



Gynecologic Cancers a Look Towards the Future

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FOX CHASE
CANCER CENTER

Preventing Gynecologic Cancer

**Implications for sisters, daughters,
nieces, and others**

Altering Cancer Risk

- Obesity
 - BMI >35 translates to:
 - 1.5-fold risk of ovary cancer
 - 6.2 fold risk of endometrial cancer
- Oral Contraceptives and Ovary Cancer
 - 25% reduction in risk for every 5 years of use
 - Partial protection lasts at least 30 years
- Prophylactic Surgery
 - 80% reduction in ovary/tubal/primary peritoneal cancer in BRCA mutation carriers
 - -100% reduction of uterine/ovary cancer in HNPCC Carriers

Who gets Gynecologic Cancer

- Ovary Cancer
 - BRCA mutation
 - Lynch Syndrome
 - Family History
 - Nulliparous
 - Obesity-1.5X risk
- Uterine Cancer
 - Lynch Syndrome
 - Cowden's syndrome
 - Obesity-6.2 risk
 - Excess estrogen
 - Tamoxifen
- Cervical Cancer
 - HPV

BRCA Mutations

- Harboring a mutation in the genes BRCA1 or BRCA2 increases your risk of ovary cancer
- If you have a BRCA mutation your brothers and sisters and sons and daughters have a 50% risk of having the gene
- There are specific screening and prophylactic surgery recommendations for carriers in terms of breast and gynecologic cancers

Ontario Study

- All 1342 Women with ovary cancer were tested for mutation in BRCA1 & 2
- 176 Women with mutations (13%)
 - BRCA1-108 (Avg. age-50); BRCA2-68 (Avg. age- 57)
- Frequency Based on Age
 - <40 9/93 (10%)
 - 40-49 68/283 (24%)
 - 50-59 51/392 (13%)
 - >60 48/574 (8%)
- Mutations and Histology
 - Serous-18%, Endometrioid-8%, Mucinous-0%, Clear Cell 2%
- High Risk Ethnicities ($\geq 25\%$)
 - Jewish
 - Italian
 - Indo-Pakistan
 - Asian

Lynch Syndrome

- Families tend to have young members of the family with colon cancer and/or uterine cancer. Sometimes other tumors (usually GI, sometimes breast)
- Due to a mutation in one of four genes
- Cancer rates for middle age women very high
 - Endometrium 4.5%/year
 - Ovary 0.5%/year
 - Colon 3%/year

