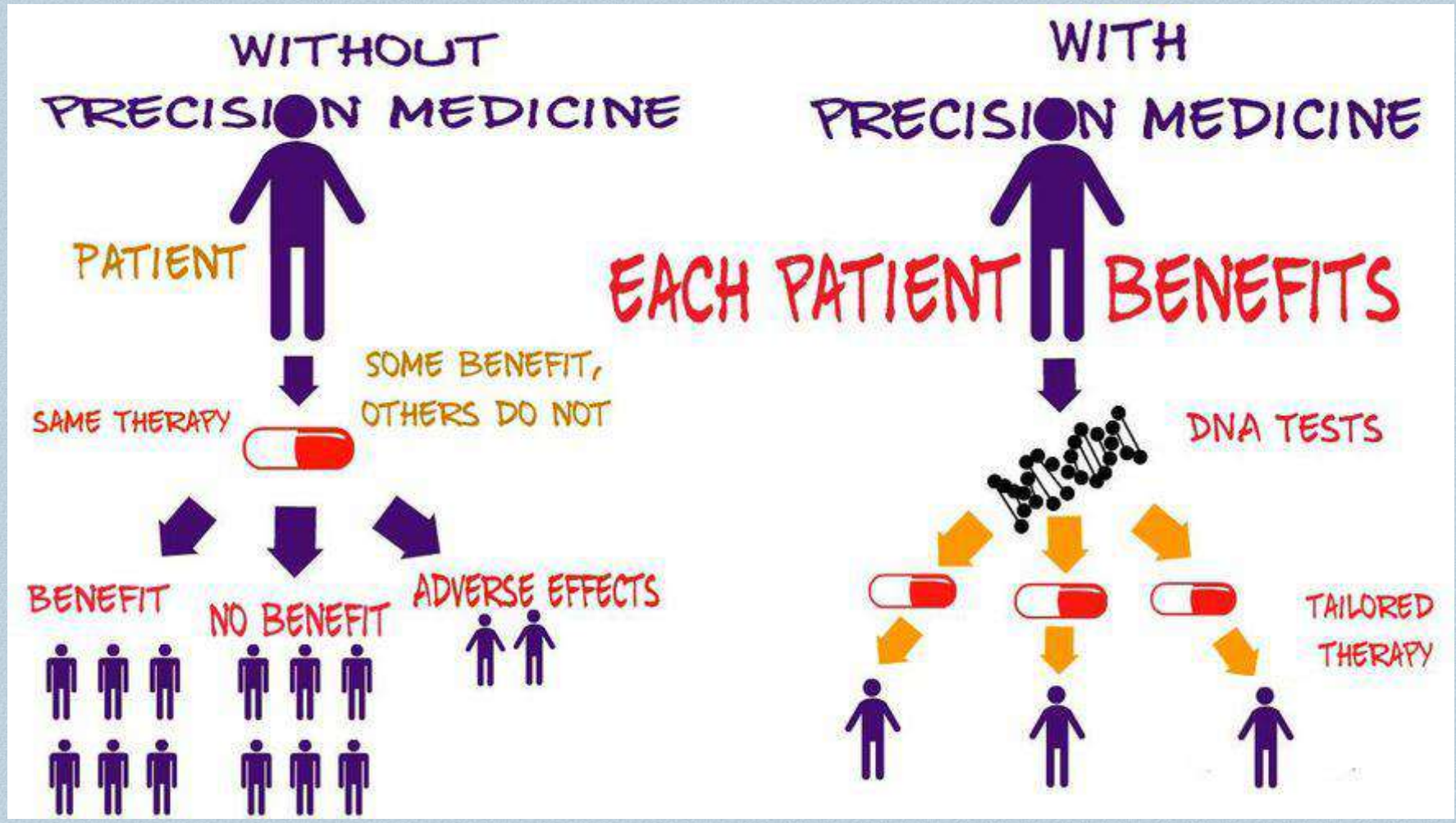
New Paradigm of Cancer Care




Manop Pithukpakorn, MD
Siririaj Genomics
Medical Genetics Division, Department of Medicine
Siriraj Center of Research Excellence in Precision Medicine

