RUTGERS
Cancer Institute
of New Jersey

Ovarian Cancer Prevention, Detection, and Precision Medicine

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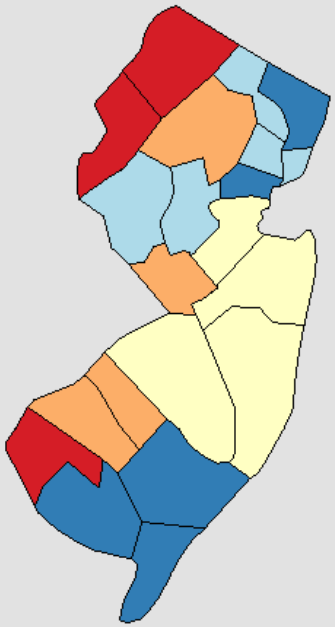
OVARIAN CANCER IN NEW JERSEY

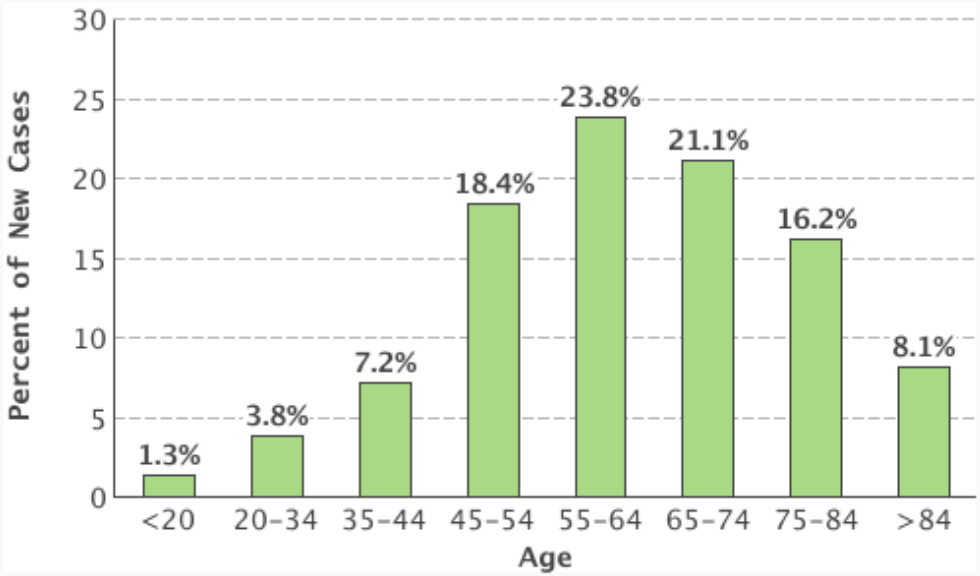
Incidence Rates† for New Jersey, 2008 - 2012
Ovary
All Races (includes Hispanic), Female, All Ages



Incidence Rates† for New Jersey, 2008 - 2012
Ovary
All Races (includes Hispanic), Female, All Ages

County, State	Annual Incidence Rate over rate period cases per 100,000 (95% Confidence Interval)	Average Cases per Year over rate period	Rate Period	Interval Range	Interval Color
New Jersey[3]	13.0 (12.6 - 13.5)	702	2008 - 2012	N/A	N/A
US (SEER + NPCR)[1]	11.8 (11.8 - 11.9)	21,341 §	2008 - 2012	N/A	N/A
Sussex County[7]	17.2 (13.4 - 21.7)	15	2008 - 2012	14.7 - 17.2	
Warren County[7]	16.4 (12.3 - 21.5)	11	2008 - 2012	14.7 - 17.2	
Salem County[7]	15.8 (10.8 - 22.5)	7	2008 - 2012	14.7 - 17.2	
Mercer County[7]	14.7 (12.5 - 17.3)	32	2008 - 2012	13.5 - 14.7	
Morris County[7]	14.3 (12.5 - 16.4)	45	2008 - 2012	13.5 - 14.7	
Camden County[7]	13.8 (12.0 - 15.9)	43	2008 - 2012	13.5 - 14.7	
Gloucester County[7]	13.8 (11.4 - 16.6)	23	2008 - 2012	13.5 - 14.7	
Middlesex County[7]	13.5 (12.0 - 15.1)	63	2008 - 2012	13.1 - 13.5	
Monmouth County[7]	13.4 (11.8 - 15.1)	54	2008 - 2012	13.1 - 13.5	
Ocean County[7]	13.4 (11.8 - 15.2)	57	2008 - 2012	13.1 - 13.5	
Burlington County[7]	13.3 (11.5 - 15.4)	38	2008 - 2012	13.1 - 13.5	
Essex County[7]	13.1 (11.6 - 14.7)	57	2008 - 2012	12.1 - 13.1	
Hunterdon County[7]	13.1 (9.7 - 17.5)	11	2008 - 2012	12.1 - 13.1	
Somerset County[7]	13.0 (10.8 - 15.6)	26	2008 - 2012	12.1 - 13.1	
Hudson County[7]	12.3 (10.7 - 14.2)	40	2008 - 2012	12.1 - 13.1	
Passaic County[7]	12.2 (10.4 - 14.2)	34	2008 - 2012	12.1 - 13.1	
Union County[7]	12.1 (10.4 - 13.9)	39	2008 - 2012	10.1 - 12.1	
Cumberland County[7]	11.8 (8.7 - 15.6)	10	2008 - 2012	10.1 - 12.1	
Bergen County[7]	11.7 (10.5 - 13.0)	70	2008 - 2012	10.1 - 12.1	
Cape May County[7]	11.3 (7.9 - 15.9)	9	2008 - 2012	10.1 - 12.1	
Atlantic County[7]	10.1 (8.1 - 12.5)	18	2008 - 2012	10.1 - 12.1	

Incidence



Ovary cancer is most frequently diagnosed among women aged 55-64.

Median Age At Diagnosis

63

SEER 18 2008-2012, All Races, Females

SEER Cancer Statistics Factsheets: Ovary Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/ovary.html

Ovarian Cancer

Signs and symptoms of ovarian cancer

- Women are more likely to have symptoms if the disease has spread beyond the ovaries, but even early- stage ovarian cancer can cause them.

- The most common symptoms include:
  - Bloating
  - Pelvic or abdominal pain
  - Trouble eating or feeling full quickly
  - Urinary symptoms such as urgency (always feeling like you have urinate) or frequency (a feeling of a need to urinate immediately)

These symptoms are also commonly caused by benign (non-cancerous) diseases and by cancers of other organs. When they are caused by ovarian cancer, they tend to be *persistent* and represent a *change from normal* − for example, they occur more often or are more severe. If a woman has these symptoms more than 12 times a month, she should see her doctor, preferably a gynecologist.

Others symptoms of ovarian cancer can include:

Fatigue
Upset stomach
Back pain
Pain during intercourse
Constipation
Menstrual changes
Abdominal swelling with weight loss

However, these symptoms are more likely to be caused by other conditions, and most of them occur just about as often in women who don’t have ovarian cancer.

RISK FACTORS

	Estimated Risk %	Estimated Relative Risk
Risk Factors		
Family History	9.4	5-7
BRCA1 mutation	30-40	18-29
BRCA2 mutation	27	16-19
Lynch (HNPCC)	10	6-7
Infertility		2-5
Nulliparity		2-3
Late menopause		1.5-2
Early menarche		1-1.5
Protective Factors		
Multiparity		0.4-0.6
Oral contraceptive use		0.6
X4 years		0.5
X8 years		0.4
X12 years		0.4-0.6
Hysterectomy or tubal ligation		

HEREDITARY CANCER SYNDROMES

1. Hereditary Breast and Ovarian Cancer Syndrome
Hereditary breast and ovarian cancer syndrome is the most common underlying cause of inherited breast or ovarian cancer.

Mutations in BRCA1 and BCA2 have been linked to hereditary breast and ovarian cancer syndrome.

BRCA1 and BRCA2 are tumor suppressor genes that maintain genomic integrity by regulating DNA double strand break repair with homologous recombination, controlling cell cycle checkpoint responses and segregating chromosomes.

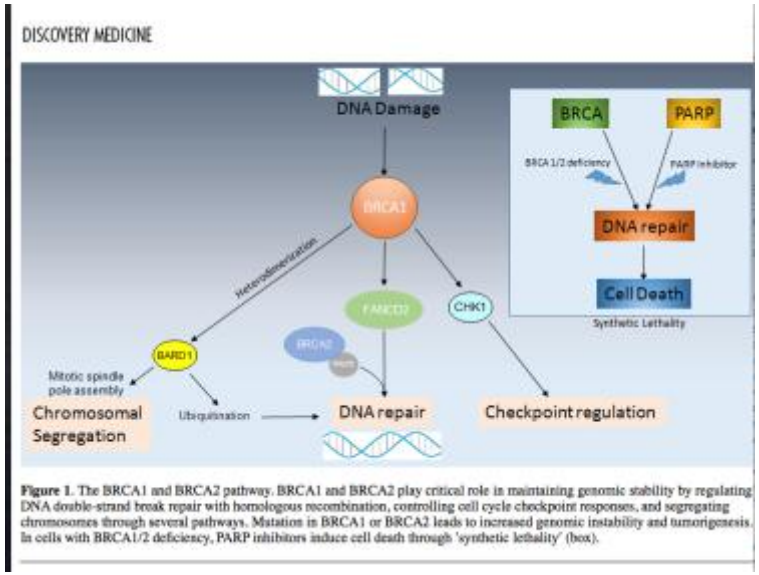


Figure 1. The BRCA1 and BRCA2 pathway. BRCA1 and BRCA2 play critical role in maintaining genomic stability by regulating DNA double-strand break repair with homologous recombination, controlling cell cycle checkpoint responses, and segregating chromosomes through several pathways. Mutation in BRCA1 or BRCA2 leads to increased genomic instability and tumorigenesis. In cells with BRCA1/2 deficiency, PARP inhibitors induce cell death through 'synthetic lethality' (box).

