Genetic and Genomic Assessment in Women with Ovarian Cancer

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

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Potential Conflicts of Interest

…capped at a level befitting an academic role
Lo B. Serving Two Masters 2010;362:669-671

2004-	Genentech, Inc.	Research DSMC Chair SABs
2006-9	CuraGen Corp.	Research Funding
2007-10	PDL BioPharma, Inc.	Research Funding
2007-	ImClone Systems, Inc.	Research Funding
2008-13	Abbott Laboratories	Scientific Advisory Boards (SABs)
2008-	Endocyte, Inc.	Research Scientific Advisory Boards
2009-	AstraZeneca	Research SABs Educational materials
2010-	Vascular Biogenics, Ltd	Research Funding SABs
2010-	Eisai Inc.	Research Funding
2010-	Amgen Inc.	Research Funding SABs
2010-11	Lifecore Biomedical	Scientific Advisory Boards
2011	Biomarin Pharma Inc.	Scientific Advisory Boards
2011-	Clovis Oncology	Scientific Advisory Boards
2013-	AbbVie	Scientific Advisory Boards DSMC
2016-	Schulman IRB	Consultant

Genetic / Genomic Ix:

1. Indications

2. g/s*BRCA* and Beyond

3. Available Platforms

4. BRCA-like signatures

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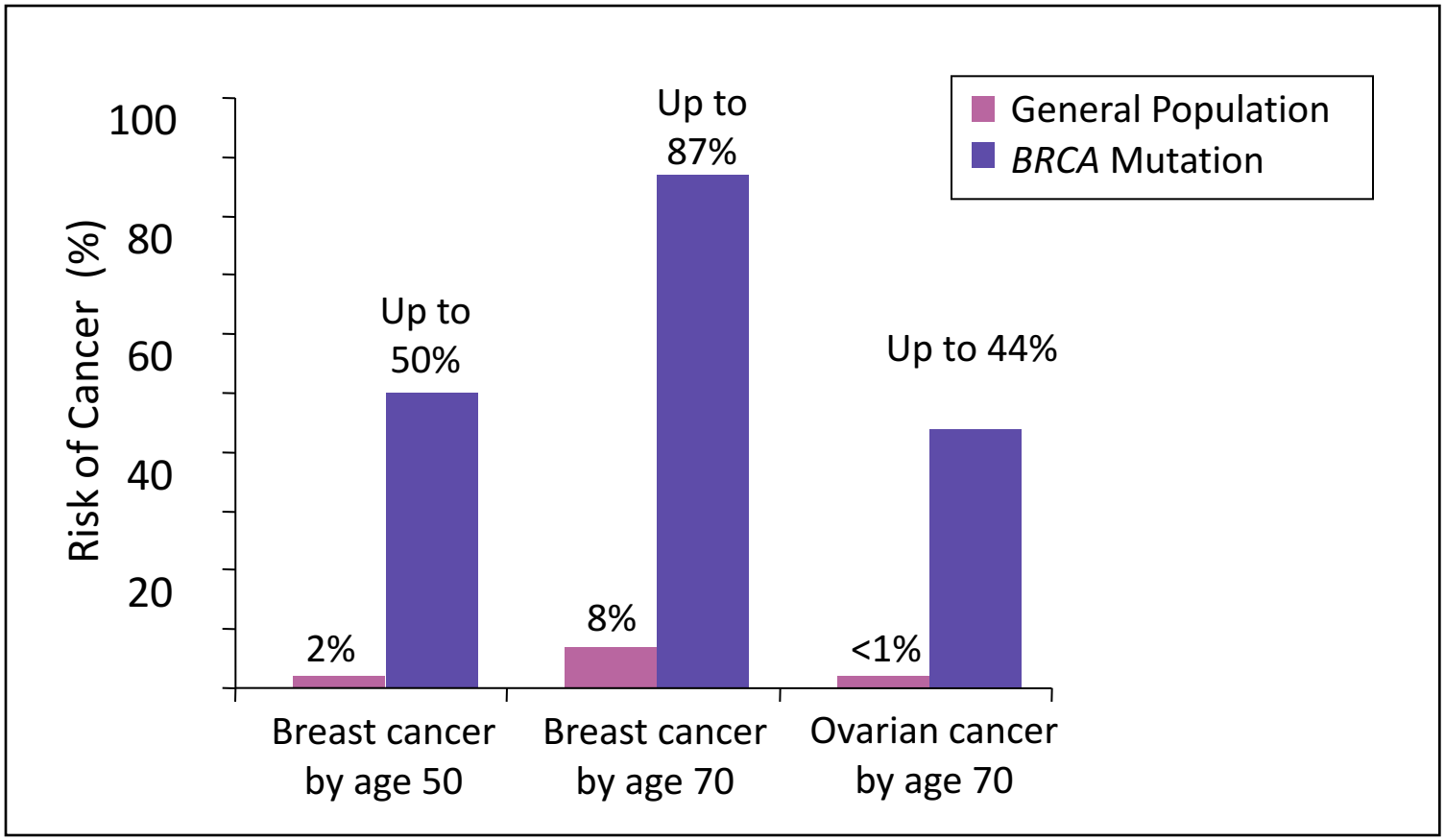
Risk Factors?