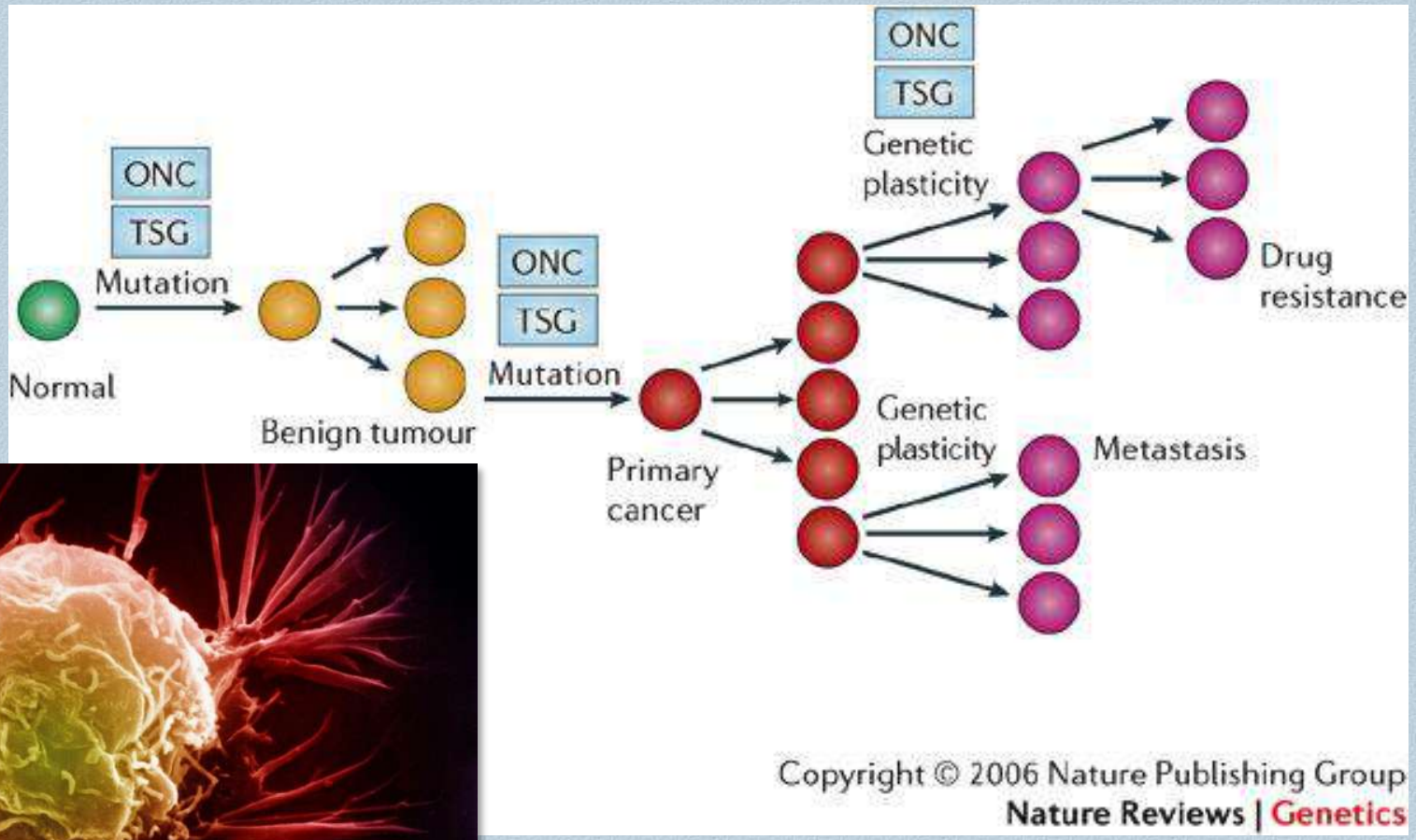
CANCER
PRECISION MEDICINE

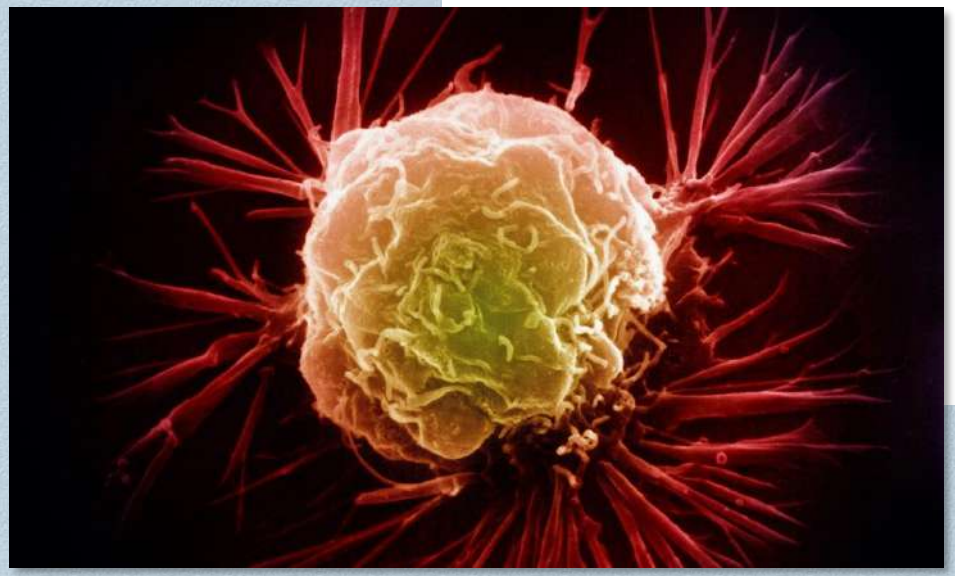
Precision Medicine



CANCER
PRECISION MEDICINE

Cancer is a genetic disorder

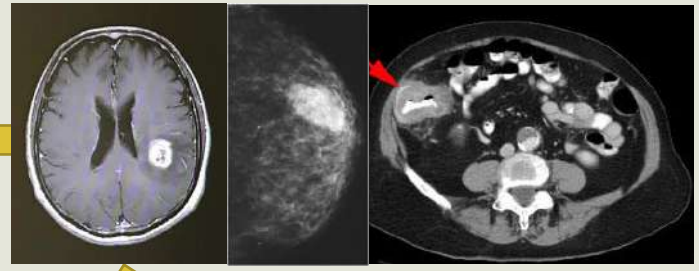




Feinberg AP, et al Nat Rev Genet 7, 21-33, 2006

CANCER PRECISION MEDICINE

Databases/AI



Patients

Genome Landscape

Bioinformatics

Blood test

Surgery/Biopsy

Pathologist

Frozen specimens

Biobanking

Diagnostics

Genome Sequencing

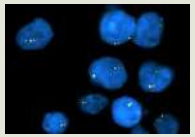
Gene expression profile

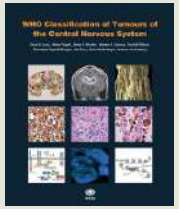
Treatment selection

Clinical Cohorts/Clinical Trials

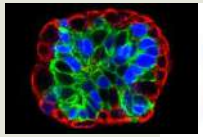
Standard & Advanced Lab

Advanced/Molecular Pathology





Cancer cell lines



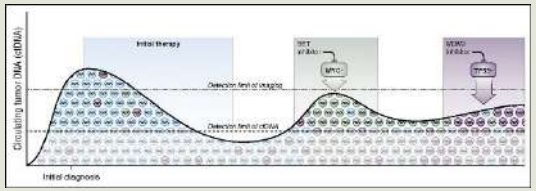
Spheroid Organoid

Orthotopic xenograft

Zebrafish Model

Drug testing/Tailored regimen

cfDNA



Screening/Disease Monitoring

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There are several different cancer treatment options[1–6]

SURGERY

Surgery can remove the tumour if it is found early and has not spread[1]

RADIOTHERAPY

Radiotherapy may be used if the location of the tumour prevents surgery, or there are cancer cells left after surgery[2,3]

CHEMOTHERAPY

Chemotherapies are moderately toxic drugs that attack fast-growing cells, such as cancer cells[4]

TARGETED THERAPY

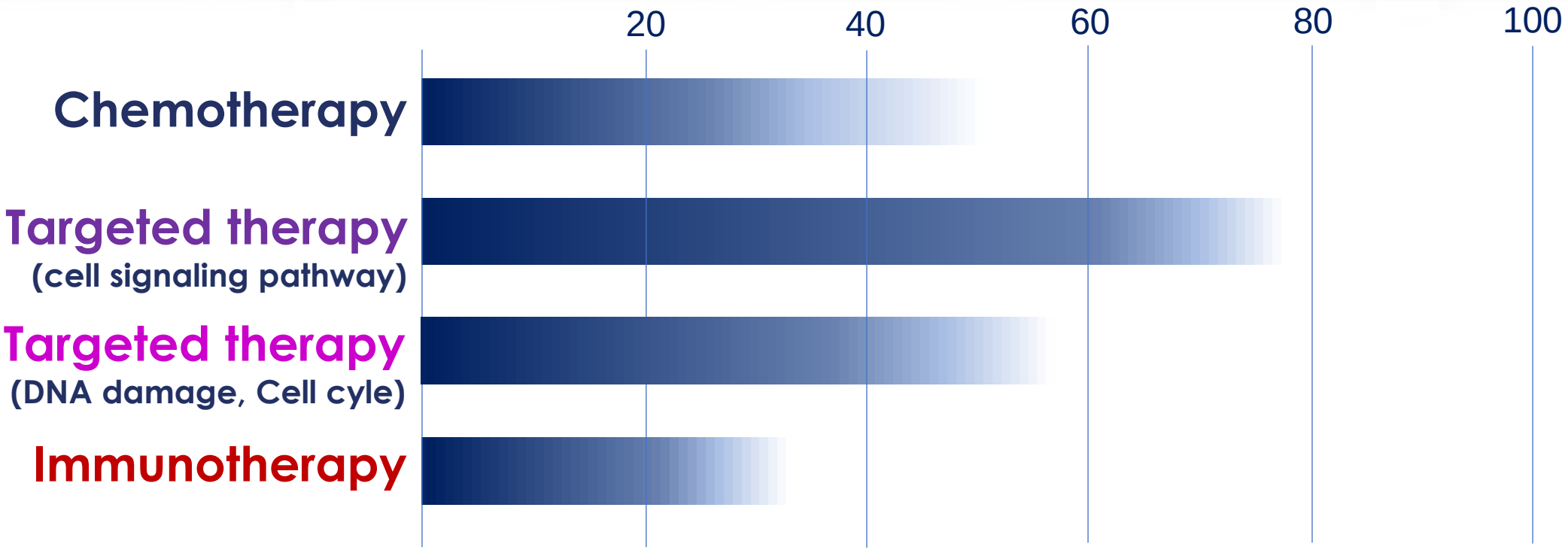
Targeted therapies target cancer cells with specific DNA mutations[5]

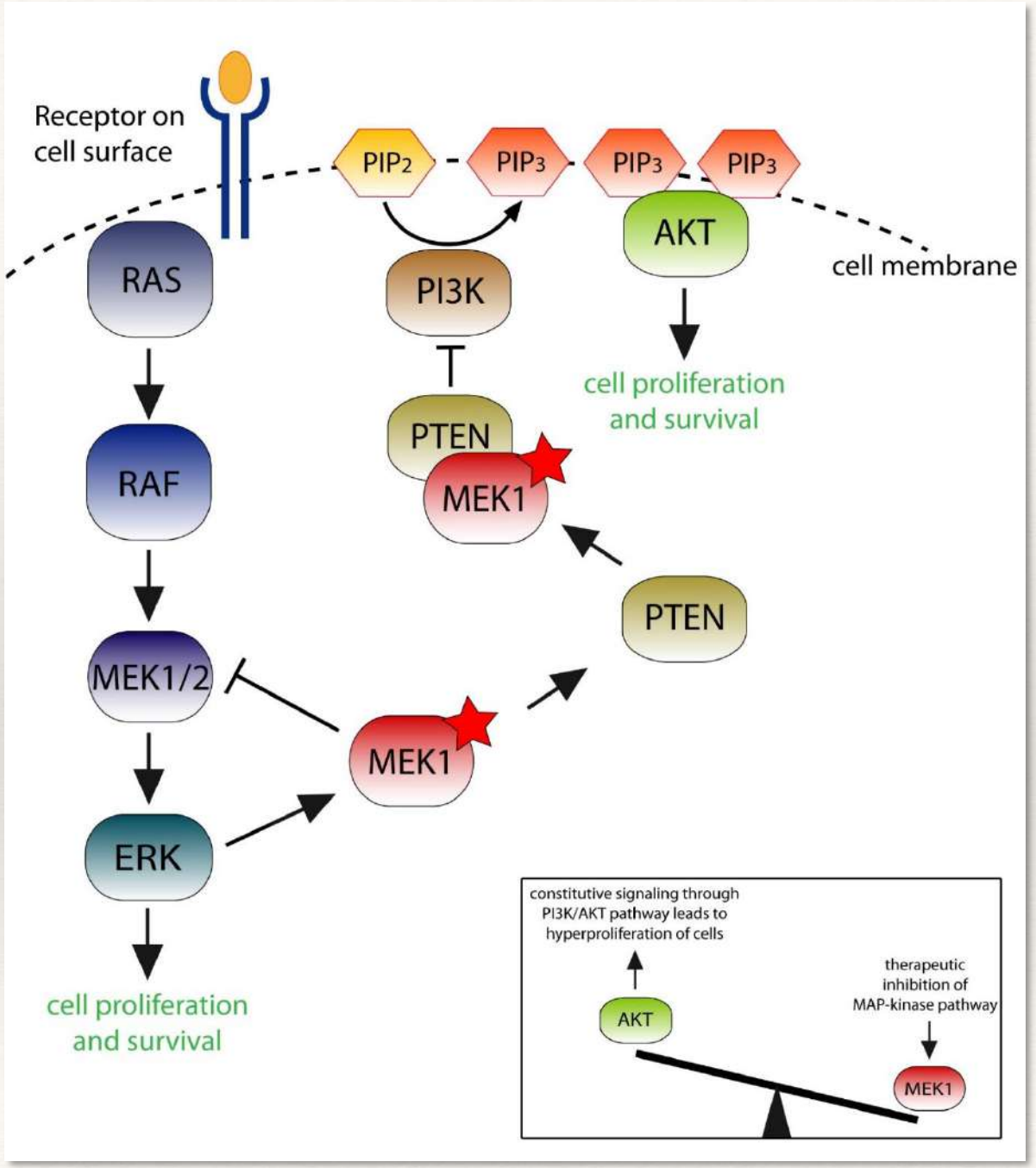
IMMUNOTHERAPY

Immunotherapies use the body's immune system to fight cancer[6]

1. Cancer Research UK. Surgery. Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/surgery/about (Accessed January 2019); 2. Cancer Research UK. Radiotherapy. Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/radiotherapy/about (Accessed January 2019); 3. Cancer Research UK. Radiotherapy for cancer treatment. Available at: https://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/radiotherapy/radiotherapy-cancer/treatment (Accessed January 2019); 4. National Cancer Institute. Chemotherapy to treat cancer. Available at: https://www.cancer.gov/about-cancer/treatment/types/