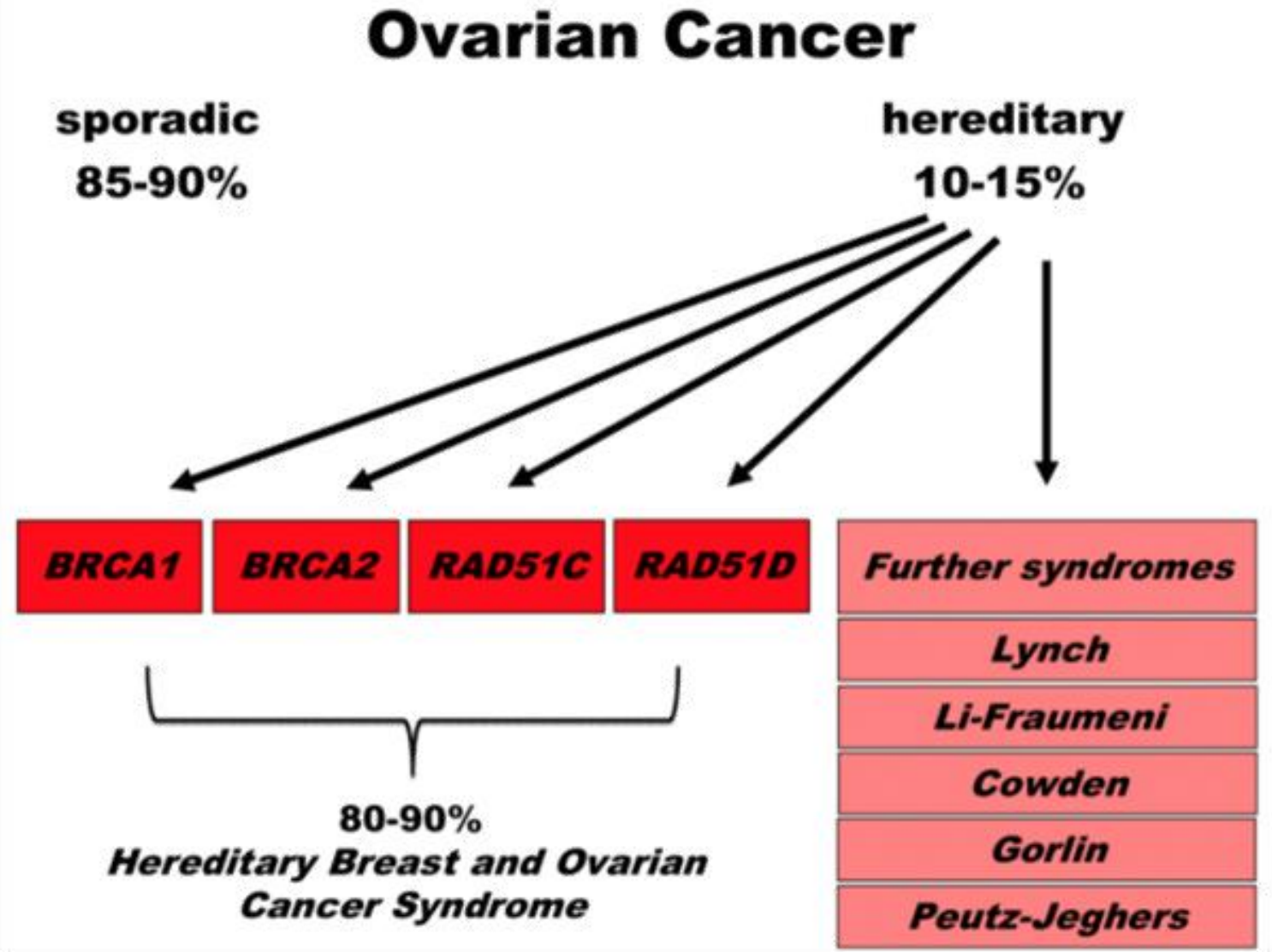


Figure 1. Schematic overview of susceptibility genes for familial ovarian cancer. Ten to fifteen percent of ovarian cases are of familial origin. Until now, 16 susceptibility genes causing at least six cancer susceptibility syndromes have been identified [12, 13]. However, approximately 80 to 90% of the hereditary ovarian cancer cases can be explained by mutations in BRCA1, BRCA2, RAD51C, and RAD51D, which cause Hereditary Breast and Ovarian Cancer Syndrome.

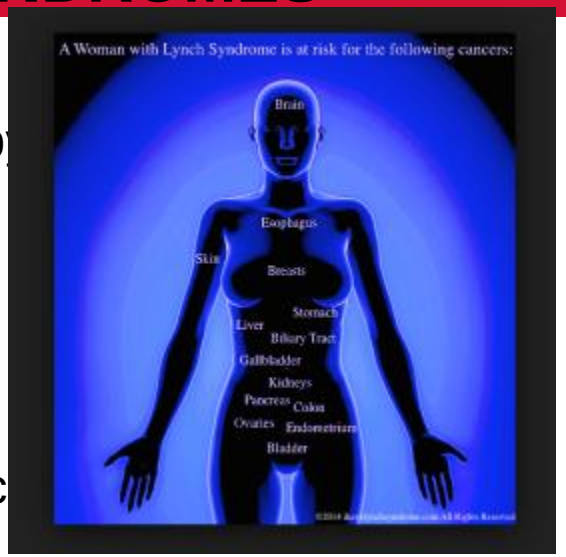
Table 1. Lifetime risks for ovarian cancer susceptibility genes [7-11].

	BRACA1	***BRACA2***	***RAD15C***	***RAD15D***
Ovarian Cancer	20% - 50%	10% - 20%	>9%	10%
Breast Cancer (female)	50% - 90%	40% - 60%	*n.s.	n.s.
Breast Cancer (male)	0%	11%	0%	?
Prostate Cancer	7%	31%	?	?

n.s., no significant difference

HEREDITARY CANCER SYNDROMES

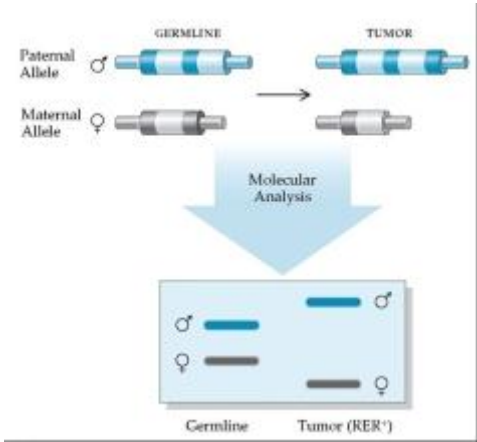
2. Lynch Syndrome



Lynch syndrome is an autosomal dominant disorder caused by germline mutation in 1 of the 4 DNA mismatch repair genes:
MSH2 on chromosome *2p16*,
MLH1 on chromosome *3p21*,
MSH6 on chromosome *2p16*, or
PMS2 on chromosome*7p22*

Germline mutations in *EPCAM* have also been linked to Lynch syndrome. *EPCAM* is upstream of *MSH2* and leads to loss of *MSH2* expression by hypermethylating the *MSH2*

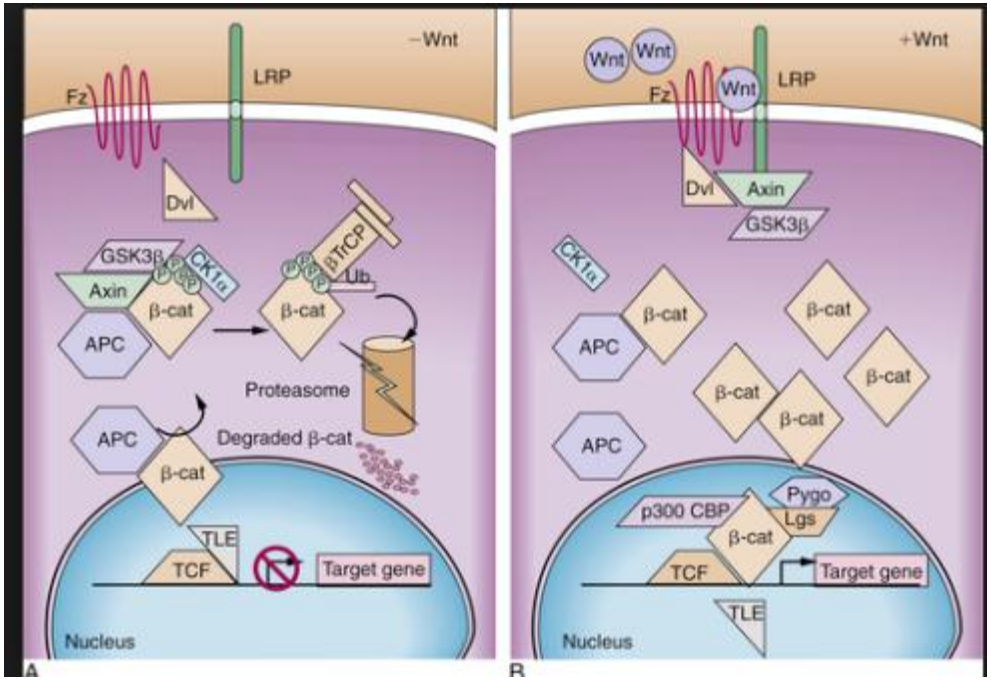
The mismatch repair system is involved in recognizing and repairing base pair mismatches. Inactivation of these genes leads to failure of DNA mismatch repair resulting in increased mutation rates, most commonly in regions of repetitive nucleotide sequences called microsatellites. The resultant microsatellite instability can be tested in tumors using PCR. Microsatellite instability is present in more than 90% of patients with lynch syndrome, making the test very sensitive for lynch Syndrome.