Papillomavirus and Cervical Cancer

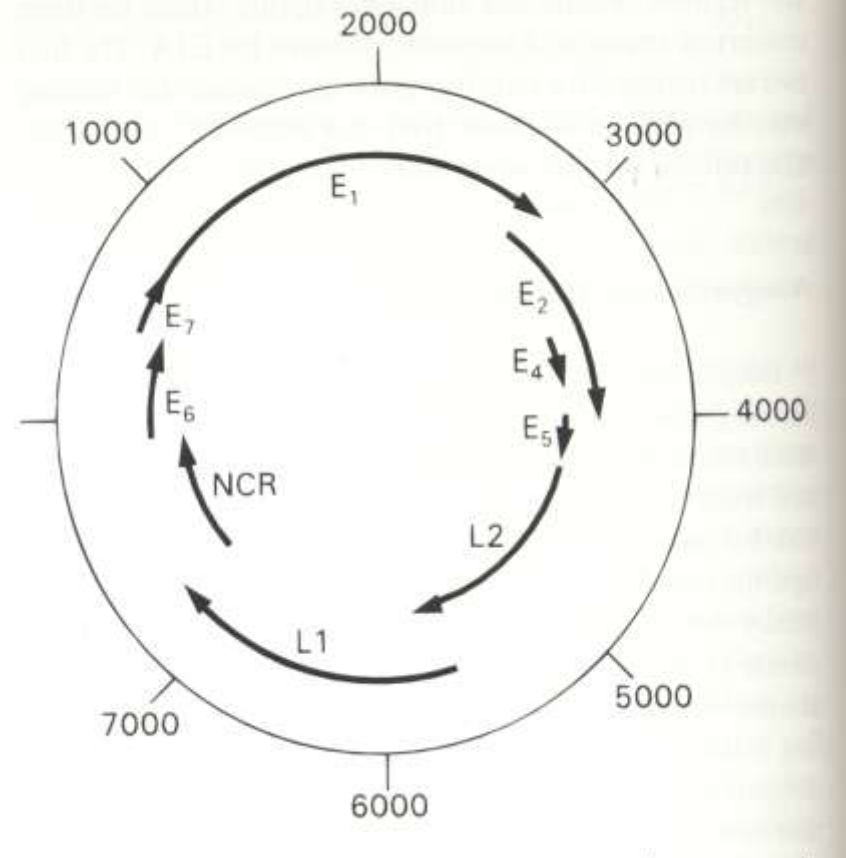
Double stranded Papovavirus
DNA virus

Completely sequenced-8000+ bp

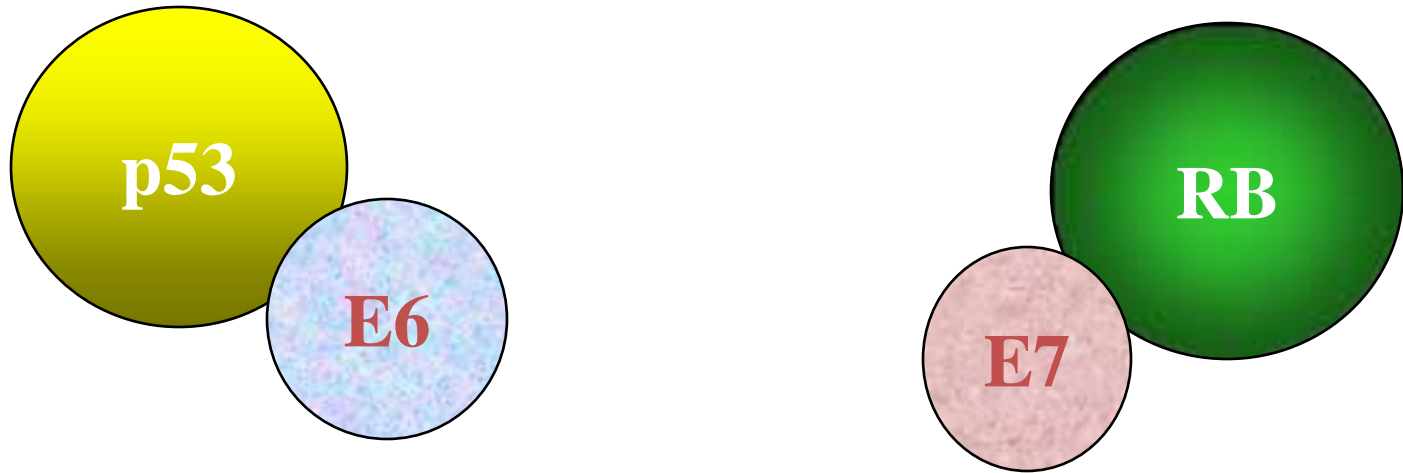
Epitheliotropic icosahedral virus

Several early (E) genes and 2 late (L)
Genes

60 different types with
limited sequence homology



HPV and Carcinogenesis

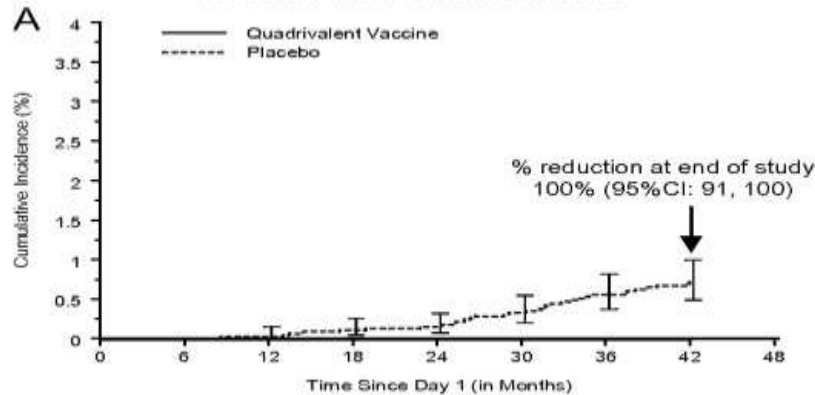


Inactivation of p53 and RB release keratinocytes from normal checkpoint control inducing cellular proliferation