- Increased risk - nulliparity, early menarche, late menopause, ovulatory stimulation, history of breast cancer, genetics, Caucasian
- Decreased risk - ≥ 5 years oral contraception, tubal ligation, non-caucasian
- Best unifying theory is that sporadic ovarian cancer is due to ‘incessant’ ovulation
- Less than 10% is inherited

Inherited Predisposition

- BRCA1 17q 185delAG, 5382insC (FA) OVCA 16-54%
- BRCA2 13q 6174delT (Rad51) OVCA 10-23%
  - General pop. 0.1-2% King Science 2003;302:643
  - Ashkenazi 2.5-10-26-41%
- RRSO 95% reduction in the risk of OVCA
- Lynch II *MSH2 MLH1* Rebbeck NEJM 2002;346:1616
- 1000 pt study Bowtell Nat Rev Cancer 2010;10:803
  Alsop JCO 2012;30:2654

BRCA Mutation Increases Breast and Ovarian Cancer Risks



Genetic Analysis

U.S. Preventive Services TASK FORCE

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Breast and/or Ovarian Cancer Genetic Assessment

NCCN Guidelines Index
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Discussion

CRITERIA FOR FURTHER GENETIC RISK EVALUATION[a]

- An individual with an ovarian[e] cancer
- An individual with a breast cancer diagnosis meeting any of the following:
  - A known mutation in a cancer susceptibility gene within the family
  - Early-age-onset breast cancer[b]
  - Triple negative (ER-, PR-, HER2-) breast cancer diagnosed ≤60 y
  - Two breast cancer primaries[c] in a single individual
  - Breast cancer at any age, and
    - ≥1 close blood relative[d] with breast cancer ≤50 y, or
    - ≥1 close blood relative[d] with invasive ovarian[e] cancer at any age, or
    - ≥2 close blood relatives[d] with breast cancer and/or pancreatic cancer at any age, or
    - Pancreatic cancer at any age, or
    - From a population at increased risk[f]
  - Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of gastrointestinal (GI) tract[h]
- An individual with no personal history of cancer but with
  - A close relative with any of the following:[d,f]
    - A known mutation in a cancer susceptibility gene within the family
    - ≥2 breast cancer primaries in a single individual
    - ≥2 individuals with breast cancer primaries on the same side of family with at least one diagnosed ≤50 y
    - Ovarian[e] cancer
    - Male breast cancer
  - First- or second-degree relative with breast cancer ≤45 y
  - Family history of three or more of the following (especially if early onset[b] and can include multiple primary cancers in same individual): breast, pancreatic cancer, prostate cancer (Gleason score ≥7), melanoma, sarcoma, adrenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer[i], colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations[g,h] and/or macrocephaly, hamartomatous polyps of GI tract[h]

→ Consider referral to cancer genetics professional[j] → See Assessment (BR/OV-2)

[a]The criteria for further risk evaluation and genetic testing are not identical. For the purposes of these guidelines, invasive and ductal carcinoma in situ breast cancers should be included. The maternal and paternal sides of the family should be considered independently for familial patterns of cancer.

[b]Clinically use age ≤50 y because studies define early onset as either ≤40 or ≤50 y.

[c]Two breast cancer primaries includes bilateral (contralateral) disease or two or more clearly separate ipsilateral primary tumors either diagnosed synchronously or asynchronously.

[d]Close blood relatives include first-, second-, and third-degree relatives. (See BR/OV-B)

[e]Includes fallopian tube and primary peritoneal cancers. *BRCA*-related ovarian cancers are associated with epithelial, non-mucinous histology. Lynch syndrome can be associated with both non-mucinous and mucinous epithelial tumors. Be attentive for clinical evidence of Lynch syndrome (See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal). Specific types of non-epithelial ovarian cancers and tumors can also be associated with other rare syndromes. Examples include an association between sex-cord tumors with annular tubules and Peutz-Jeghers syndrome or Sertoli-Leydig tumors and DICER1-related disorders.

[f]For populations at increased risk due to founder mutations, requirements for inclusion may be modified.

[g]For dermatologic manifestations, see COWD-1.

[h]For hamartomatous colon polyps in conjunction with breast cancer and hyperpigmented macules of the lips and oral mucosa, *STK11* testing should be considered. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal—Peutz-Jeghers syndrome. Melanoma has been reported in some *BRCA*-related families.

[i]For lobular breast cancer with a family history of diffuse gastric cancer, *CDH1* gene testing should be considered.

[j]For further details regarding the nuances of genetic counseling and testing, see BR/OV-A.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Who Should We Test?

Everyone

Genetic / Genomic Ix:

1. Indications
2. **g/s*BRCA* and Beyond**
3. Available Platforms
4. BRCA-like signatures

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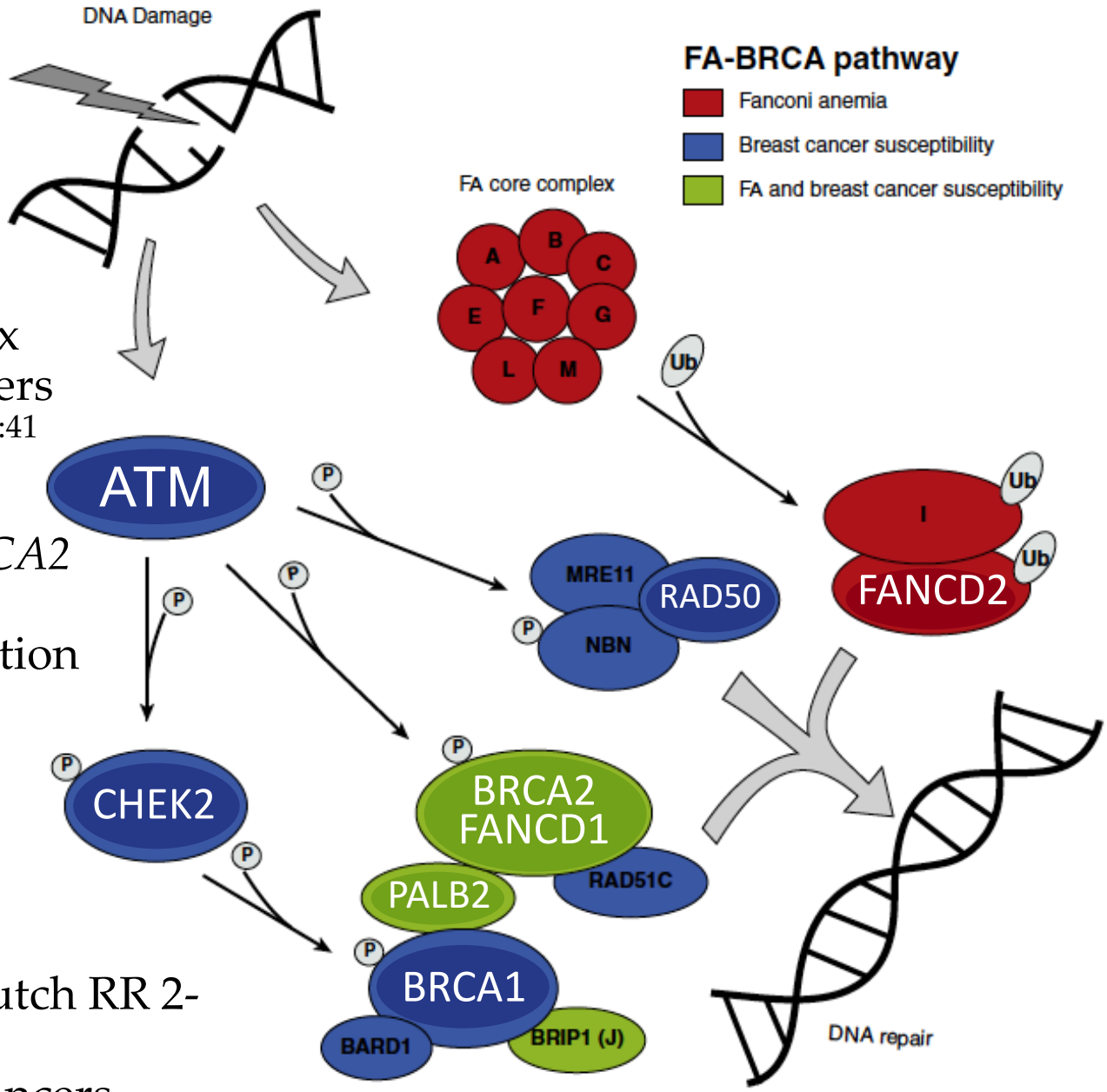
TP53
PTEN (Cowden)
STK11 (Peutz-Jeghers)

ATM
Ataxia Telangiectasia
Penetrance 15% RR 2-4x
Breast, pancreatic cancers
Roberts Cancer Discovery 2012;2:41

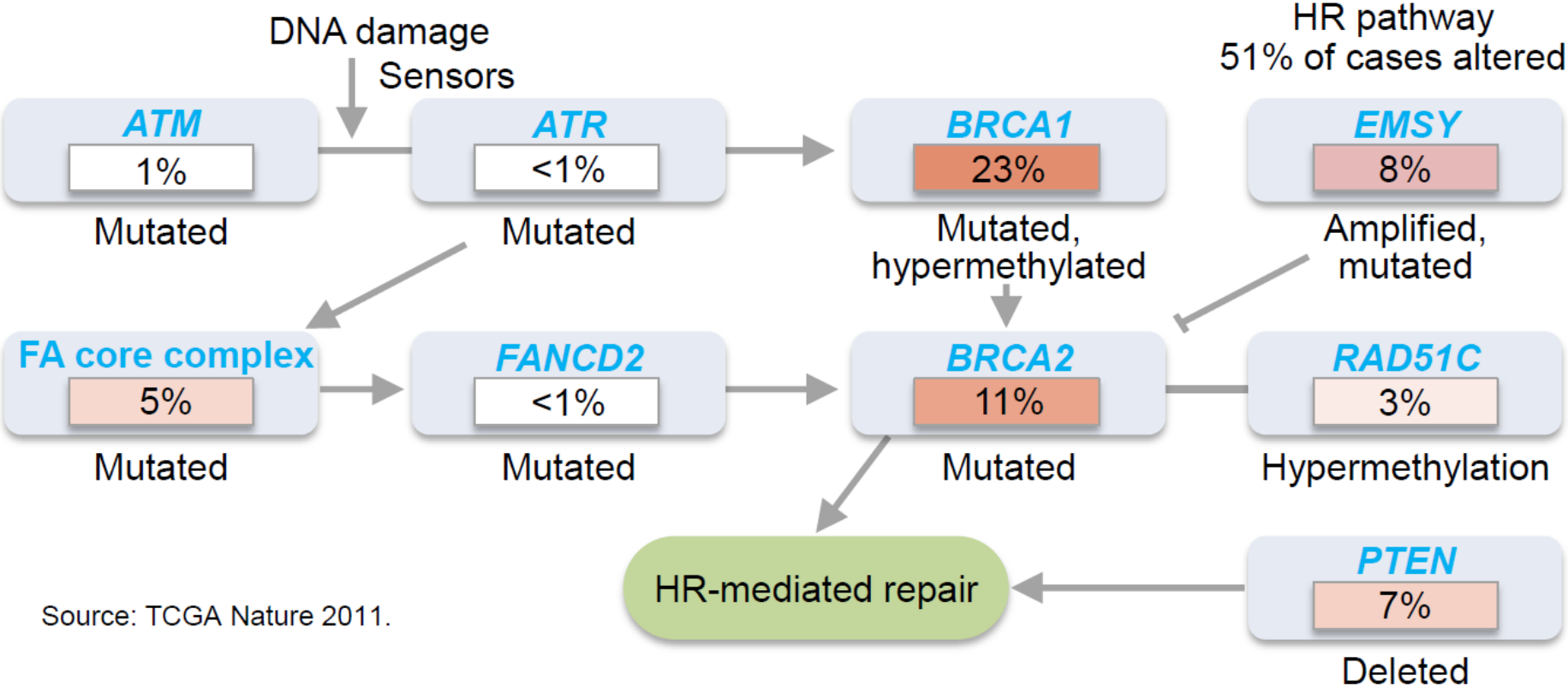
PALB2
Partner & localizer *BRCA2*
Mut. carrier rate 0.08%
1592delT Finnish mutation
40% cancer by 70yo
TNBC, ovarian, & pancreatic cancers
Antoniou NEJM 2014;371:1651

CHEK2
1100delC 1% carrier Dutch RR 2-5x
Breast, OVCA, other cancers
Huzarski Breast Cancer Res Treat 2014;444:397



Pennington & Swisher Gynecol Oncol 2012;124(2):347

Up to 50% of HGOC patients may be tBRCA^{mut} or tBRCA-like per TCGA



Source: TCGA Nature 2011.