HEREDITARY CANCER SYNDROMES

3. Familial Adenomatous Polyposis (FAP)

FAP and its variants are caused by germline mutations in the adenomatous poplyposis coli (APC) gene. APS is a tumor suppressor gene and encodes for the APC protein that mediates Wnt signaling-regulated degradation of B-catenin. Mutations in APC also cause abnormal cell migration and chromosomal instability. The *APC* gene may also have a role in DNA repair by modulating the base excision repair pathway.

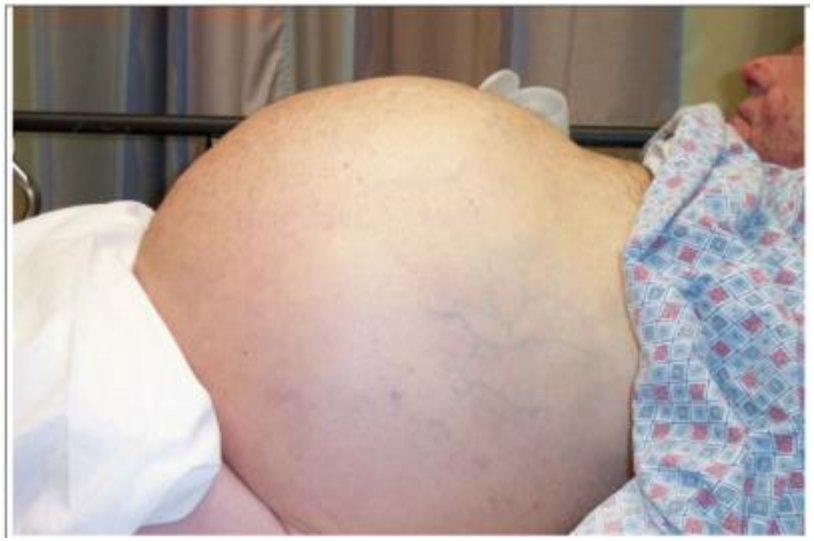


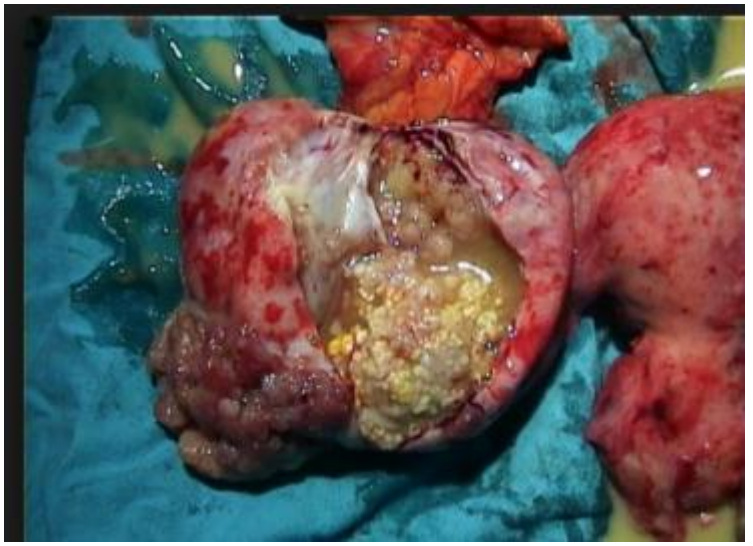
4. **Li-Fraumeni Syndrome**

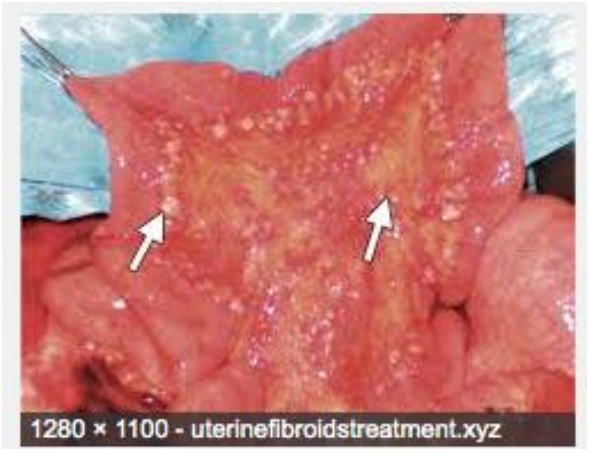
Li-Fraumeni syndrome is an autosomal dominant hereditary disorder in which the risk of early-onset malignancies is increased. It is a result of germline *TP53* mutations.

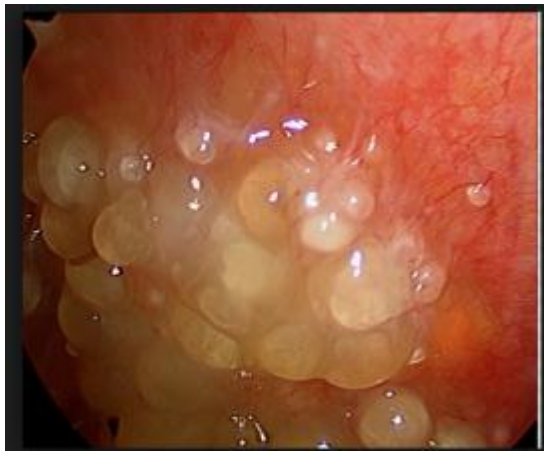
Screening Options

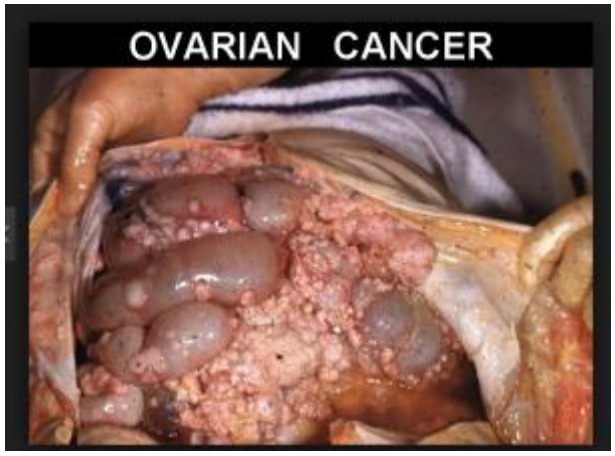
For women at increased risk due to family history or genetic mutations, screening with transvaginal ultrasound or a blood test to detect CA-125 is sometimes recommended.