Overall response rate of cancer treatment approach





Gene alterations

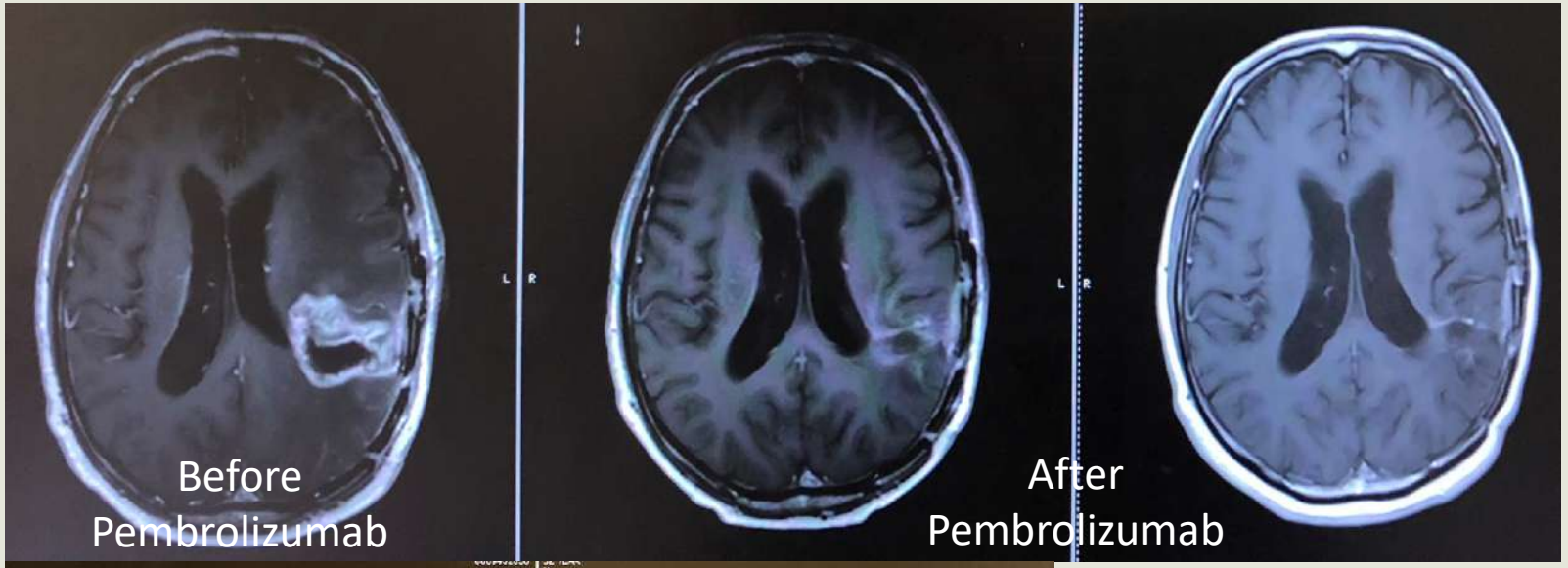
Mutant proteins

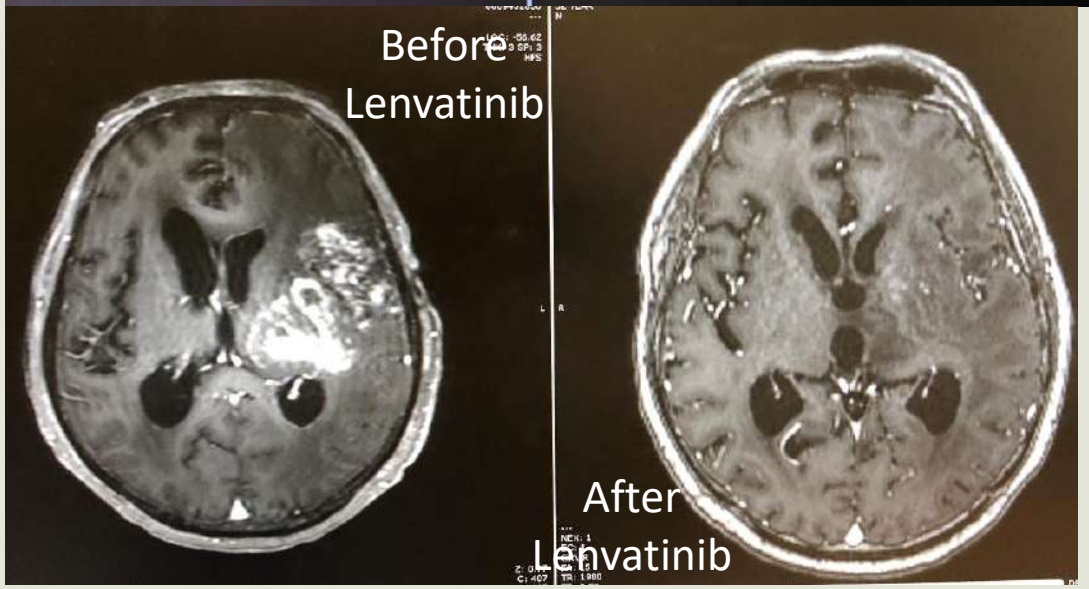
Drugs

Abnormal functions

CANCER PRECISION MEDICINE

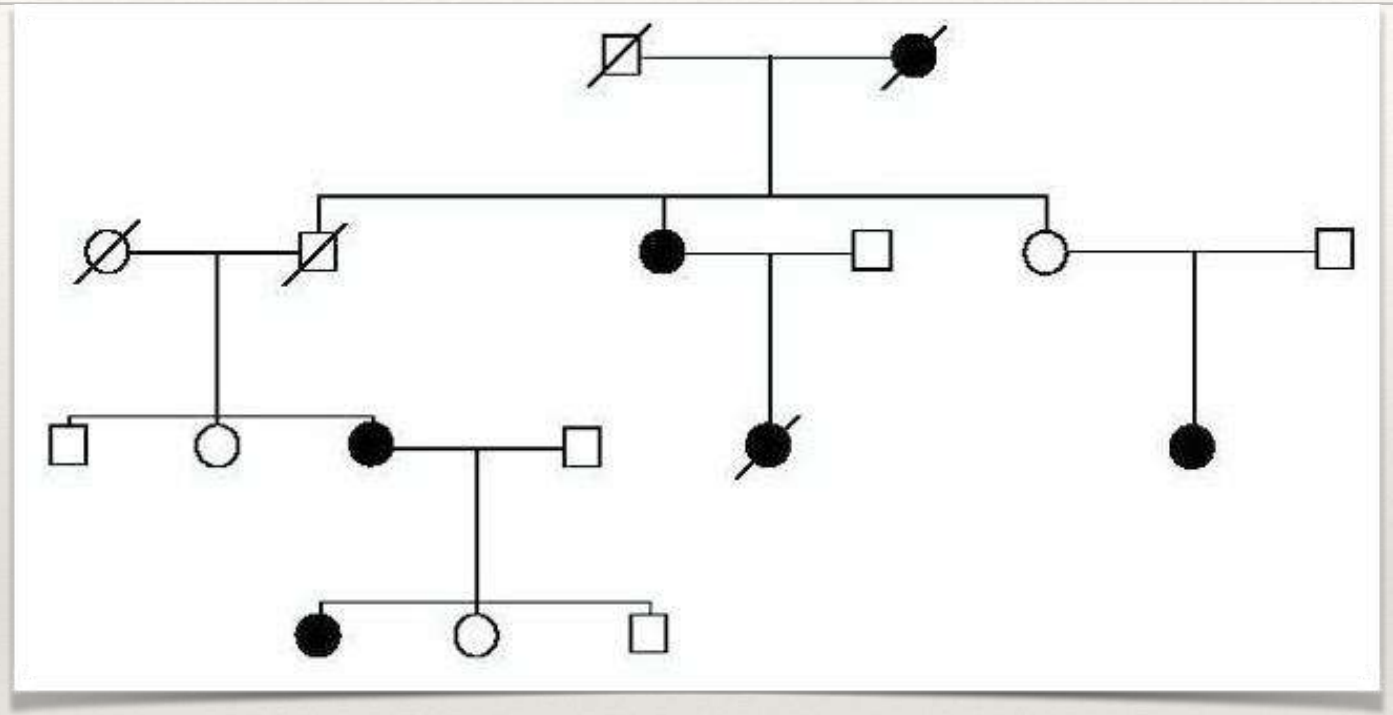
Tumor sequencing can guide treatment in selected cases