Adapted from Swisher et al, ECCO 2015

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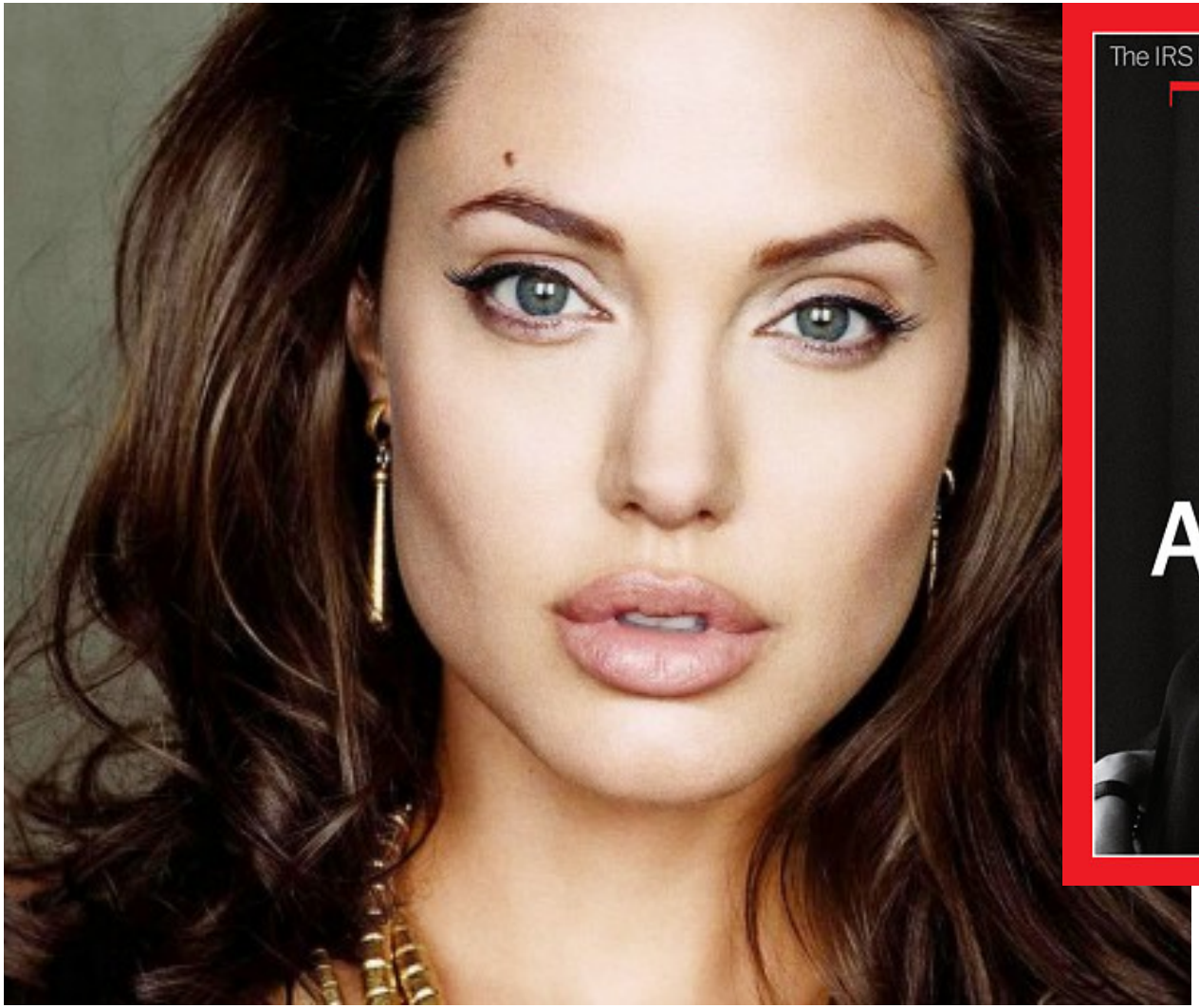
Jolie Revelation



NYT
May 14th 2013

Mother and Daughter

- **Marcheline Bertrand**
- Died 2007
- Ovarian Cancer
- Aged 56
- Actress
- … Mother

BRCA Patent Issues

Supreme Court

June 13, 2013

Molecular Pathology v. Myriad Genetics, Inc.

Unanimous decision

Invalidated Myriad's claims

Discovery & Prior Art

CAN patent: methods

Panel Testing

Gene	Cancers	Syndrome Name
APC	Colorectal, adenomatous polyps	Familial adenomatous polyposis (FAP)
ATM	Breast, pancreas	
BARD1	Breast	
BMPR1A and SMAD4	Colorectal	Juvenile polypsis syndrome (JPS)
BRCA1 and BRCA2	Breast, ovarian, prostate	Hereditary breast and ovarian cancer (HBOC)
BRIP1	Breast	
CDH1	Lobular breast, diffuse stomach, colorectal	Hereditary diffuse gastric cancer (HDGC)
CDK4	Melanoma	
CDKN2A	Melanoma, pancreas	
CHEK2	Breast, colorectal	
MLH1, MSH2, MSH6, PMS2 and EPCAM	Colorectal, endometrial (uterine), ovarian, stomach	Lynch syndrome/HNPCC
MRE11A	Breast	
MUTYH (MYH)	Colorectal	MYH-associated polyposis (MAP) syndrome
NBN	Breast	
NF1	Breast	Neurofibromatosis type 1
PALB2	Breast, pancreas	
PTEN	Breast, thyroid, uterine	Cowden syndrome/PTEN hamartoma syndrome
RAD50	Breast	
RAD51C	Breast, ovary	
RAD51D	Breast, ovary	
STK11	Breast, colorectal, stomach	Peutz-Jeghers syndrome
TP53	Breast, sarcoma, adrenocortical, brain	Li-Fraumeni syndrome