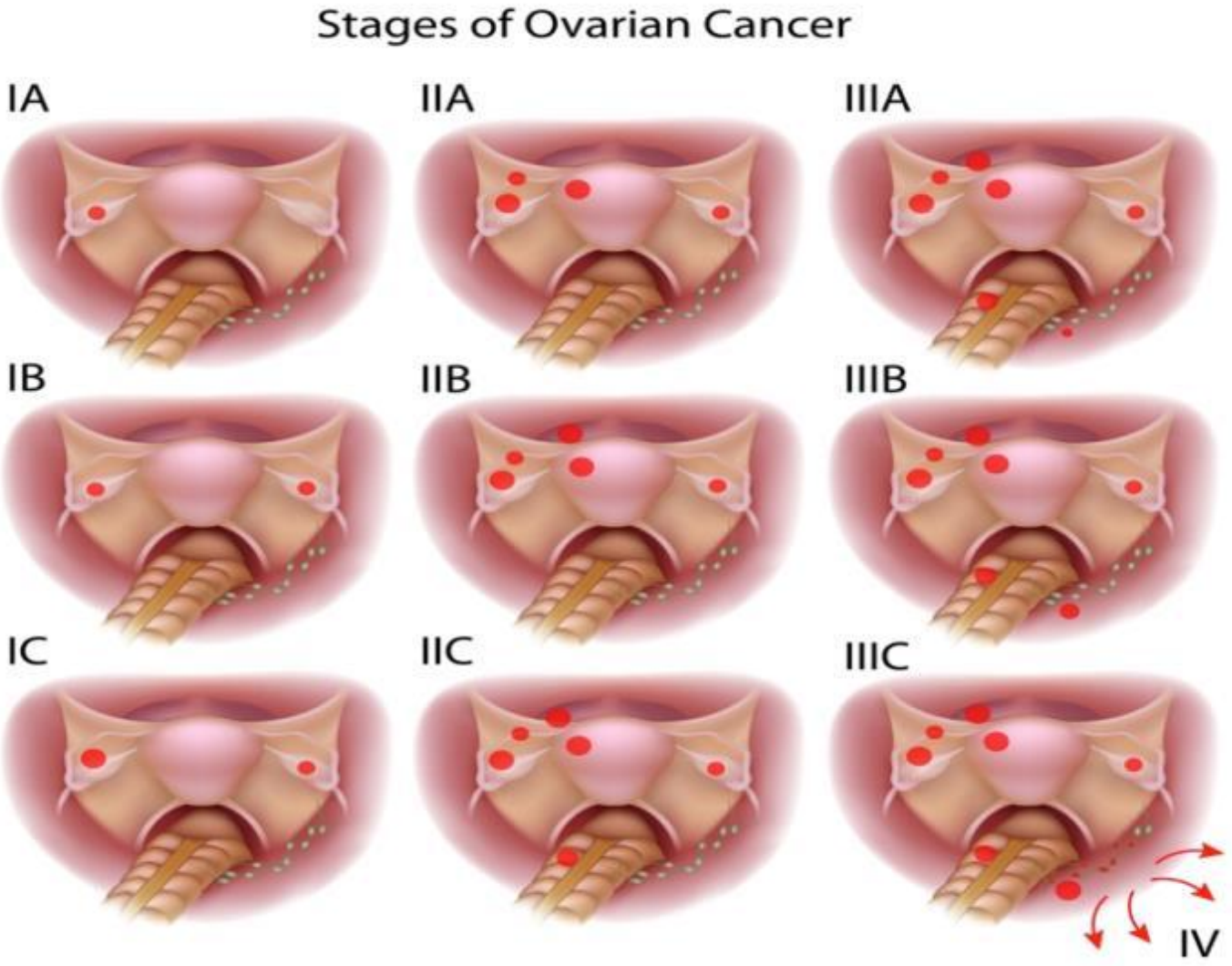








OVARIAN CANCER STAGING

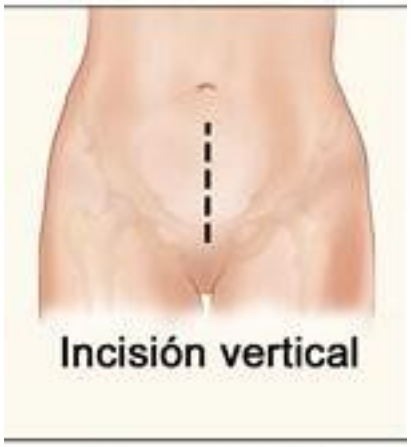


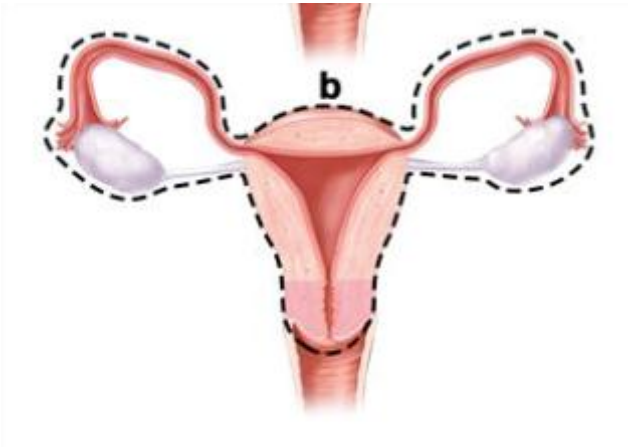
Three kinds of standard treatment are used

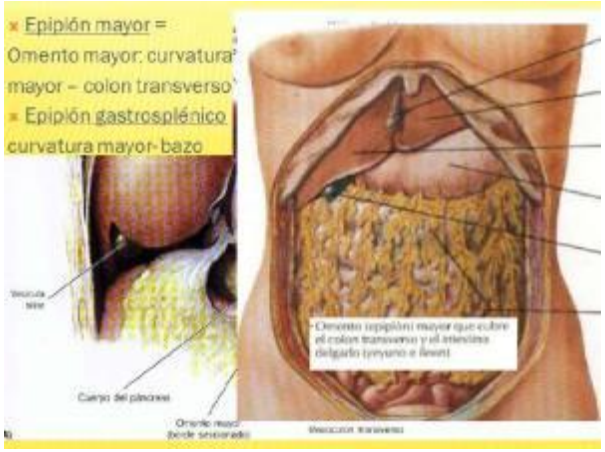
- Surgery
- Chemotherapy
- Targeted therapy

Three kinds of standard treatment are used

- Surgery Goal is optimal cytoreduction (no disease left behind or disease less than 1mm in size)
- Chemotherapy
- Targeted therapy







Three kinds of standard treatment are used

- Surgery
- Chemotherapy Cytoreduce disease before or after surgery. It can be intravenous, intraperitoneal or oral.
- Targeted therapy

Drugs approved for Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

This page list cancer drugs approved by the Food and Drug Administration (FDA) for Ovarian, Fallopian Tube, or Primary Peritoneal Cancer. The list includes generic and brand names. This page also list common drug combinations used in these cancer types. The individual drugs in the combinations are FDA-approved. However, drug combinations themselves usually are not approved, but are widely used.
There may be drugs used in in Ovarian, Fallopian Tube, or Primary Peritoneal Cancer that are not listed here.

Avastin (Bevacizumab)
Bevacizumab
Carboplatin
Clafen (Cyclophosphamide)
Cisplatin
Cyclophosphamide
Cytoxan (Cyclophosphamide)
Doxorubicin Hydrochloride
Dox-SL (Doxorubicin Hydrochloride Liposome)
DOXIL (Doxorubicin Hydrochloride Liposome)
Doxorubicin Hydrochloride Liposome
Evacet (Doxorubicin Hydrochloride Liposome)
Gemcitabine Hydrochloride
Gemzar (Gemcitabine Hydrochloride)
Hycamtin (Topotecan Hydrochloride)
LipoDox (Doxorubicin Hydrochloride Liposome)
Lynparza (Olaparib)
Neosar (Cyclophosphamide)
Olaparib
Paclitaxel
Paraplat (Carboplatin)
Paraplatin (Carboplatin)
Platinol (Cisplatin)
Platinol-AQ (Cisplatin)
Taxol (Paclitaxel)
Thiotepa
Topotecan Hydrochloride

Three kinds of standard treatment are used

- Surgery
- Chemotherapy
- Targeted therapy

Olaparib is approved to treat:

- Ovarian cancer that is advanced. It is used in paptients who have certain mutations in the BRCA1 and BRCA2 genes and have already been treated with at least three other types of chemotherapy.

- An anti-angiogenic agent, or blood vessel inhibitor called cediranib (which inhibits VEGFR) and olaparib, a PARP inhibitor, are each clinically active in recurrent ovarian cancer. Preclinical laboratory studies suggest these agents add to and enhance the activity of each other, and an early phase 1 study showed that the combination of cediranib and olaparib was well-tolerated with minimal side effects.

Immunotherapy

Types of Immunotherapy

- Monoclonal antibodies: can cause an immune response or bind to an important target disallowing its function
- Adoptive cell transfer: boosts the natural ability of the person's own T cells to fight cancer
- Cytokines: interferons and interleukins
- Vaccines: oncolytic viruses the future

Antibody	Target	Reference	Phase	Clinical Response	Immune Response
Oregovomab	CA125	49	II	3 SD 10 PD	Oregovomab and CA125-specific antibody and T cell responses
		50	I	4 NED 2 CR 7 PD	HAMA, anti-oregovomab and anti-CA125 antibodies
Abagovomab	CA125	53	I	NA	HAMA, anti-anti-idiotypic and antiCA125 antibodies, CA125-specific CD4 and CD8 T cells
		54	Ib/II	4 CR 30 SD 62 PD 23 NA	Anti-anti-idiotypic and antiCA125 antibodies, Antibody dependent cell-mediated cytotoxicity
		55	I	12 SD 21 PD	HAMA and anti-anti-idiotypic antibodies, CA125-specific IFN-γ producing T cells
HMFG1	MUC1	56	I	1 SD 25 RD	Anti-HMFG1 and anti-MUC1 antibodies
Catumaxomab	EpCAM, CD3	60,61	II/III	Longer puncture-free survival and time to next paracentesis	Human anti-mouse antibodies
Trastuzamab	HER2/neu	63	II	1 CR 2 PR 16 SD 22 PD	No anti-trastuzumab antibody formation
MOv18	FR-α	65	I	NA	No anti-c-MOv18 antibodies
MORAb-003	FR-α	66	I	9 SD 16 PD 1 NE	Limited anti-MORAb-003 antibodies
Bevacizumab	VEGF	69	II	2 CR 11 PR 32 SD 17 PD	NA
		70	II	0 CR 7 PR 27 SD 5 PD 5 NE	NA
		67	III	168 Responders (CR/PR) 82 Non-responders (SD/PD) 7 unknown	NA
		68	III	No difference in OS; significant improval in PFS	NA

Table 3. Monoclonal Antibodies studies in Ovarian Cancer

SD, stable disease; PD, progressive disease; NED, no evidence of disease; CR, complete response; HAMA, human anti-mouse antibody; NA, not available; RD, recurrent disease; NE, not evaluable

Table 2. Peptide-based Vaccines studied in Ovarian Cancer

Target	MHC-I or MHC-II restricted	Phase	Reference	Clinical Response	Immune Response
HER2/neu	II	I/II	27,28	NA	HER2/neu-specific IgG antibody and T cell responses
NY-ESO-1	both	I	29	NA	NY-ESO-1 specific CD4 and CD8 T cell responses
	I	I	30	3 CR 6 PD	NY-ESO-1 specific CD8 T cell responses
p53	I	II	31	2 NED 12 RD	p53-specific CD8 T cell responses
	n/a	II	32,33	2 SD 18 PD	p53-specific, Th2 dominant CD4 T cell responses
WT-1	I	Case report	34	SD x 1 y	Weak correlation between CA125 and the mononuclear phagocyte/lymphocyte ratio
	I	II	35	1 SD 4 PD 1 NE	NA
STn	II	I	36	3 CR 2 PD 2 NA	Anti-STn Th1 T cell responses
	NA	II	37	Median OS 12.7 mo	Anti-STnIgG and IgM antibody responses, Anti-OSM (ovine submaxillarymucin) antibody responses
Lewis^y	NA	I	44	5 NED 19 RD	Anti- Lewis^y antibody responses

NA, not available; CR, complete response; PD, progressive disease; n/a, not applicable, NED, no evidence of disease; RD, recurrent disease; SD, stable disease; NE, not evaluable

Table 1. Immunotherapeutic strategies under investigation in Ovarian Cancer

Innate Immunity	Adaptive Immunity	Immunomodulation
Cytokines	Peptide vaccines	Treg blockade
Adoptive transfer of NK cells	Viral-based peptide vaccines	CTLA-4 blockade
	Whole tumor antigen vaccine	Pegylated liposomal doxorubicin
	Monoclonal antibodies	
	Adoptive transfer of T cells	
	Dendritic cell-based vaccines	

Median OS by chemotherapy cohort

Chemotherapy cohorts	Avastin + chemotherapy	Chemotherapy alone	HR (95% CI)
Avastin + paclitaxel	22.4 months (n=60)	13.2 months (n=55)	0.64 (0.41–1.01)
Avastin + topotecan	13.8 months (n=57)	13.3 months (n=63)	1.12 (0.73–1.73)
Avastin + PLD	13.7 months (n=62)	14.1 months (n=64)	0.94 (0.63–1.42)

Chemotherapy cohorts	Avastin + chemotherapy	Chemotherapy alone
Avastin + paclitaxel	53% (95% CI, 39–68) (n=45)	30% (95% CI, 17–44) (n=43)
Avastin + topotecan	17% (95% CI, 6–28) (n=46)	2% (95% CI, 0–6) (n=50)
Avastin + PLD	16% (95% CI, 6–26) (n=51)	8% (95% CI, 0–15) (n=51)

AURELIA study: Efficacy data overview in ITT population[1]

Endpoints	Avastin + chemotherapy	Chemotherapy alone	HR (95% CI)	*P* value
Median PFS (Primary endpoint)	6.8 months (n=179)	3.4 months (n=182)	0.38 (0.30–0.49)	<0.0001
Median OS (Secondary endpoint)	16.6 months (n=179)	13.3 months (n=182)	0.89 (0.69–1.14)	
ORR (Secondary endpoint)	28% (n=142) (95% CI, 21–36)	13% (n=144) (95% CI, 7–18)		

Chemotherapy included paclitaxel, pegylated liposomal doxorubicin, or topotecan.