Cancer–agnostic

Familial Cancer

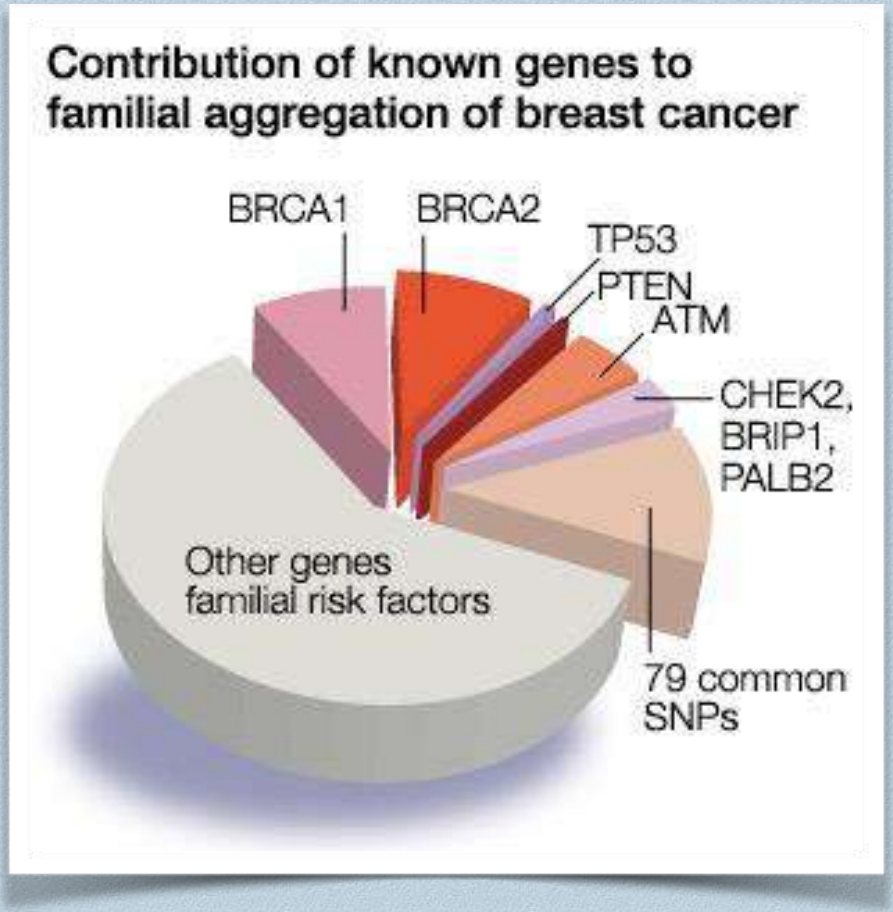


- Multiple reasons
- Hereditary cancer with definite pattern of inheritance

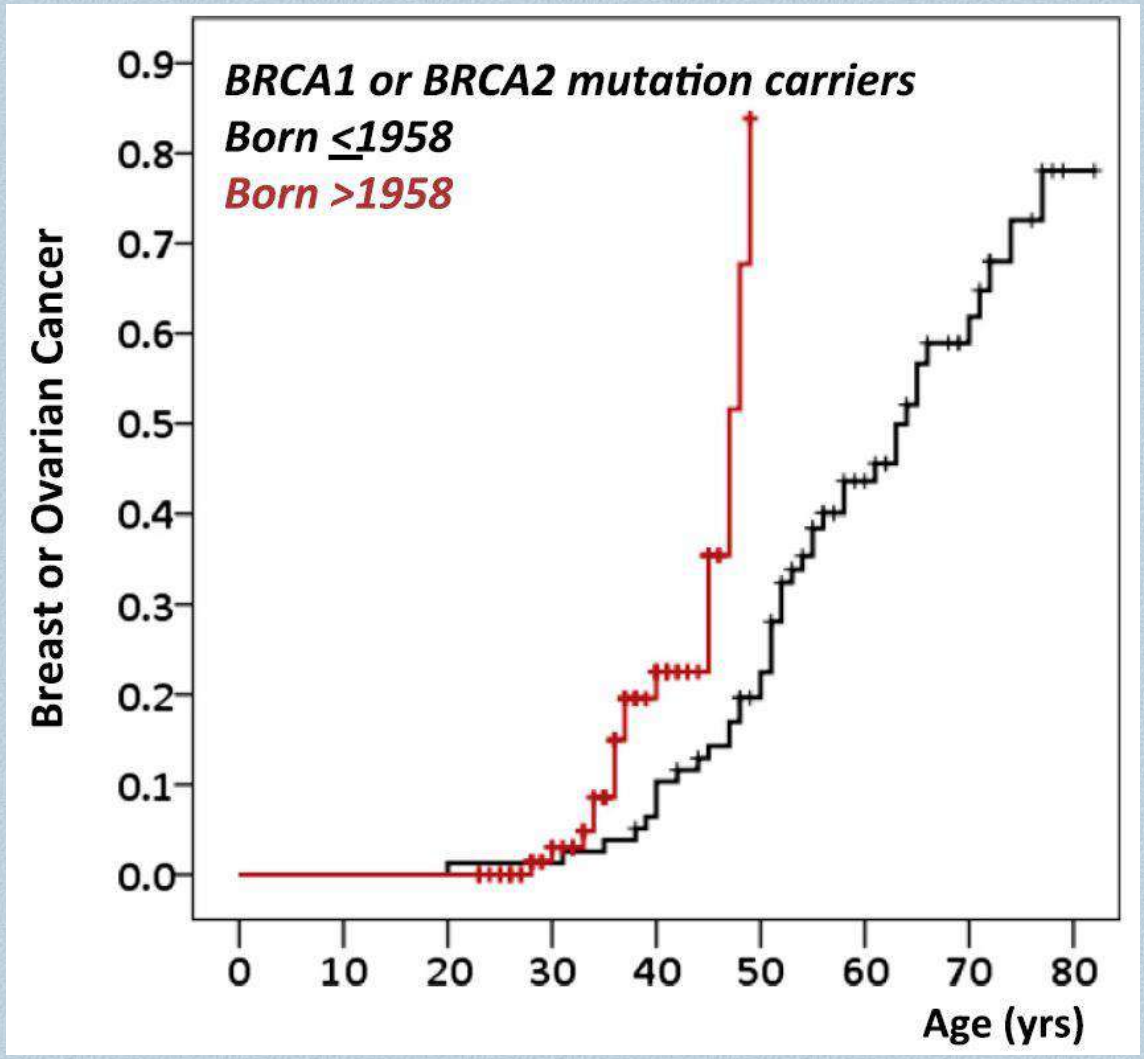
CANCER PRECISION MEDICINE

BRCA1/2 and other genetic risk

- The most common identified genetic mutation of familial breast cancer
- Mutation frequency 1:500–1:1,000
- Less in Asian more in Caucasian, Jewish, Icelander