Genetic / Genomic Ix:

1. Indications
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4. **BRCA-like signatures**

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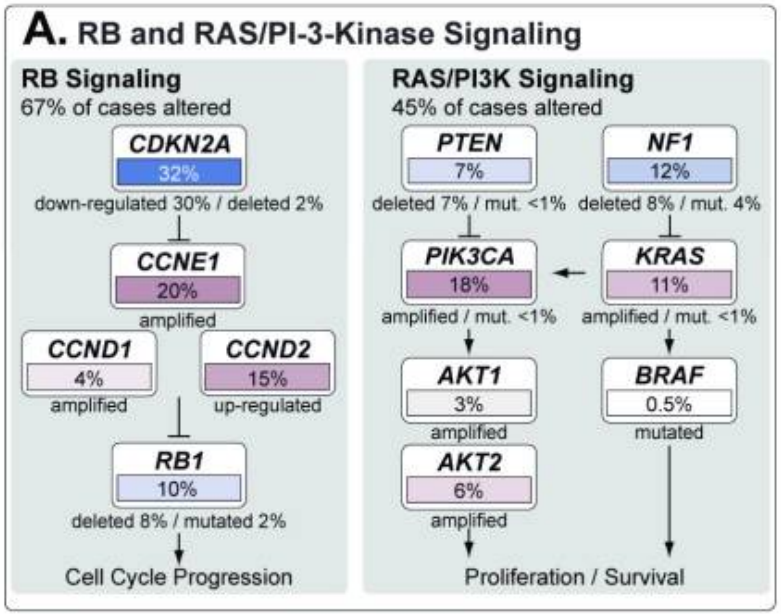
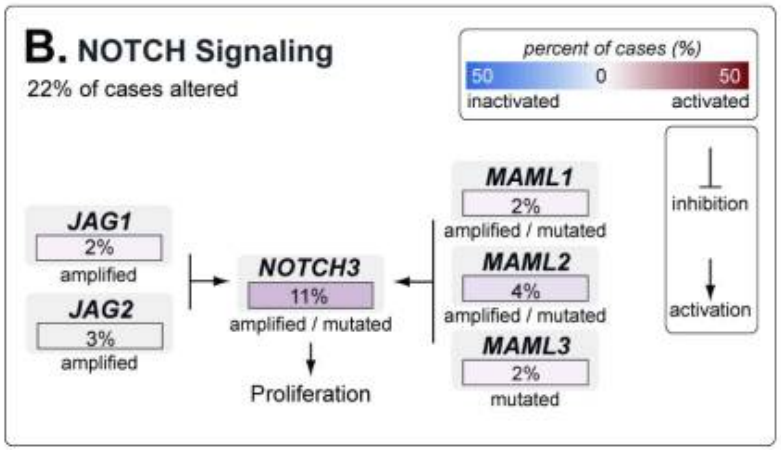
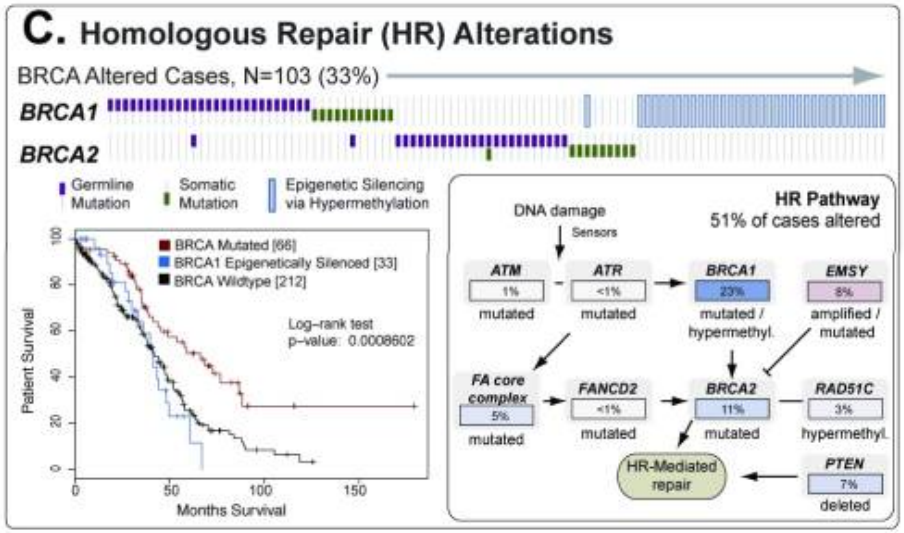
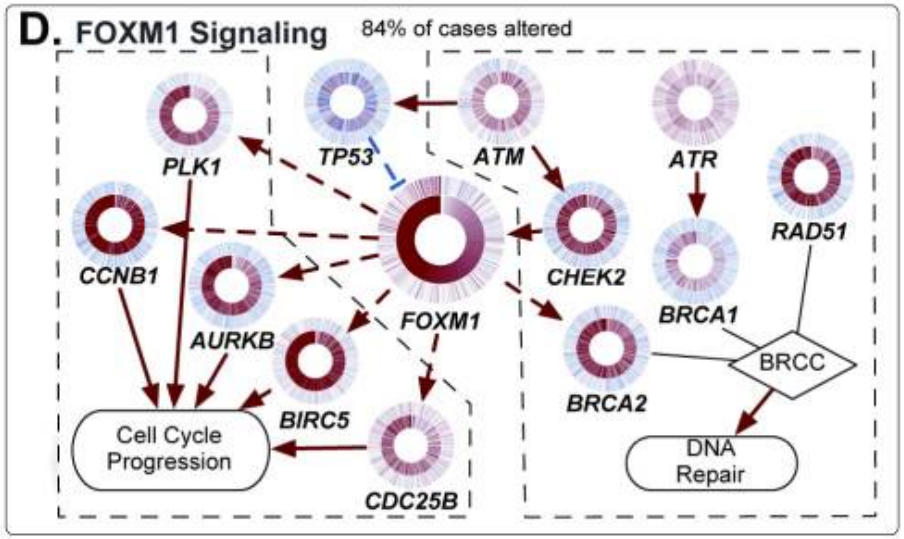
TGCA Serous