OS=overall survival; ORR=objective response rate.

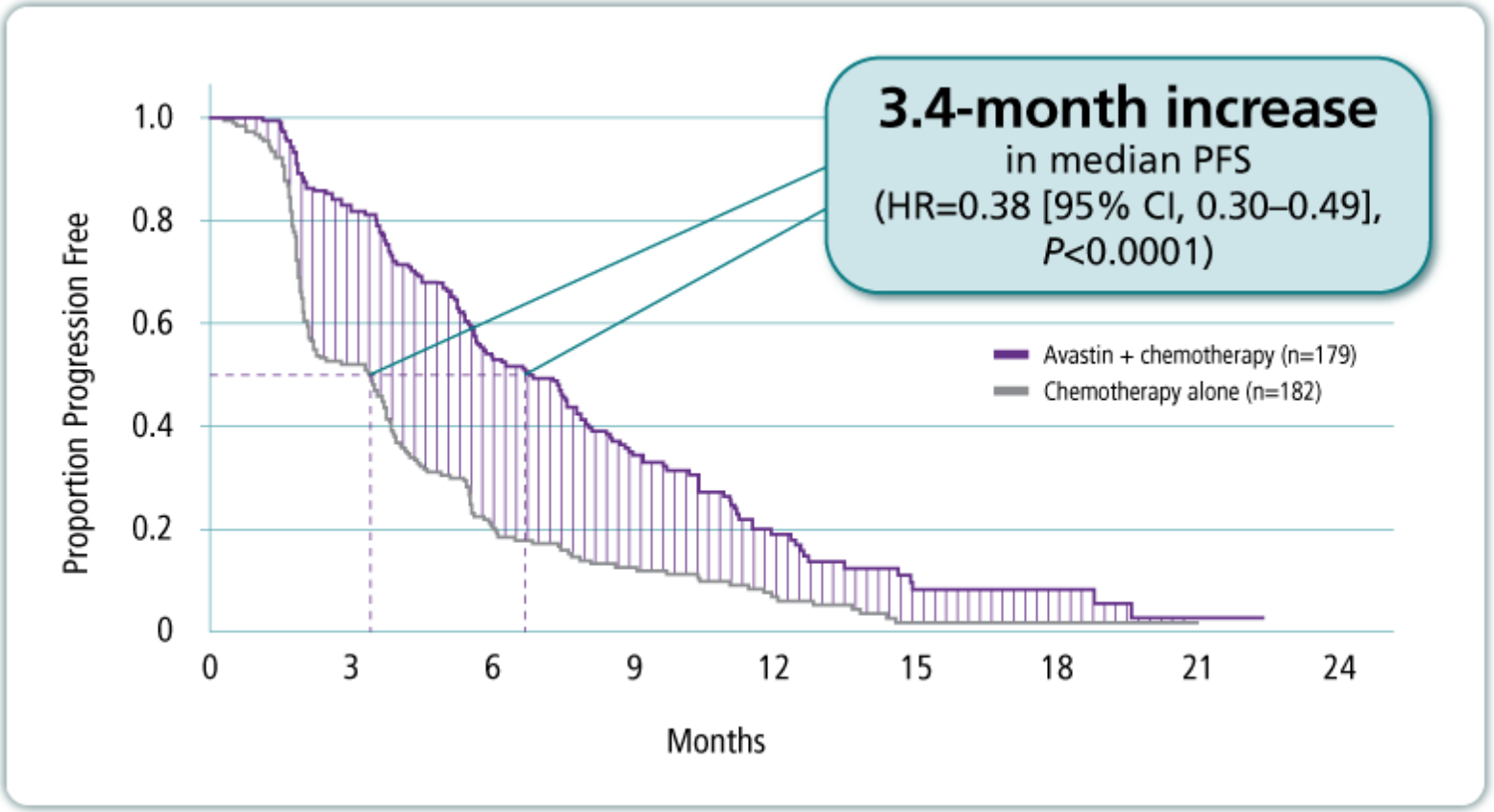
The first biologic regimen to show an increase in PFS, OS, and ORR in prOC[1]:

- Avastin plus chemotherapy demonstrated
  - A 3.4-month increase in median PFS vs chemotherapy alone (6.8 vs 3.4 months)
  - A 3.3-month increase in median OS vs chemotherapy alone (16.6 vs 13.3 months)
  - A 28% ORR (vs 13% with chemotherapy alone)

Avastin plus chemotherapy significanlty increased median PFS over chemotherapy alone in the AURELIA study (6.8 vs 3.4 months) [1]

AURELIA study: PFS results in patients with prOC who received no more than 2 prior chemotherapy regimens [1]

- 3.4-month increase in median PMF: 6.8 months with Avastin plus chemotherapy alone
  -Hazard ratio (HR)=.038 (95% confidence intercal (CI), 0.30-0.49); *P*<0.0001



Chemotherapy included paclitaxel, pegylated liposomal doxorubicin, or topotecan.

- Avastin plus chemotherapy demonstrated
  - A 62% reduction in the risk of progression vs chemotherapy alone
  - Doubled median PFS vs chemotherapy alone (6.8 months vs 3.4 months.
- Statistically significant improvement in investigator-assessed PFS was supported by a retrospective independent review analysis

The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine

Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH

September 17, 2015

Executive Summary

In his State of the Union Address on January 20, 2015, President Obama announced his intention to launch a Precision Medicine Initiative (PMI) “to bring us closer to curing diseases like cancer and diabetes, and to give all of us access to the personalized information we need to keep ourselves and our families healthier.” The President shared his vision for the Initiative to enhance innovation in biomedical research with the ultimate goal of moving the U.S. into an era where medical treatment can be tailored to each patient.

Precision medicine is an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle.

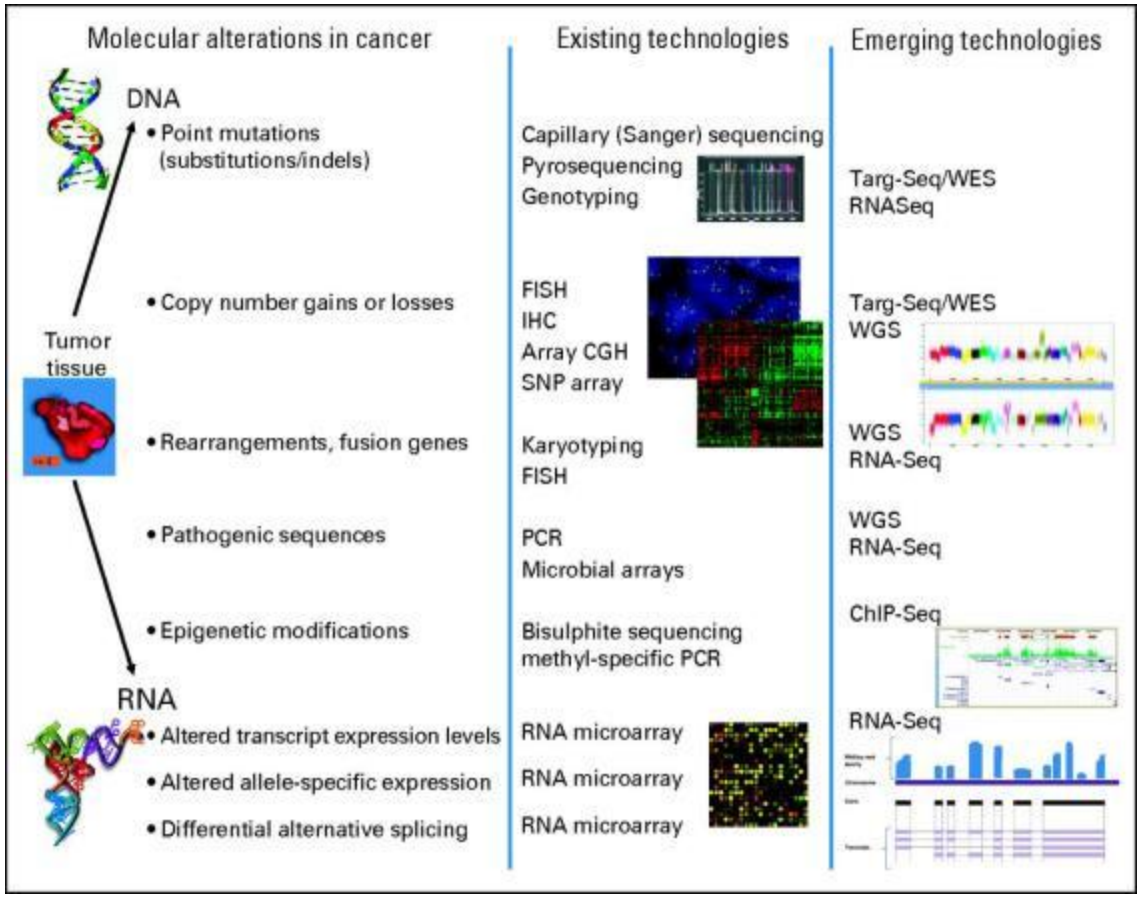
Precision medicine seeks to redefine our understanding of disease onset and progression, treatment response, and health outcomes through the more precise measurement of molecular, environmental, and behavioral factors that contribute to health and disease.