Rate of highly abnormal Pap Smears with Vaccination

Negative to 14 HPV types population

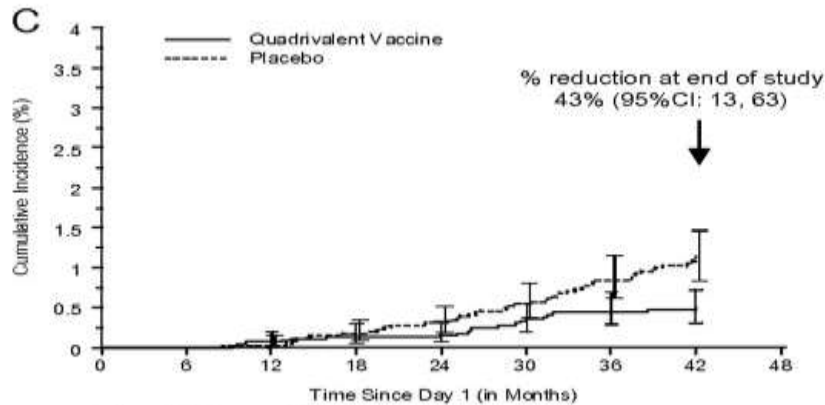
HPV6/11/16/18-related CIN3/AIS



Number of Subjects at Risk

Quadrivalent Vaccine	4616	4613	4567	4521	4480	4423	4319	3336	287
Placebo	4680	4675	4627	4581	4524	4463	4351	3375	264

All CIN3/AIS irrespective of causal HPV type



Number of Subjects at Risk

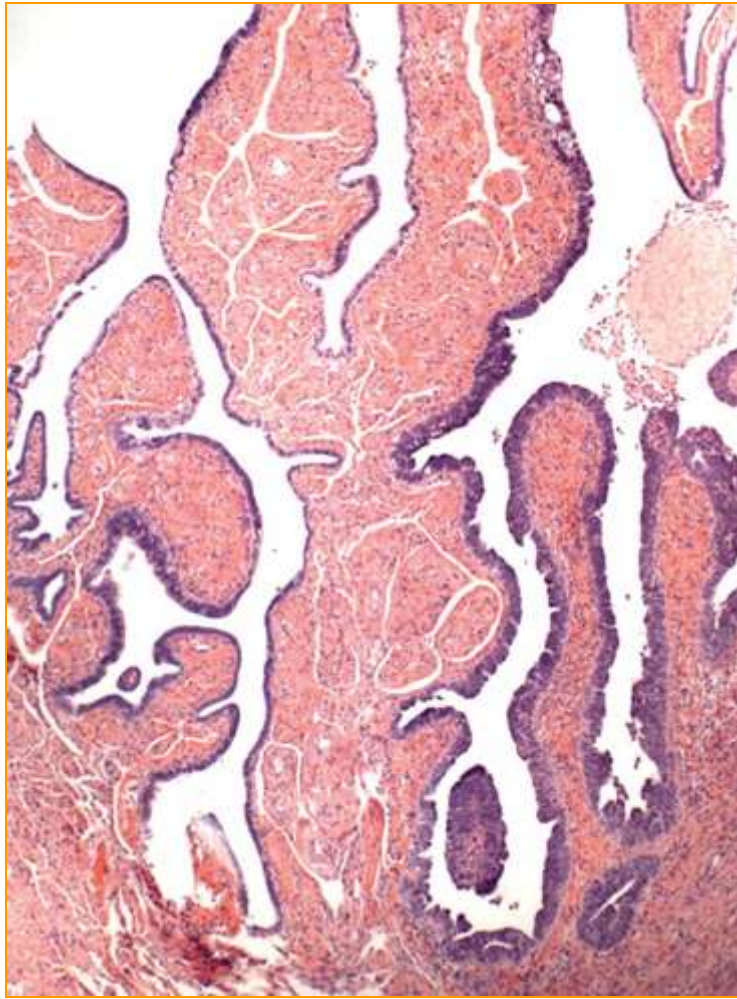
Quadrivalent Vaccine	4616	4613	4566	4519	4479	4420	4317	3336	286
Placebo	4680	4675	4627	4580	4523	4462	4349	3372	264

Ovarian Cancer Screening
Where are we in screening
&
Why is this so hard?