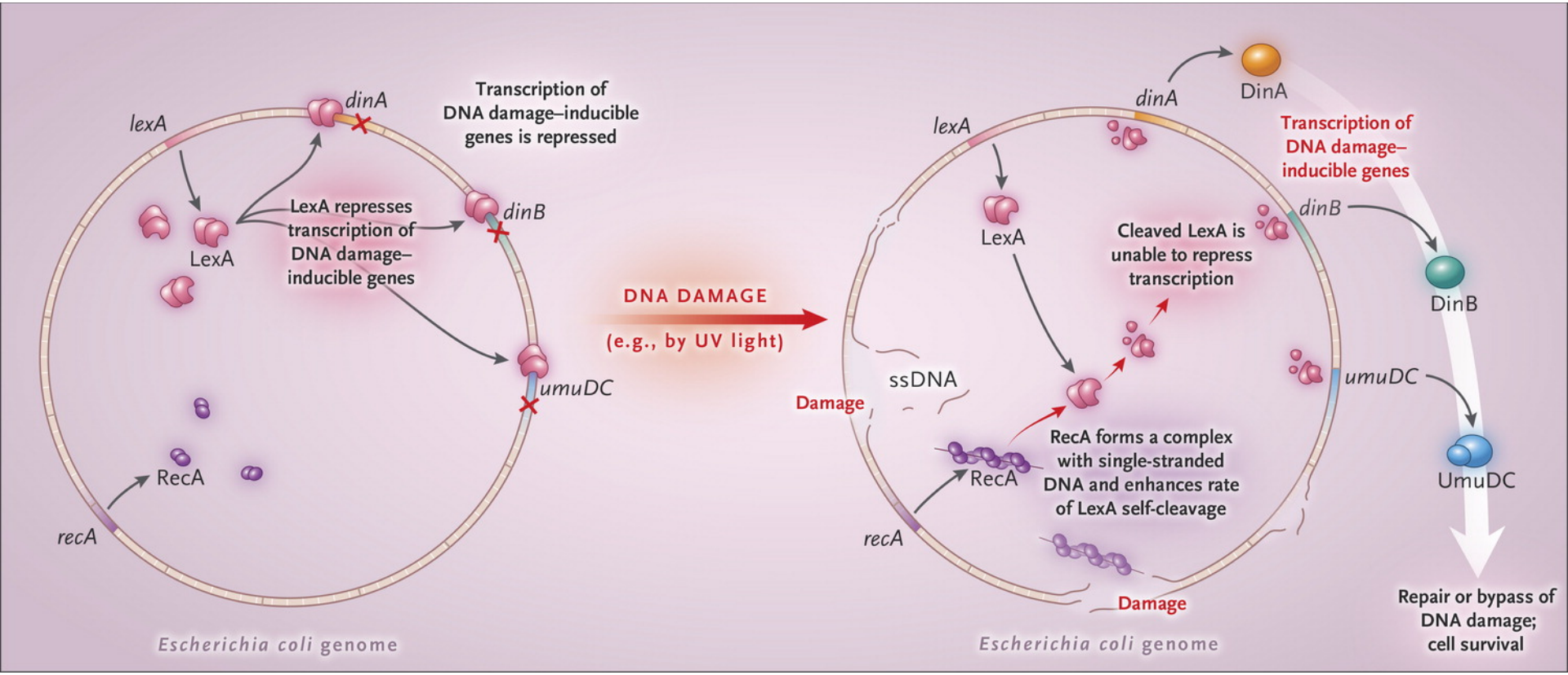






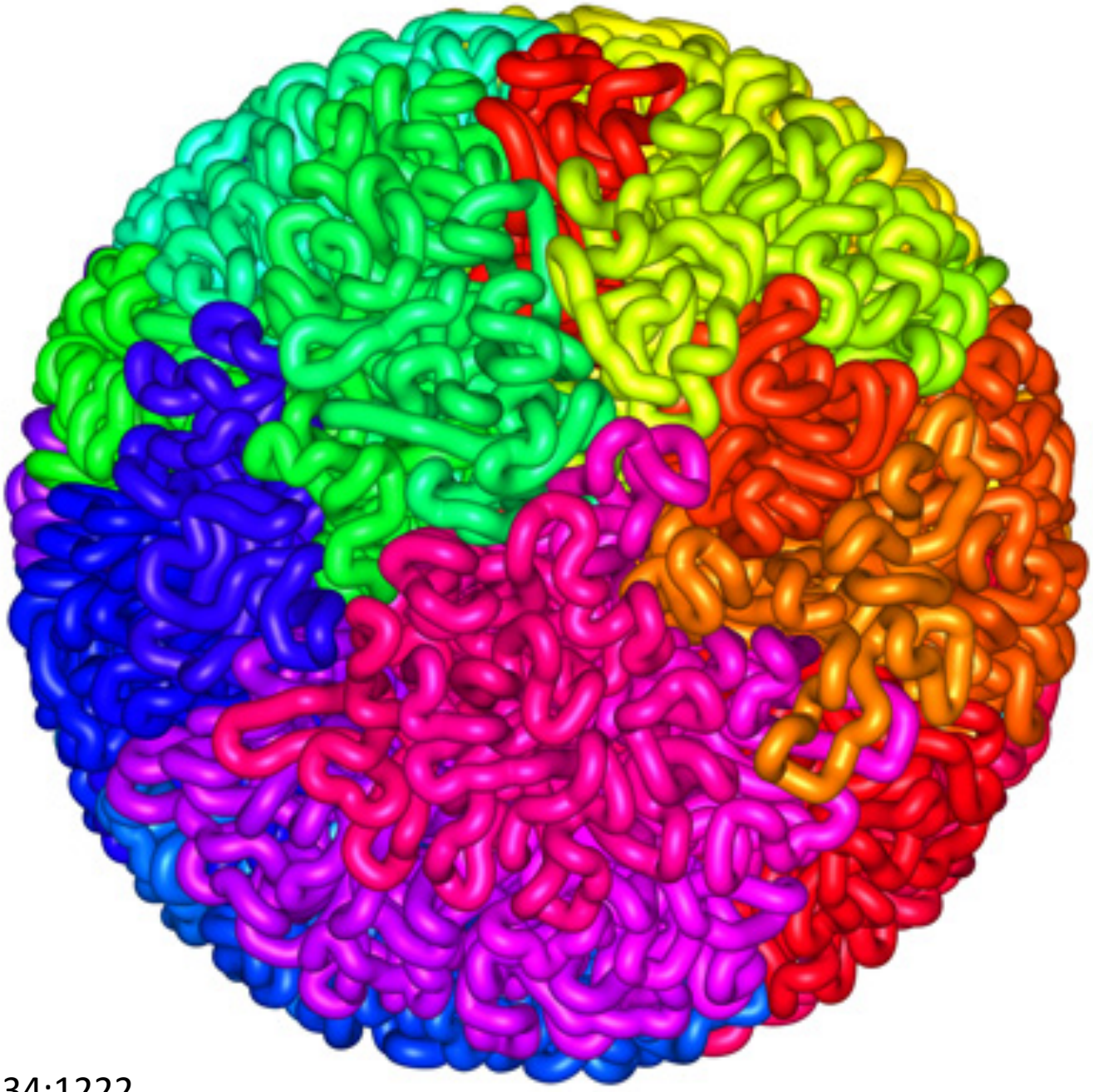


Nature 2011;474(7353):609



LexA represses expression of a number of genes by binding to their promoters. When DNA damage occurs, RecA-single-strand DNA complexes form and act as a coprotease for the self-cleavage activity of LexA. As a result, several DNA damage–inducible (din) genes are expressed, including DNA polymerases. >40 genes are induced in the SOS response that promote repair of DNA damage and survival.