This understanding will lead to more accurate diagnoses, more rational disease prevention strategies, better treatment selection, and the development of novel therapies..

The Precision Medicine Initiative Cohort Program Working Group Report to the Advisory Committee to the Director, NIH
September 17, 2015

Advances in Technologies

- Next Generation or Massively Parallel Sequencing led to increased sensitivity.
- Detection of multiple types of alterations.
- Decreased cost (First effort at whole genome sequencing (WGS) in 2008 cost $1.6M.)



Laura E. MacConaill JCO 2013;31:1815-1824

JOURNAL OF CLINICAL ONCOLOGY ASCO

Biopsy

- Biorepository
- Surgery
- Pathology

Molecular Profiling

- CLIA Panels – Outside Vendors
- RUCDR / Infinite Biologics
- Functional Genomics
- Systems Biology

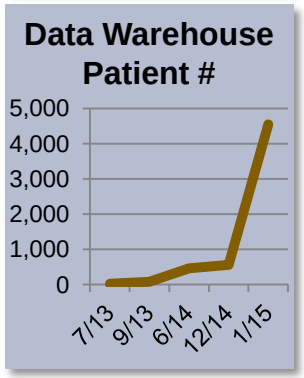
Molecular Tumor Board

Precision Treatment

- Clinical Trials Office
- Research Pharmacy
- PK / PD
- Biometrics
- Phase I Clinical Trial Program
- Industry Partnerships

Data Repository

- Bioinformatics$
- EMR / Data Warehouse

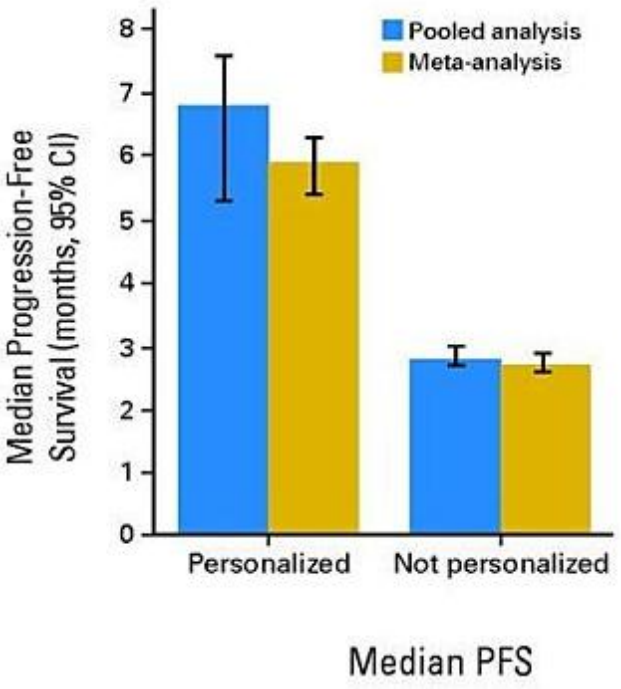


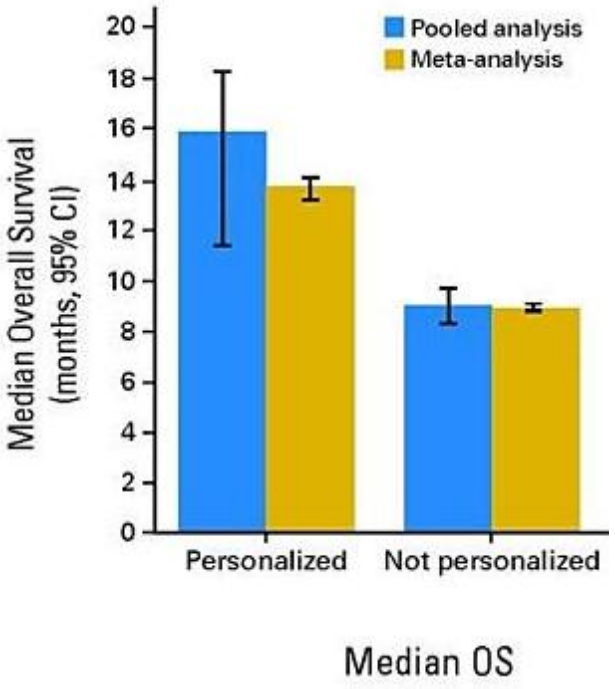
Outcomes and Discovery

- Precision Medicine Translational Laboratory
- Systems Biology
- SEER /Registry
- Metabolomics
- Public /Private Partnerships

Benefit of Personalized Therapy

- 570 studies
- Retrospective of personalized (cognate biomarker indication or 50% with marker) vs. not personalized.
- RR 31% vs. 10.5%; PFS 5.9mo vs. 2.7mo; OS 13.7 vs. 8.9mo
- Genomic biomarker had greater OS vs. protein biomarker