Hereditary Breast Ovarian Cancer



The New York Times

The Opinion Pages

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY

OP-ED CONTRIBUTOR

My Medical Choice

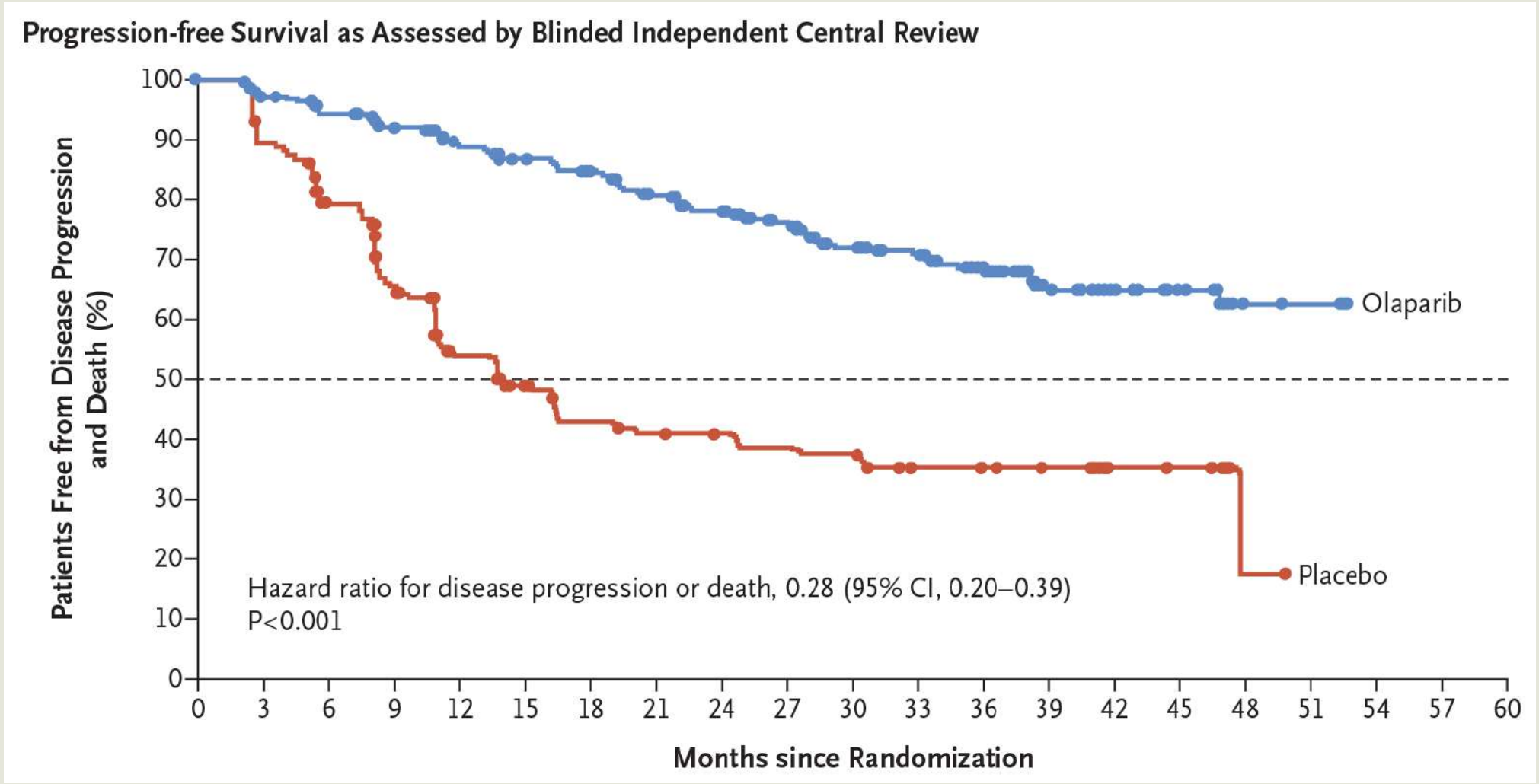
By ANGELINA JOLIE

Published: May 14, 2013 | 1712 Comments

CANCER PRECISION MEDICINE

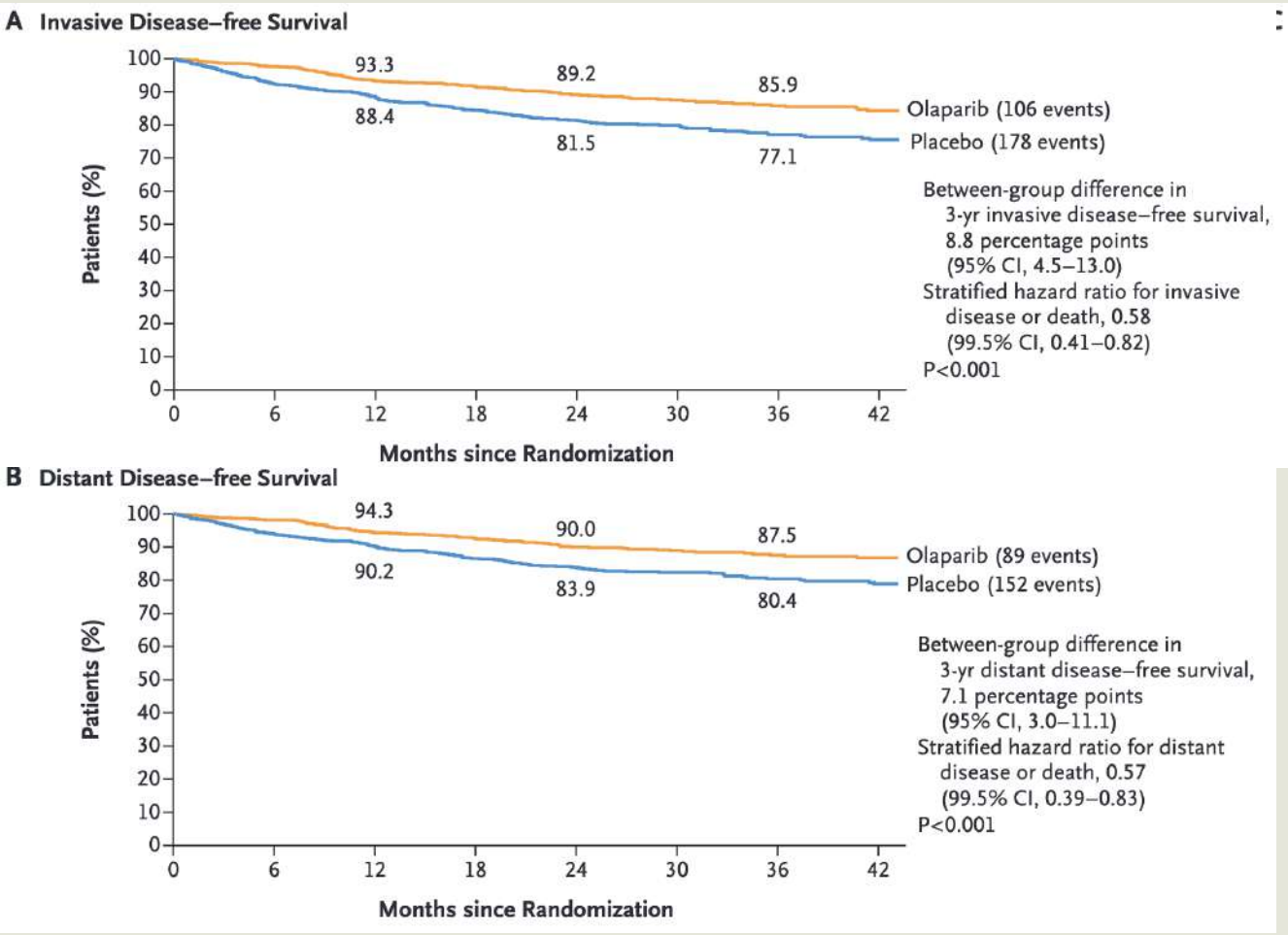
Gabai-Kapara E, et al. Proc Natl Acad Sci 111 (39) 14205–14210, September 2014

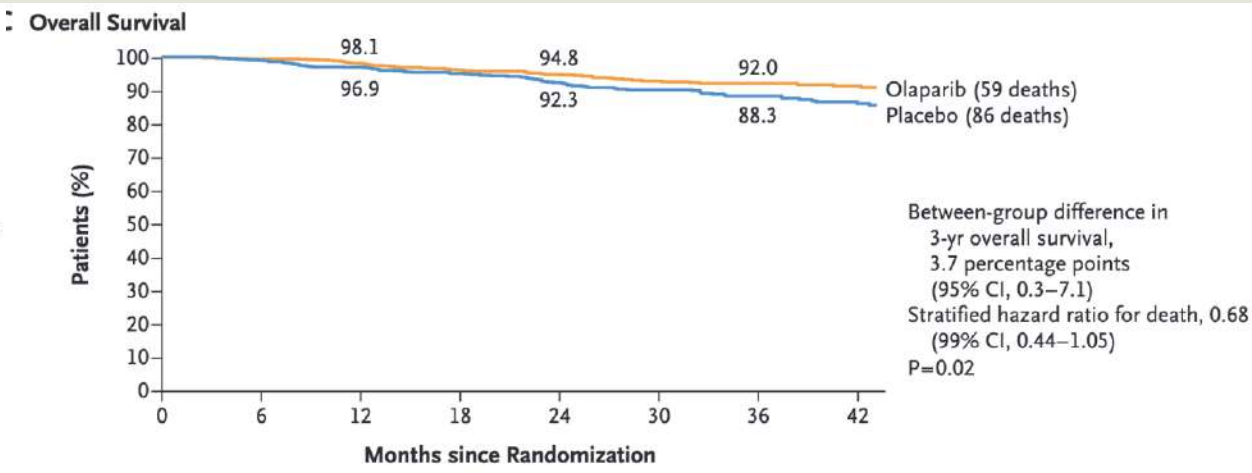
Olaparib as the 1st line agent in BRCA1/2 associated ovarian cancer



Moore K, et al. N Engl J Med. Published on December 27, 2018

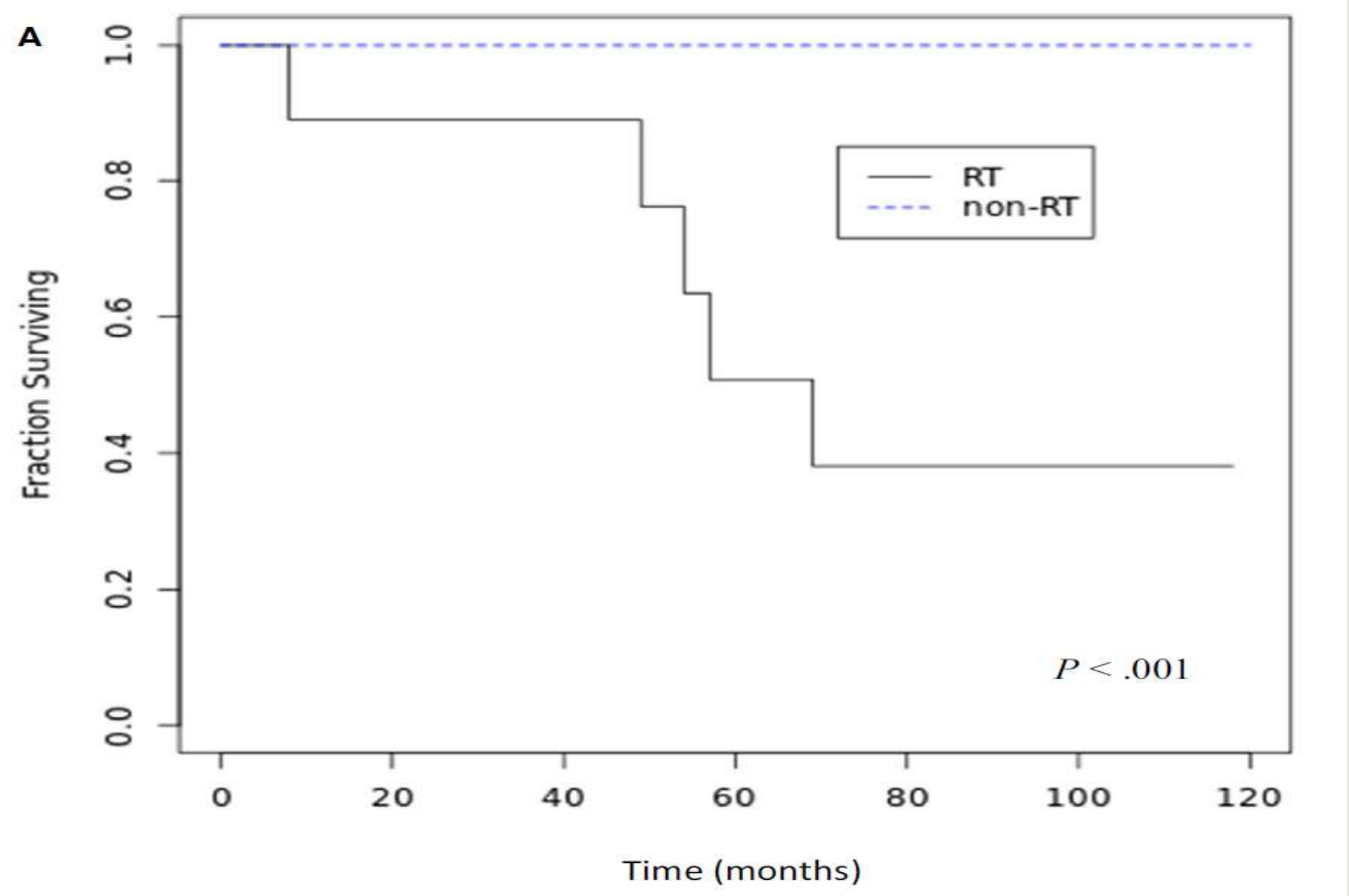
Olaparib in BRCA1/2 mutated early breast CA