PLCO Study

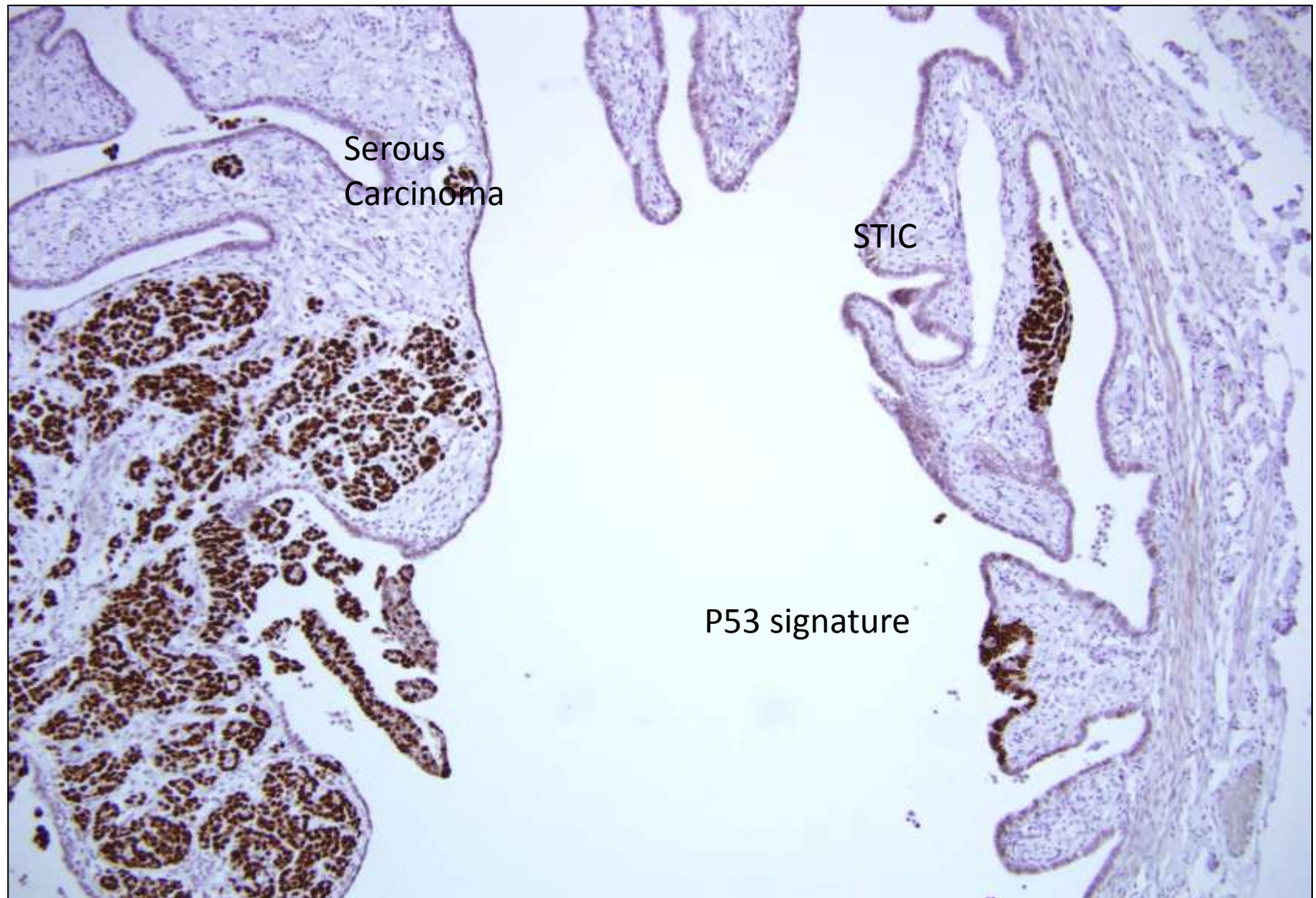
- 78,218 Women-Ages 55-74; randomized 1:1
- Screening Arm
 - CA-125 annually x 6yrs
 - TVUS annually x 4yrs
- Ovary Cancer
 - Screened-212, observed-176
- Ovary Cancer Deaths
 - Screened 118, observed-100
- Surgeries in screened group
 - 3285 surgeries in the screened group with 166 cx