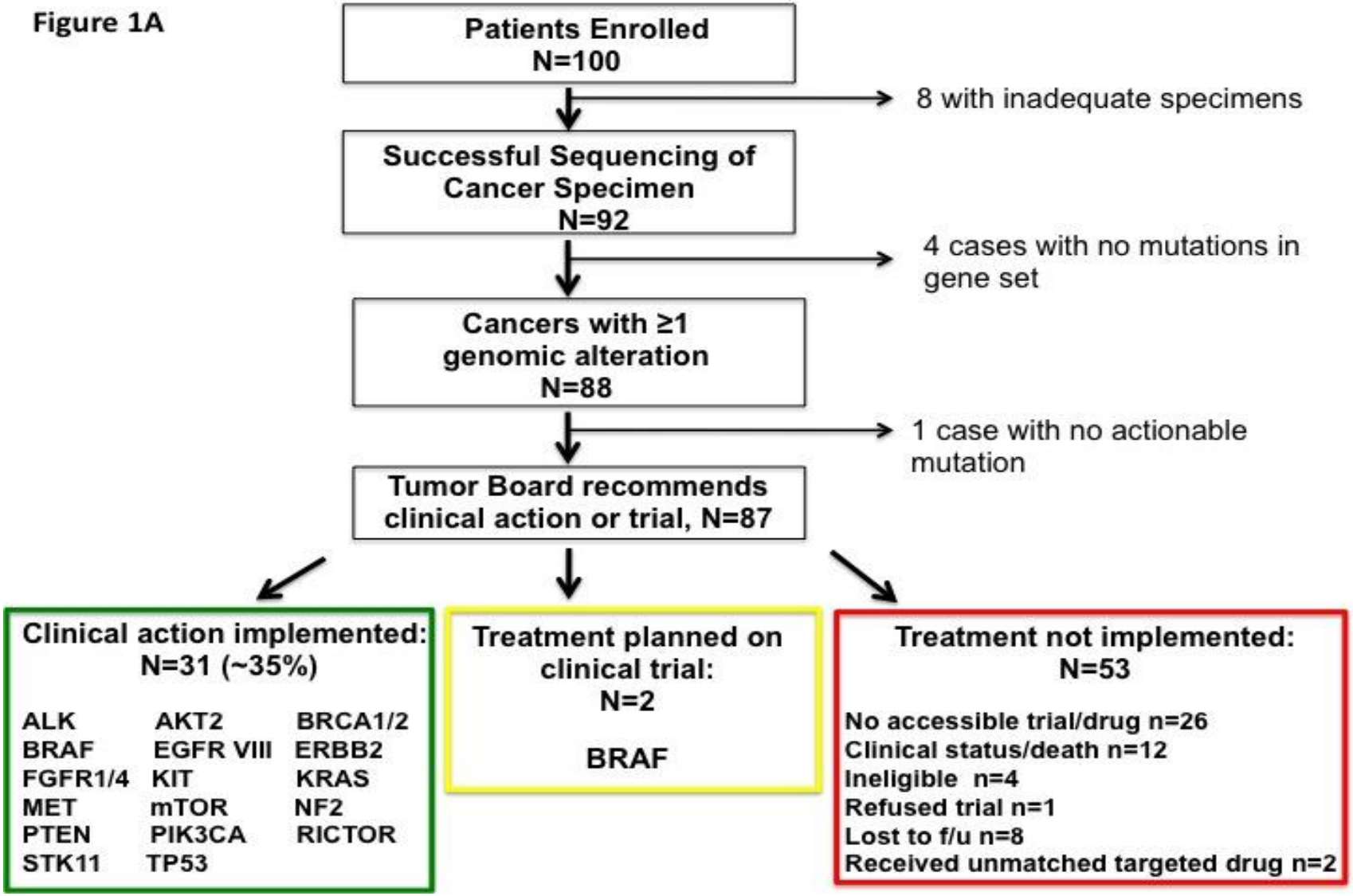


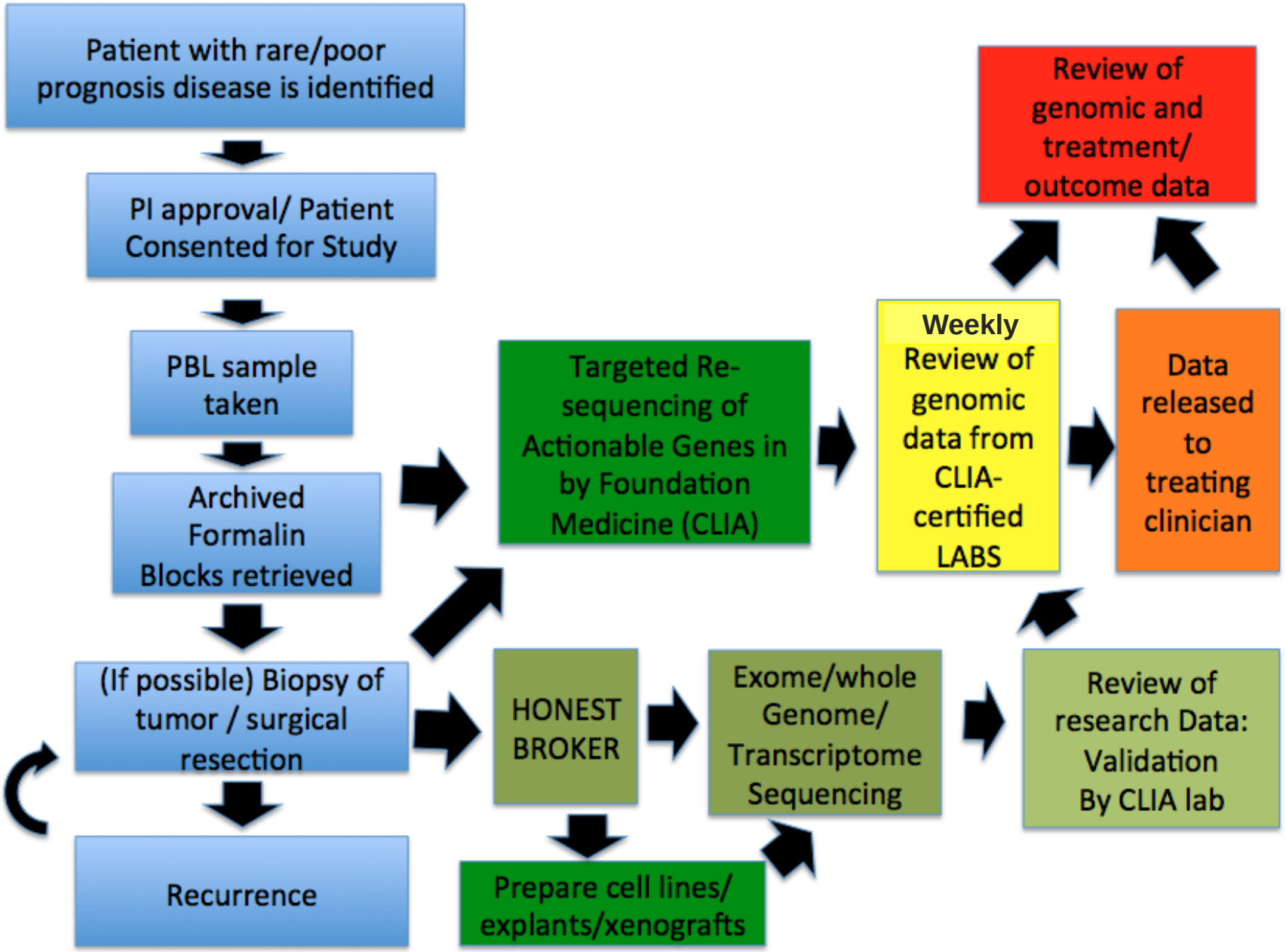


Maria Schwaederle et al. JCO
doi:10.1200/JCO.2015.61.5997

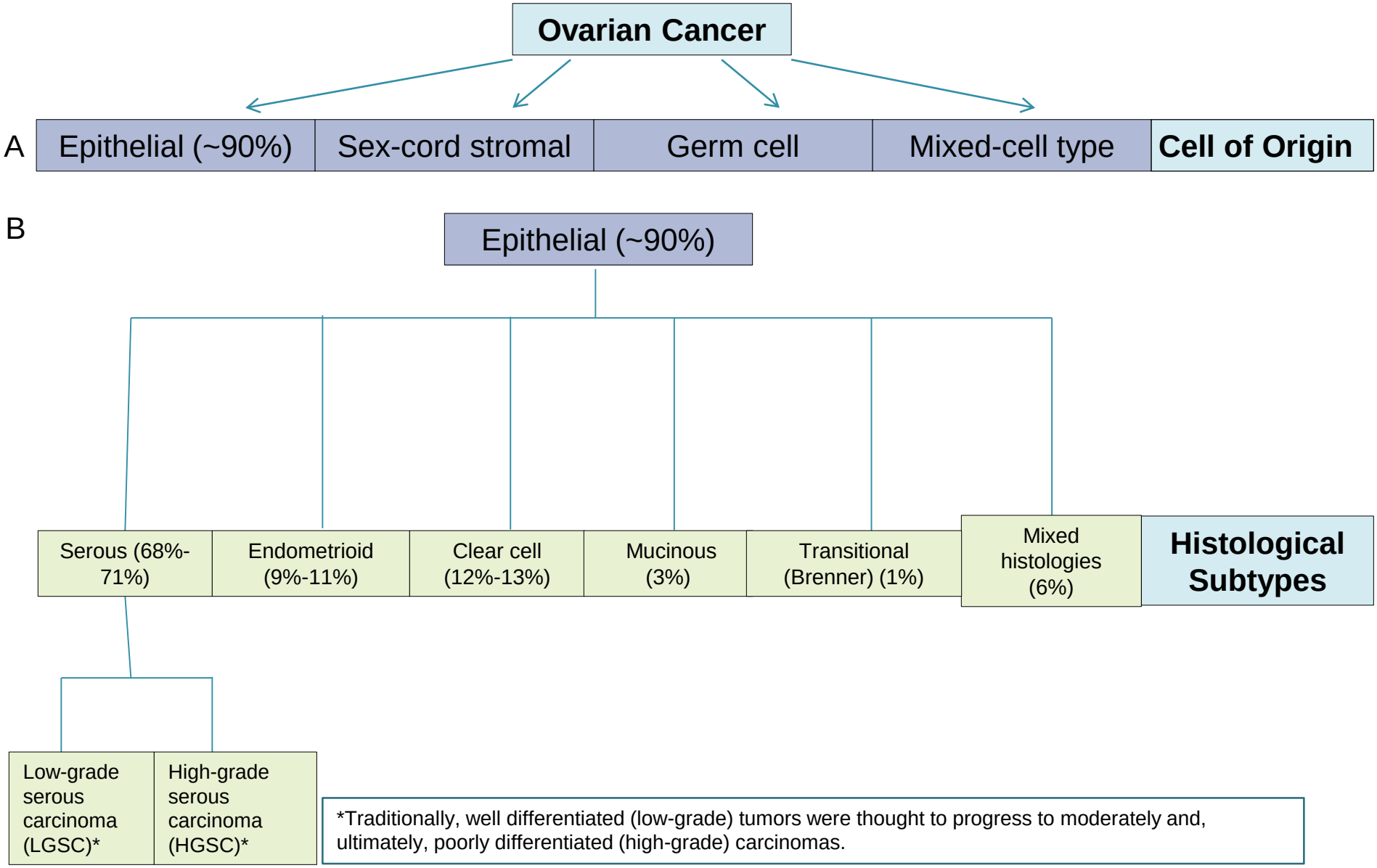
JOURNAL OF CLINICAL ONCOLOGY ASCO

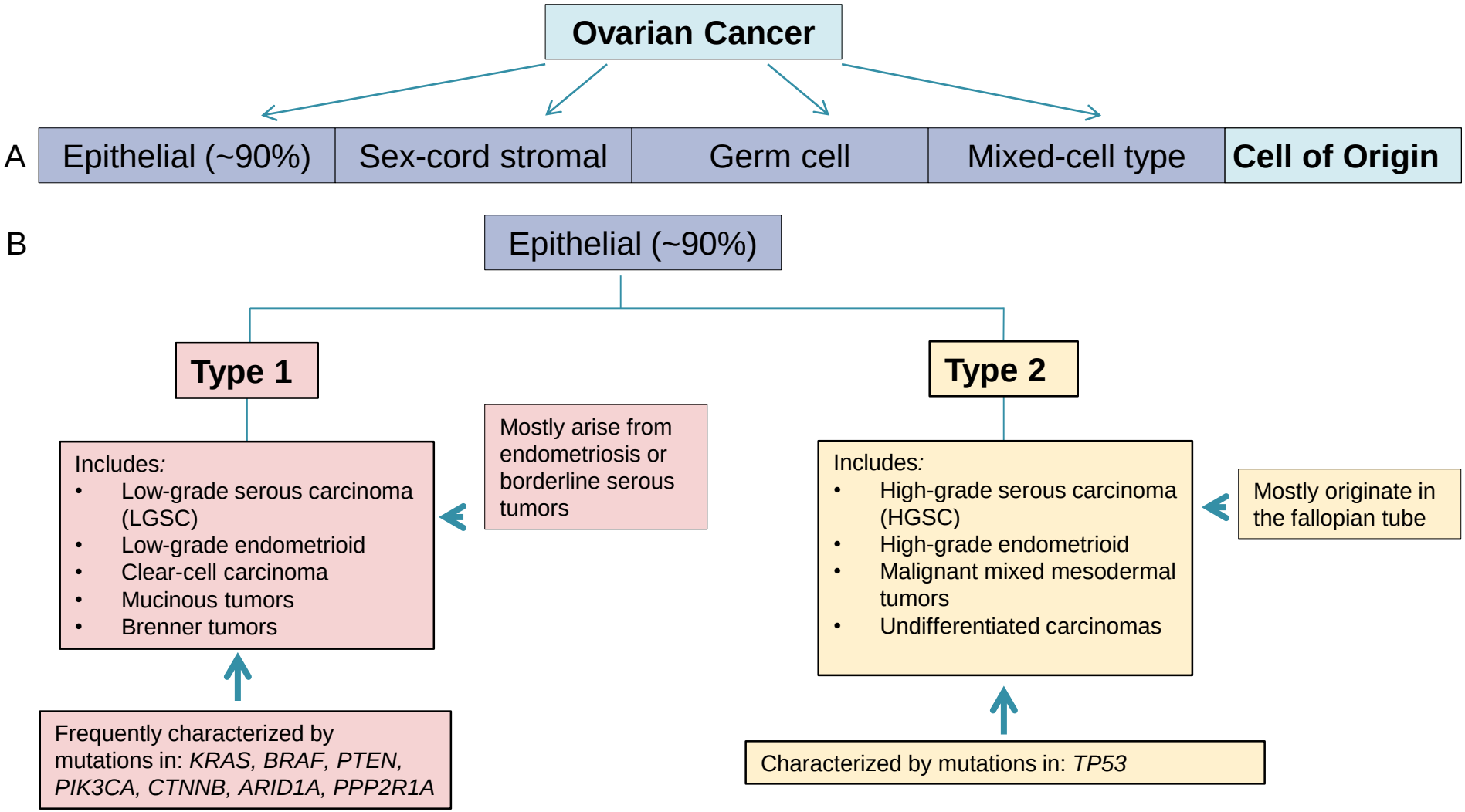
Figure 1A

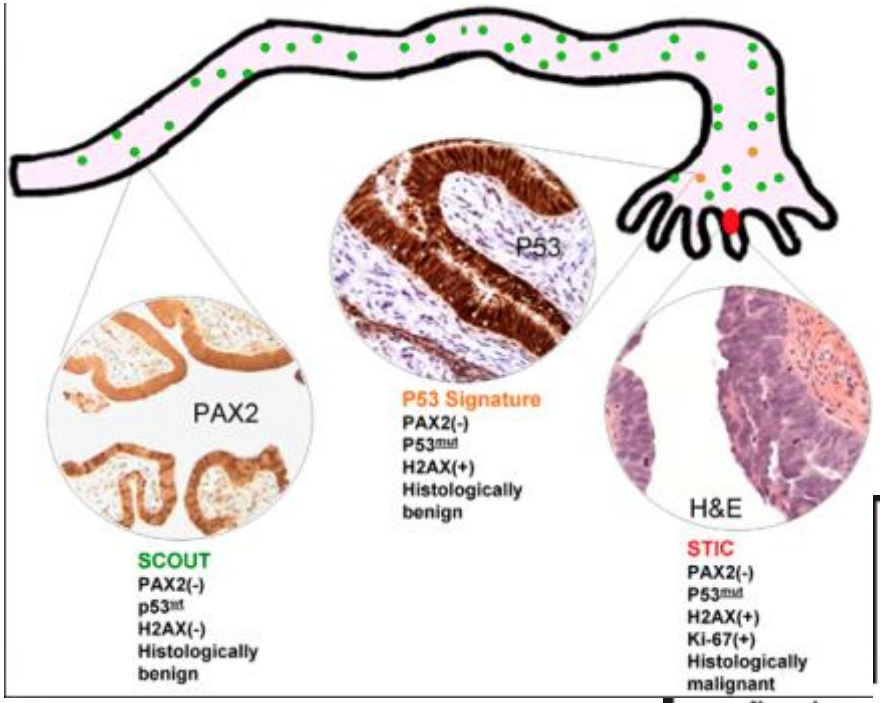

Patients Enrolled
N=100
8 with inadequate specimens
Successful Sequencing of Cancer Specimen
N=92
4 cases with no mutations in gene set
Cancers with ≥1 genomic alteration
N=88
1 case with no actionable mutation
Tumor Board recommends clinical action or trial, N=87
Clinical action implemented:
N=31 (~35%)
ALK AKT2 BRCA1/2
BRAF EGFR VIII ERBB2
FGFR1/4 KIT KRAS
MET mTOR NF2
PTEN PIK3CA RICTOR
STK11 TP53
Treatment planned on clinical trial:
N=2
BRAF
Treatment not implemented:
N=53
No accessible trial/drug n=26
Clinical status/death n=12
Ineligible n=4
Refused trial n=1
Lost to f/u n=8
Received unmatched targeted drug n=2

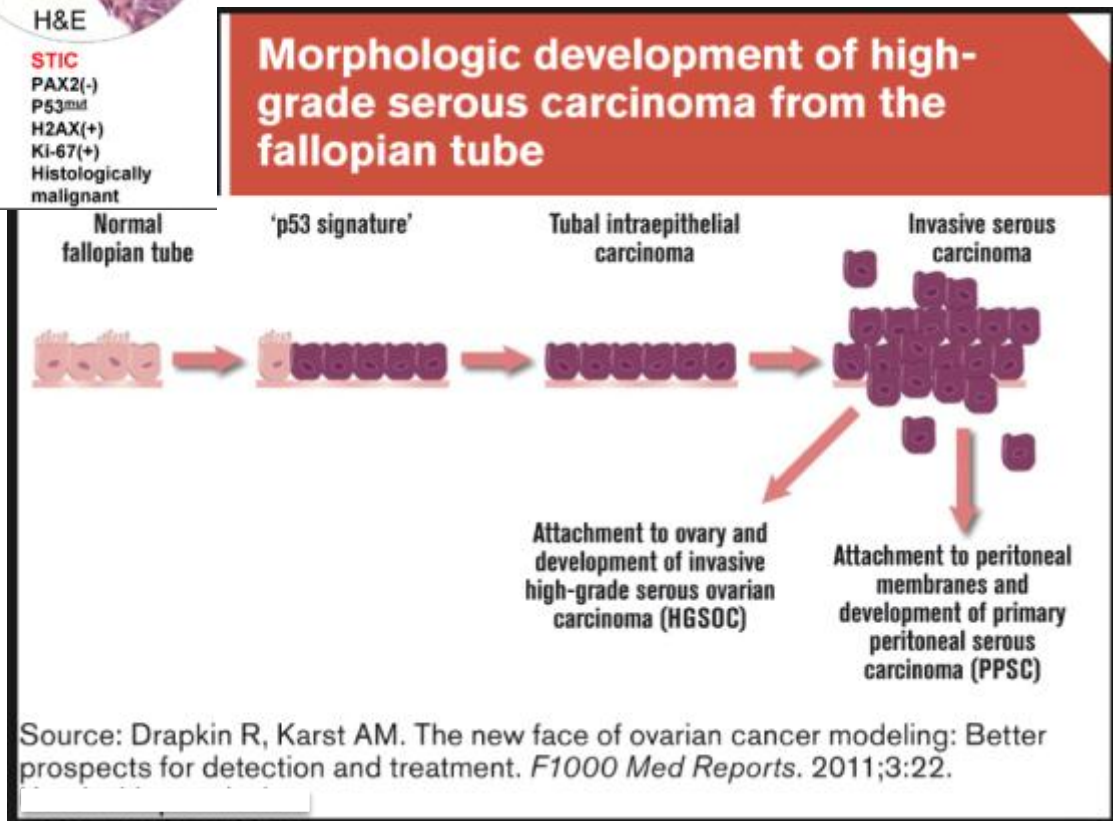

Patient with rare/poor prognosis disease is identified
PI approval/ Patient Consented for Study
PBL sample taken
Archived Formalin Blocks retrieved
(If possible) Biopsy of tumor / surgical resection
Recurrence
Targeted Re-sequencing of Actionable Genes in by Foundation Medicine (CLIA)
HONEST BROKER
Prepare cell lines/ explants/xenografts
Exome/whole Genome/ Transcriptome Sequencing
Weekly Review of genomic data from CLIA-certified LABS
Review of research Data: Validation By CLIA lab
Data released to treating clinician
Review of genomic and treatment/ outcome data

Molecular Tumor Board
RUTGERS CANCER INSTITUE OF NEW JERSEY


Ovarian Cancer
A
Epithelial (~90%)
Sex-cord stromal
Germ cell
Mixed-cell type
Cell of Origin
B
Epithelial (~90%)
Serous (68%-71%)