Tutt ANJ, et al. N Engl J Med 2021; 384:2394-2405 Published on June 24, 2021

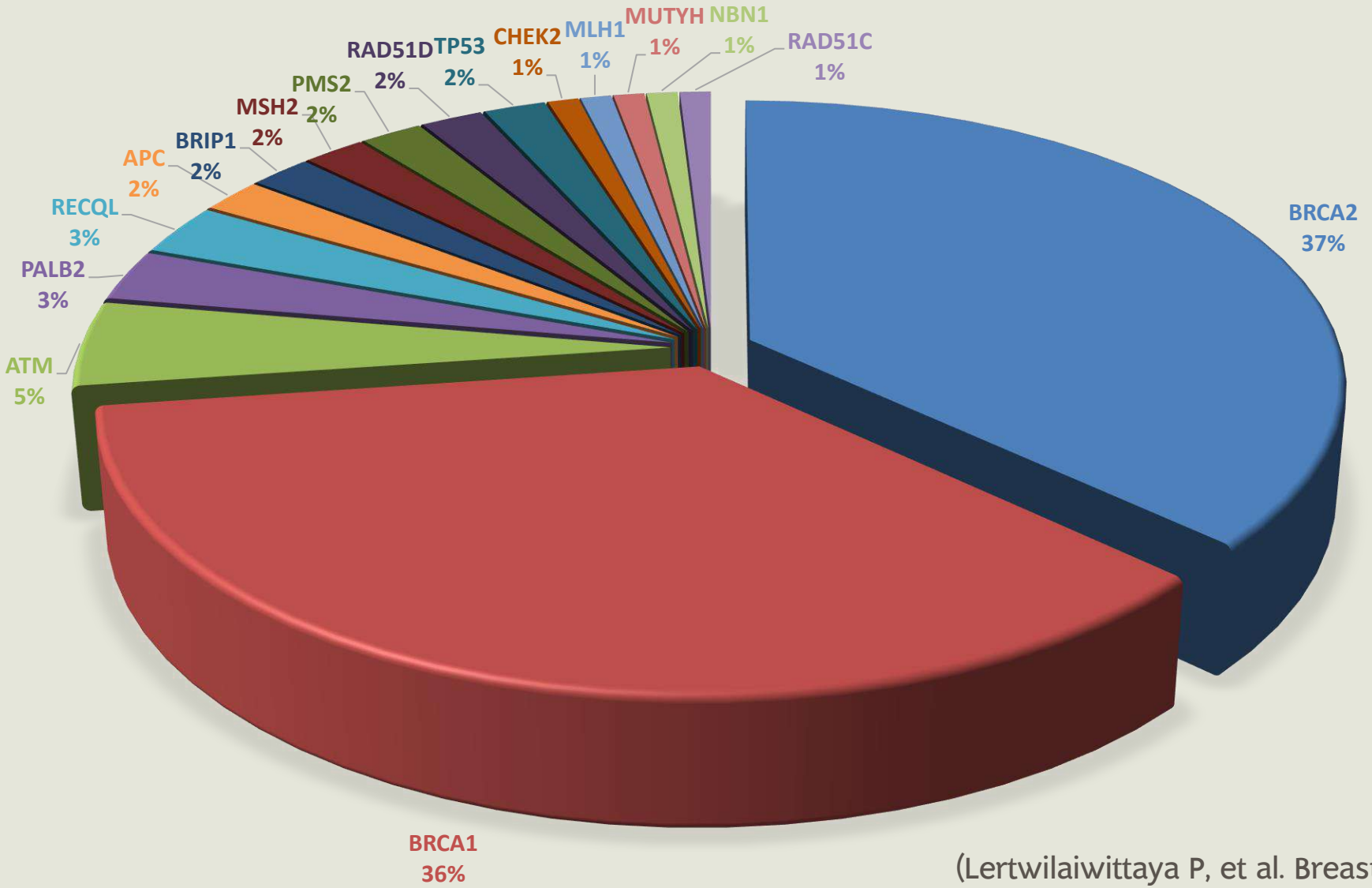
Radiation should be avoided in TP53 associated breast CA



- 50% risk of second primary cancer/local recurrence after post-op RT for curative treatment, median time 3.5 years (8.6 years for non-RT)

Hendrickson PG, et al. Cancer Med 2020;9:7954–7963

Germline Mutations in Thai Breast-Ovarian Cancer Spectrum



APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, RECQL, SMAD4, STK11, TP53, VHL, XRCC2

Probands with clinical suspicion of hereditary breast cancer (NCCN guideline 2019) N=389

Pathogenic/likely pathogenic variants (P/LP) identified in

24% of CA breast

37% of CA ovary

14% of CA pancreas

29% of CA prostate

BRCA1/2 P/LP variants account for 80% of all mutations in CA breast and 57% in CA ovary

VUS 40%

(Lertwilaiwittaya P, et al. Breast Cancer Res Treat. 2021 Jul;188(1):237-248)

GENOMICS THAILAND

Implementing Genomic Medicine in Thailand's Healthcare System

Rare diseases

Pharmacogenomics

NCD

Other conditions, Healthy cohorts

Cancer

Biobank

Whole Genome Sequencing

Genome Data

Bioinformatics

Aggregation of Genome Data

Bioinformatics

Pool Data together to create **Population-level Genome Database** of Thai Population

Analysis of Genomic Association in Specific Conditions (Cancer, NCD, Autoimmune Diseases, Infectious Diseases, etc)

Bioinformatics

Frontier Research

Reference Database of Thai Population and Implication to ASEAN

Bioinformatics

Translational Research

Thai (and region) specific gene panel, diagnostic test, databases for further research and clinical trials

Output:
-**Polygenic risk score**
-**Specific gene panel** for diagnosis, to determine risk of disease, complication, treatment response, prognosis
-Further research on **new genetic information of each disease** >> new tests, new drugs, new treatment

Healthcare

Actionable/Pathogenic Variants

Immediate/Short Term Benefit (diagnosis, treatment, prevention, screening)

Cancer (familial cancer)
Rare diseases
Pharmacogenomics

Guidelines for diagnosis and treatment
Integrate into healthcare system

Draft version, Do not disclose

Germline Test

Cancer Patients

Blood

- CA Breast < 45 years old
- CA Breast < 50 years old
  - First degree relative of CA breast, pancreas, ovary, prostate
- TNBC
- Any CA Breast with family history of CA breast, pancreas, prostate, sarcoma at least 1 first degree relative or at least 2 members or early onset (< 50 years old)
- Any bilateral CA Breast
- Any CA Breast with other primary CA
- Male breast cancer or early onset prostate cancer (<50 years old)
- CA ovary, pancreas, adrenal cortex, choroid plexus
- Colonic adenomatous polyps >10 or harmatoma >2 or serrated > 4
- CA colon or endometrium with
  - Family history in 1st degree relative cases or fulfill Amsterdam criteria
  - Metachronous/synchronous
  - MMR deficiency/MSI-H
  - Age <50 years old
- Any patient with 2 primary cancers or age <50 years old
- Clinical phenotype suggestive of hereditary cancer syndromes

NCCN Guidelines – Genetic/Familial High-Risk Assessment: Breast & Ovarian and Colorectal Cancers
Latest Update: Breast & Ovarian Version 1/2022, CRC Version 1/2021