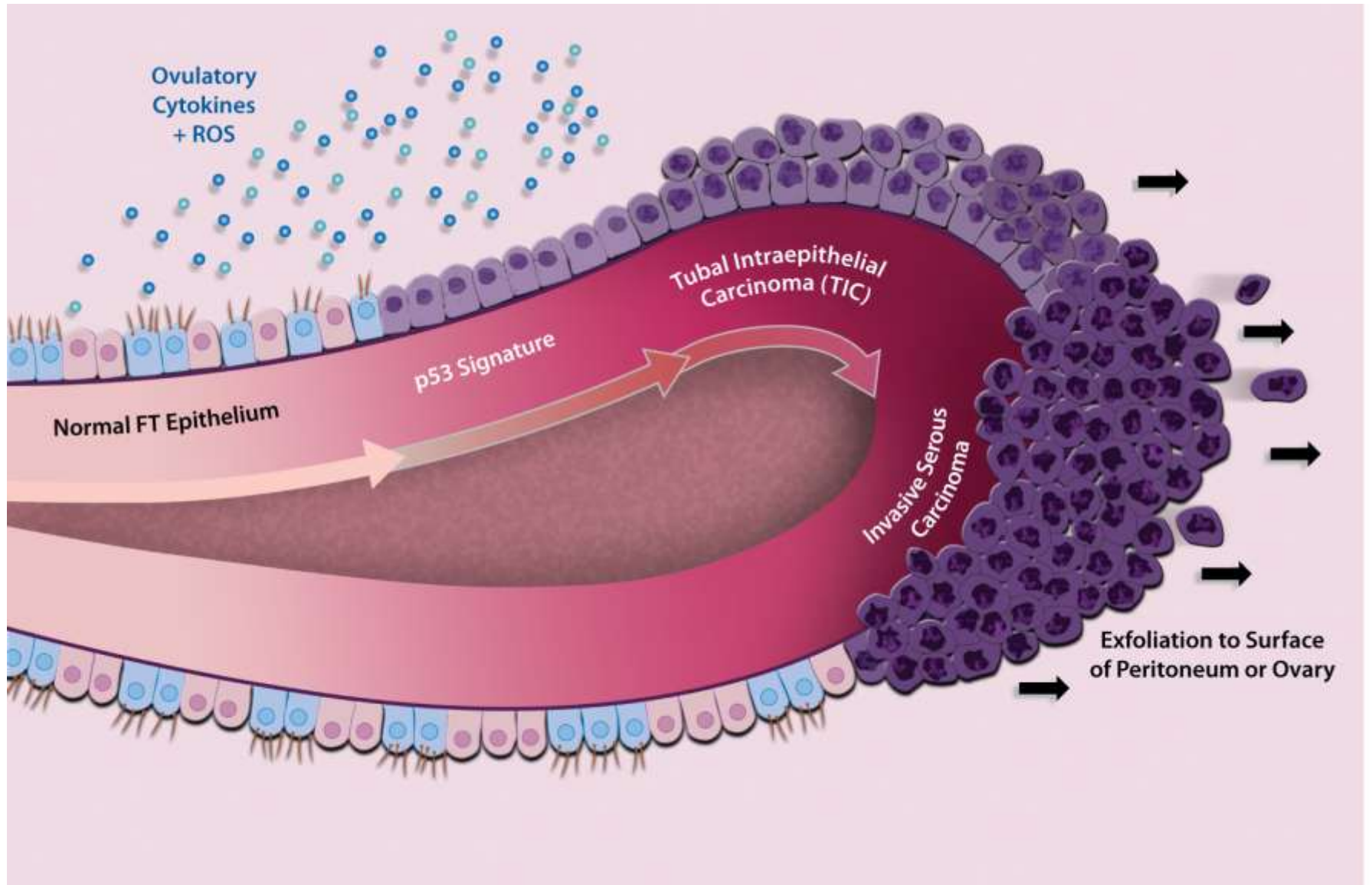
Serous Tubal Intraepithelial Carcinoma (STIC)