Endometrioid (9%-11%)
Clear cell (12%-13%)
Mucinous (3%)
Transitional (Brenner) (1%)
Mixed histologies (6%)
Histological Subtypes
Low-grade serous carcinoma (LGSC)*
High-grade serous carcinoma (HGSC)*
*Traditionally, well differentiated (low-grade) tumors were thought to progress to moderately and, ultimately, poorly differentiated (high-grade) carcinomas.


Ovarian Cancer
A
Epithelial (~90%)
Sex-cord stromal
Germ cell
Mixed-cell type
Cell of Origin
B
Epithelial (~90%)
Type 1
Type 2
Includes:
• Low-grade serous carcinoma (LGSC)
• Low-grade endometrioid
• Clear-cell carcinoma
• Mucinous tumors
• Brenner tumors
Mostly arise from endometriosis or borderline serous tumors
Includes:
• High-grade serous carcinoma (HGSC)
• High-grade endometrioid
• Malignant mixed mesodermal tumors
• Undifferentiated carcinomas
Mostly originate in the fallopian tube
Frequently characterized by mutations in: KRAS, BRAF, PTEN, PIK3CA, CTNNB, ARID1A, PPP2R1A
Characterized by mutations in: TP53


PAX2
P53
H&E
P53 Signature
PAX2(-)
P53mut
H2AX(+)
Histologically benign
SCOUT
PAX2(-)
p53mt
H2AX(-)
Histologically benign
STIC
PAX2(-)
P53mut
H2AX(+)
Ki-67(+)
Histologically malignant


Morphologic development of high-grade serous carcinoma from the fallopian tube
Normal fallopian tube
'p53 signature'
Tubal intraepithelial carcinoma
Invasive serous carcinoma
Attachment to ovary and development of invasive high-grade serous ovarian carcinoma (HGSOC)
Attachment to peritoneal membranes and development of primary peritoneal serous carcinoma (PPSC)
Source: Drapkin R, Karst AM. The new face of ovarian cancer modeling: Better prospects for detection and treatment. F1000 Med Reports. 2011;3:22.

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