Jasin M. N Engl J Med 2015;373:1492-1495

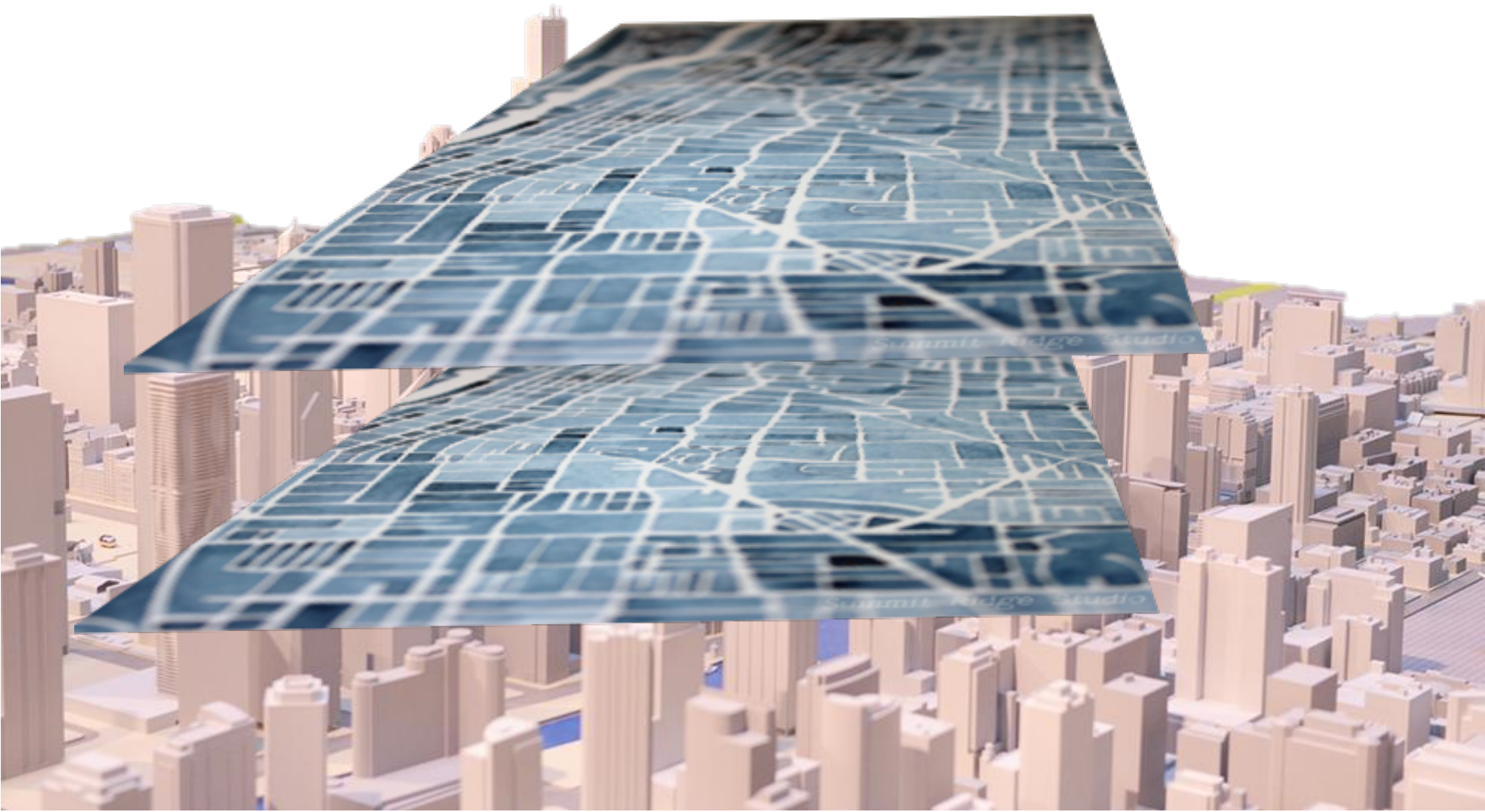


Lieberman AE
Science 2011;334:1222

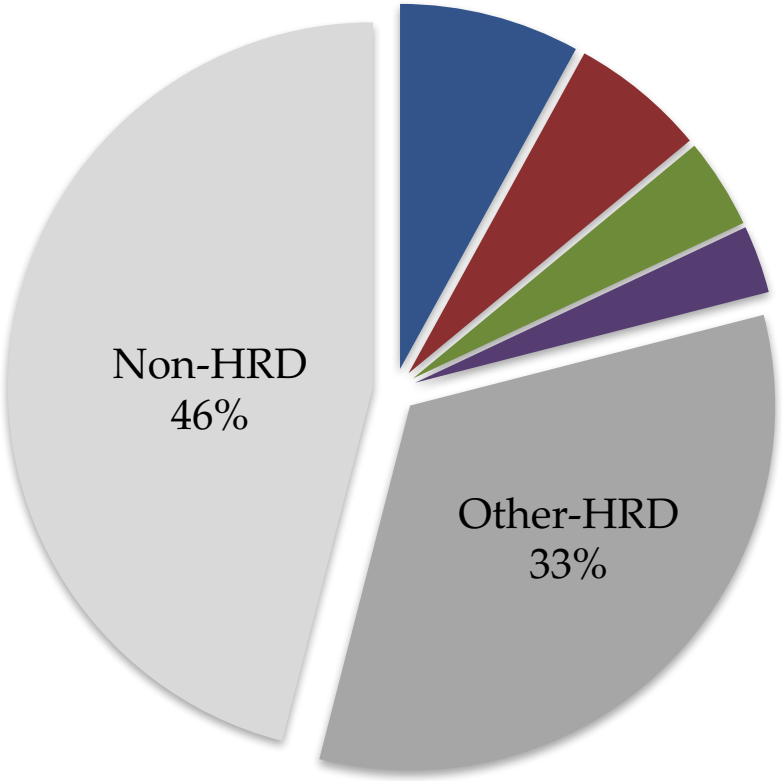
2015 Lasker Winners

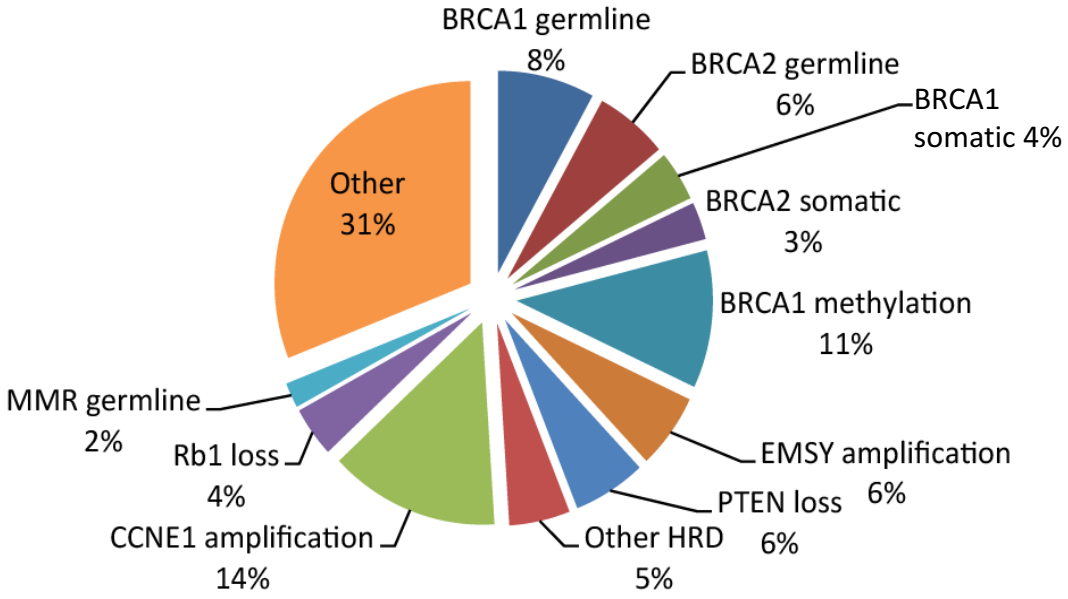
Elledge and Witkin

Seminal discoveries in DNA Damage Response



Contributions of BRCA1 and BRCA2 Mutations (Genetic, Somatic, and Epigenetic) to Serous Ovarian Cancer





Konstantinopoulos
Cancer Disc 2015;5:1137

Staples and Goodman - PARP Inhibitors in Ovarian Cancer
In: "Ovarian Cancer - A Clinical and Translational Update"
www.intechopen.com/download/pdf/42671

The Cancer Genome Atlas — Understanding genomics to improve cancer care

Disruptions in Homologous Recombination and DNA Repair

- BRCA1 mutated - 9%
- BRCA2 mutated - 8%
- EMSY amplified/mutated - 8%
- BRCA1 Hypermethylated - 12%
- PTEN loss or mutation - 7%
- DNA damage sensors/FANC - 7%
- RAD51C hypermethylated - 3%

Total - 51%

Genetic / Genomic Ix:

1. Test every pt with OVCA
2. BRCA g, s, and Beyond
3. Panel or Tissue Testing
4. BRCAness Predictive

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