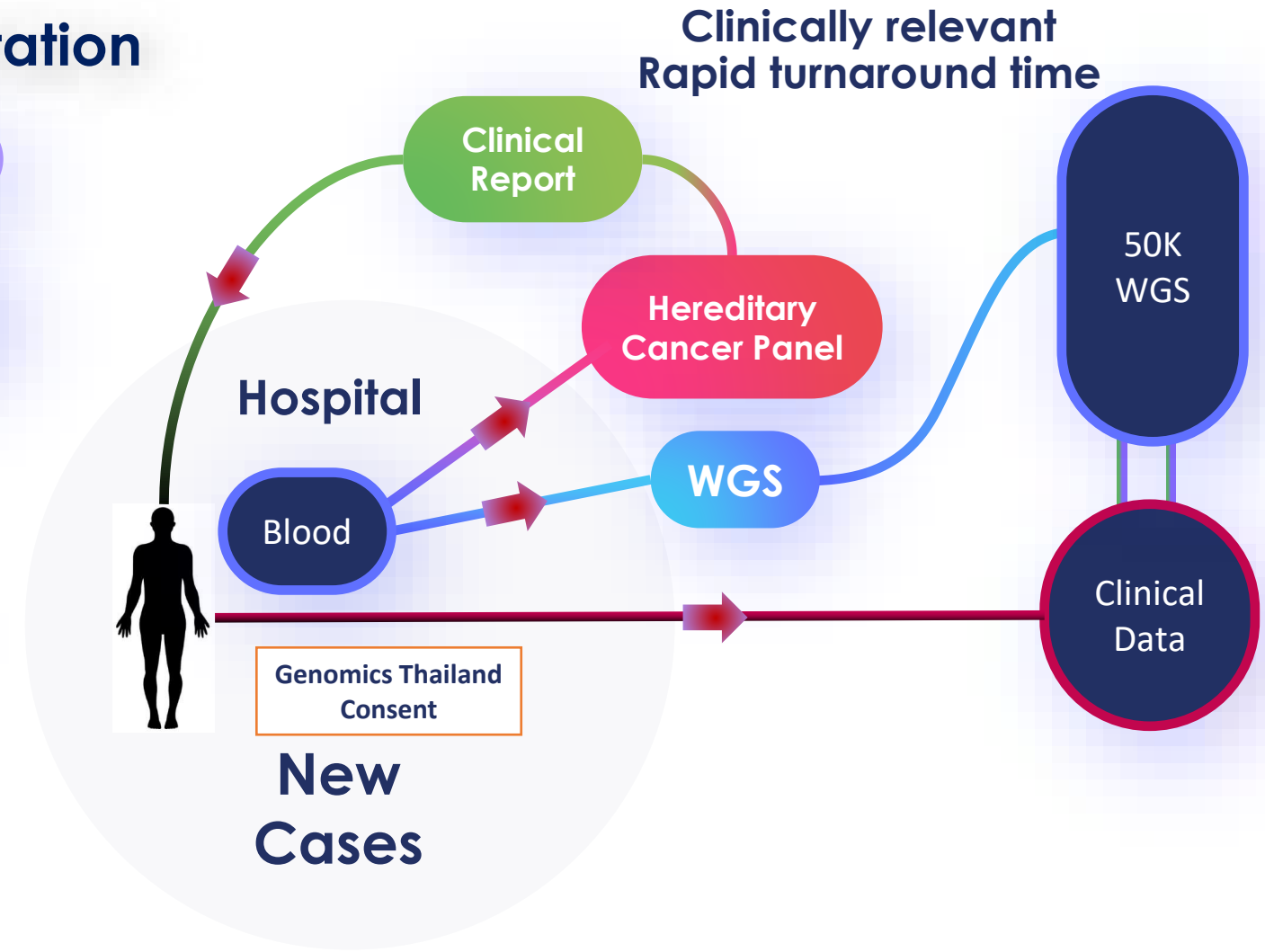
Clinical Implementation

Proficiency Test

Cost Utility Analysis

Cancer Genes

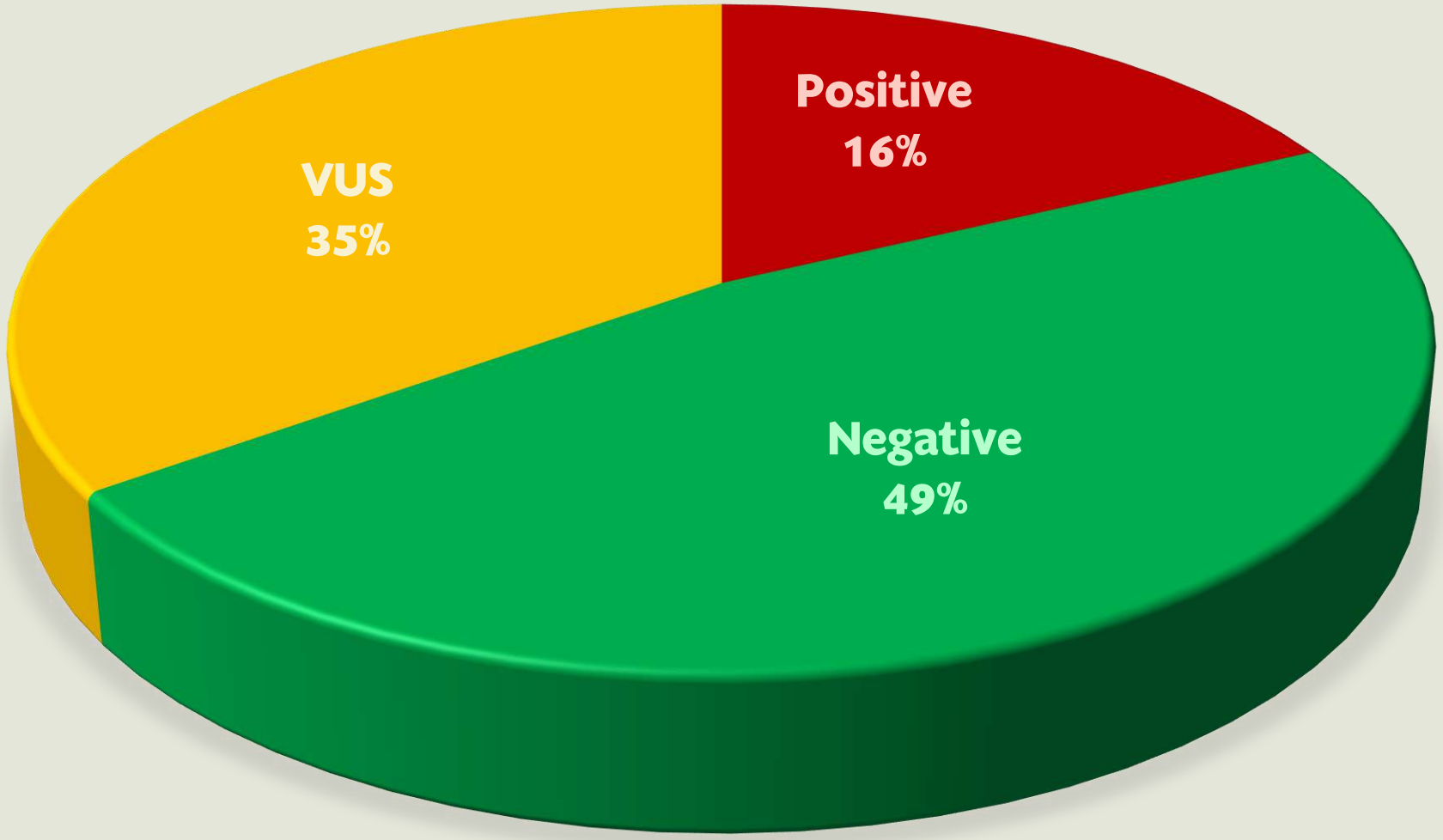
APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC2



Whole genome SNV
Secondary findings
Pharmacogenomics
Polygenic risk scores

Siriraj Genomics

Germline Mutations in Thai Cancer Patients



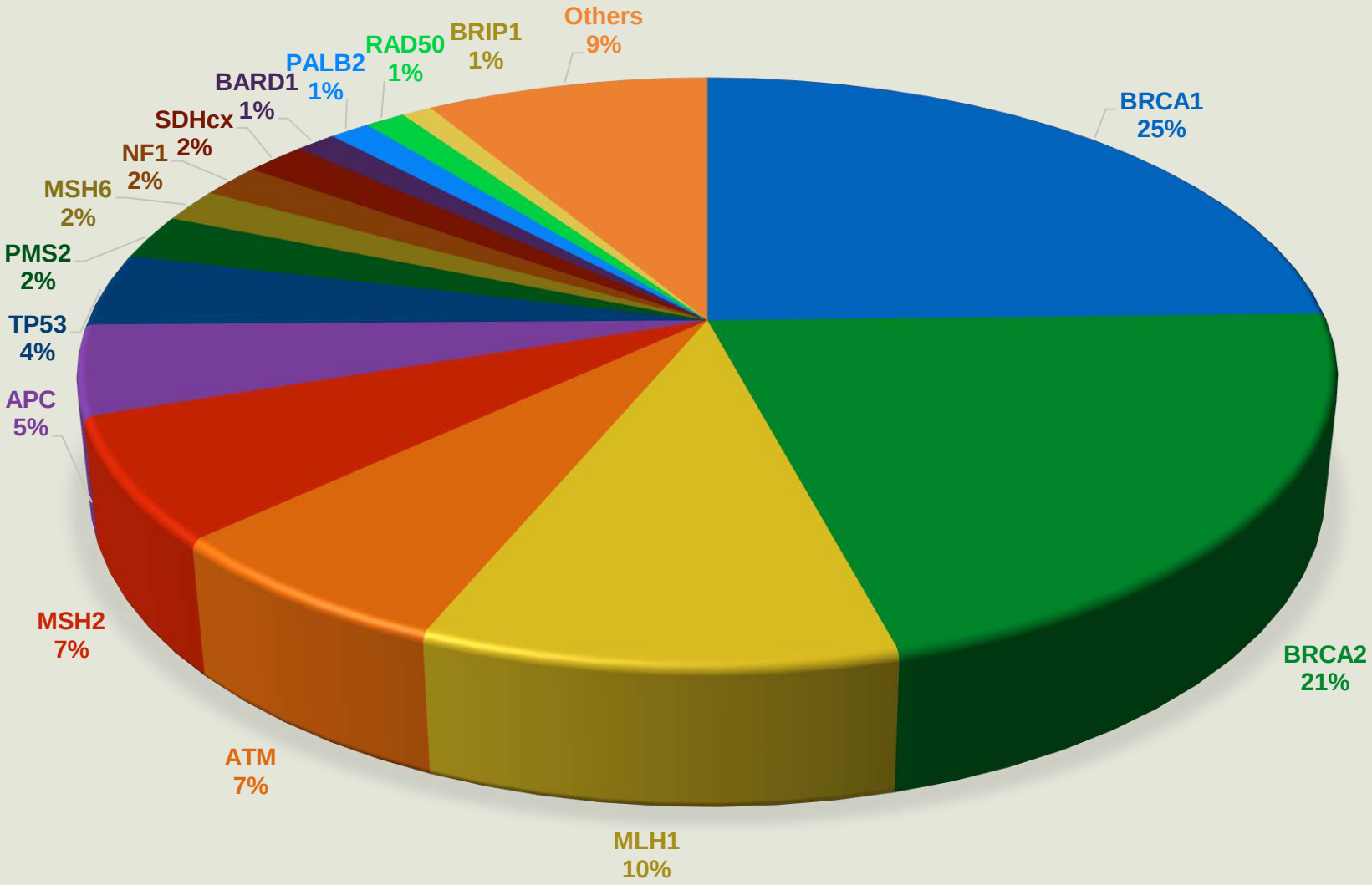
Probands with clinical suspicion of hereditary cancer N=4,340

Pathogenic/likely pathogenic variants (P/LP) identified 16%

VUS 35% (Unpublished data)

APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC2

Germline Mutations in Thai Cancer Patients



APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NTHL1, PALB2, PMS2, POLD1, POLE, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53, VHL, XRCC2

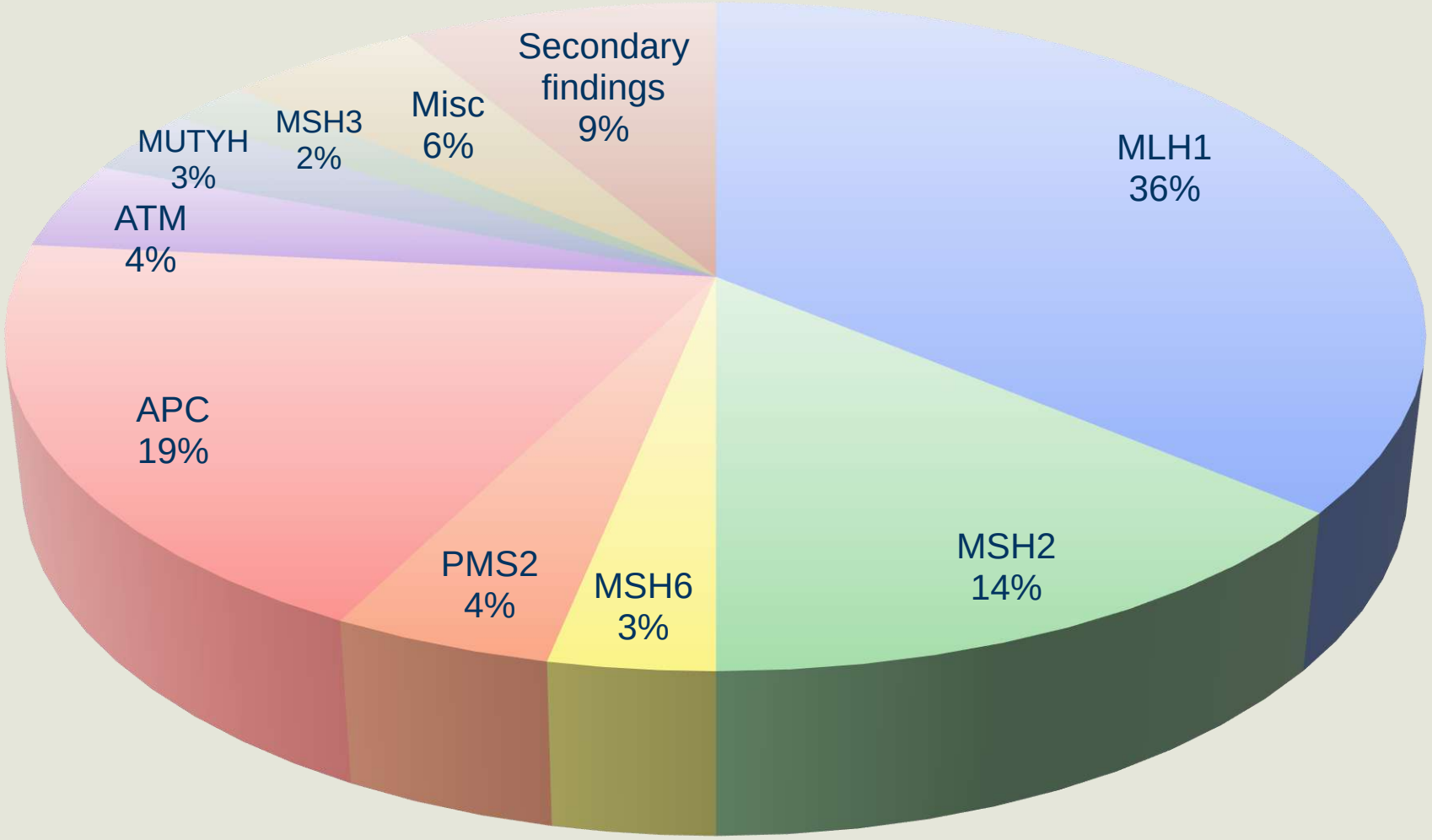
Probands with clinical suspicion of hereditary cancer N=4,340

Pathogenic/likely pathogenic variants (P/LP) identified 16%

VUS 35% (Unpublished data)

CANCER PRECISION MEDICINE

Germline Mutations in Thai Colorectal Cancer Patients



Probands with clinical suspicion of hereditary colorectal cancer N=405

Pathogenic/likely pathogenic variants (P/LP) identified 23%

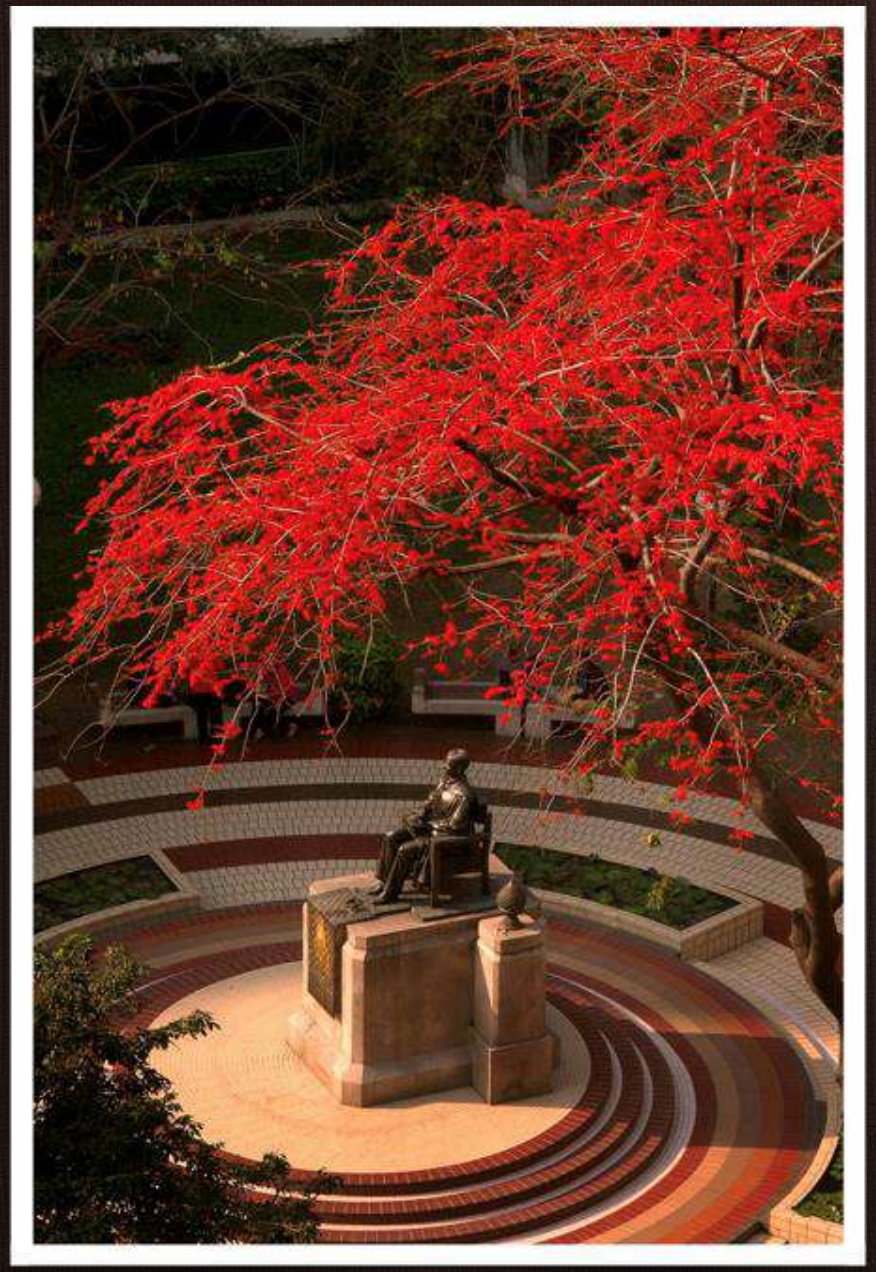
Lynch syndrome 57%
APC polyposis 19%
Other CRC genes 15%
Secondary findings (BRCA) 9%

(Unpublished data)

APC, ATM, AXIN2, BARD1, *BMPR1A*, BRCA1, BRCA2, BRIP1, *CDH1*, CDK4, CDKN2A, CHEK2, *EPCAM*, FANCC, *MLH1, MSH2, MSH3, MSH6, MUTYH*, NBN, *NTHL1*, PALB2, *PMS2, POLD1, POLE, PTEN*, RAD51C, RAD51D, *SMAD4, STK11, TP53*, VHL, XRCC2

บอร์ด สปสช.เคาะสิทธิประโยชน์ใหม่ 6 รายการ ค้นหายีนมะเร็งเต้านม-แจกยา PEP ป้องกันเอชไอวี

14 ธันวาคม 2564 | 2925 | 24 | แชร์



Siriraj Genomics

Mahidol University
Faculty of Medicine
Siriraj Hospital

Questions & Answers

CANCER PRECISION MEDICINE