A common early serous carcinoma detected in ~ 5% of BSOs from BRCA+ Women

p53 signature, STIC, and invasive carcinoma in tubal fimbria

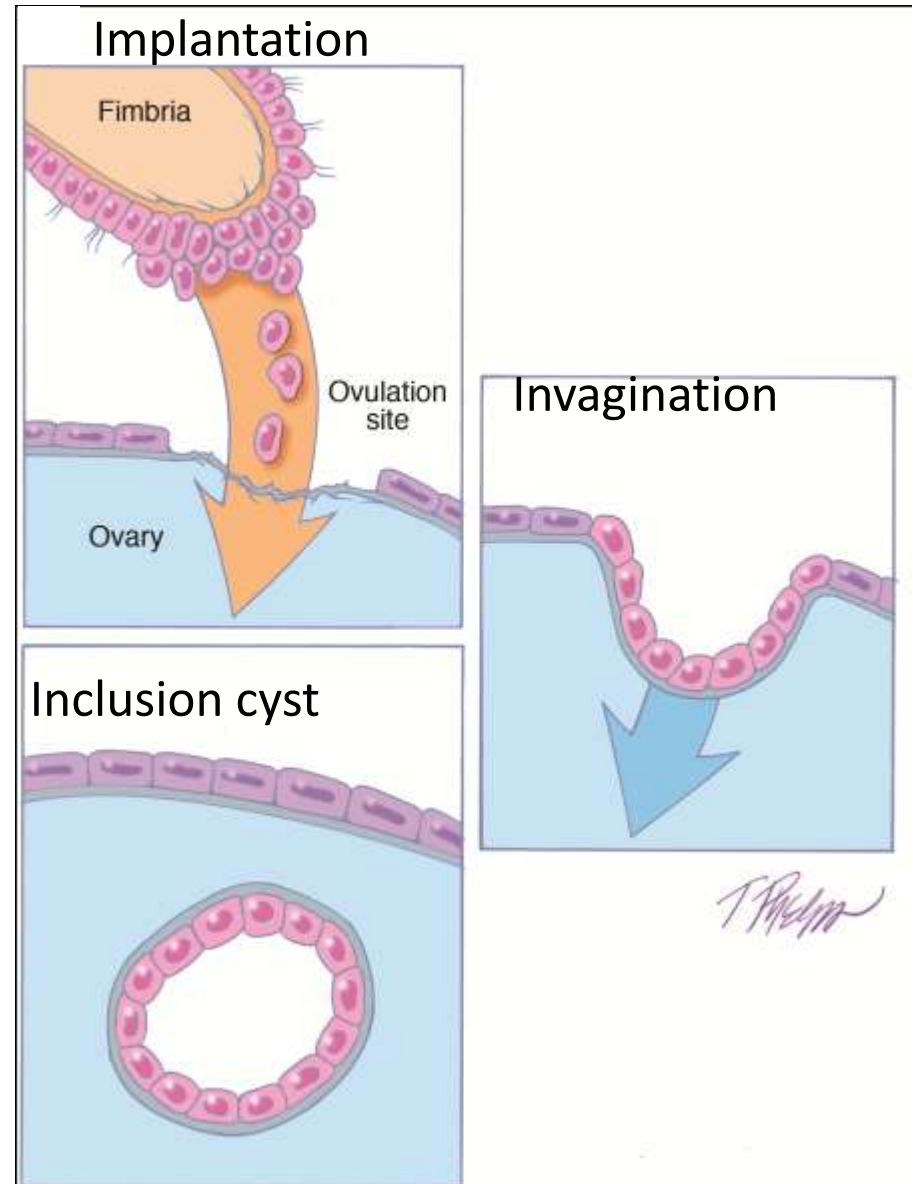




Formation of Cortical Inclusion Cyst

A unifying theory

Cortical inclusion cyst is derived from implanted tubal epithelium not from OSE



From R. Kurman, 2010

Treatment

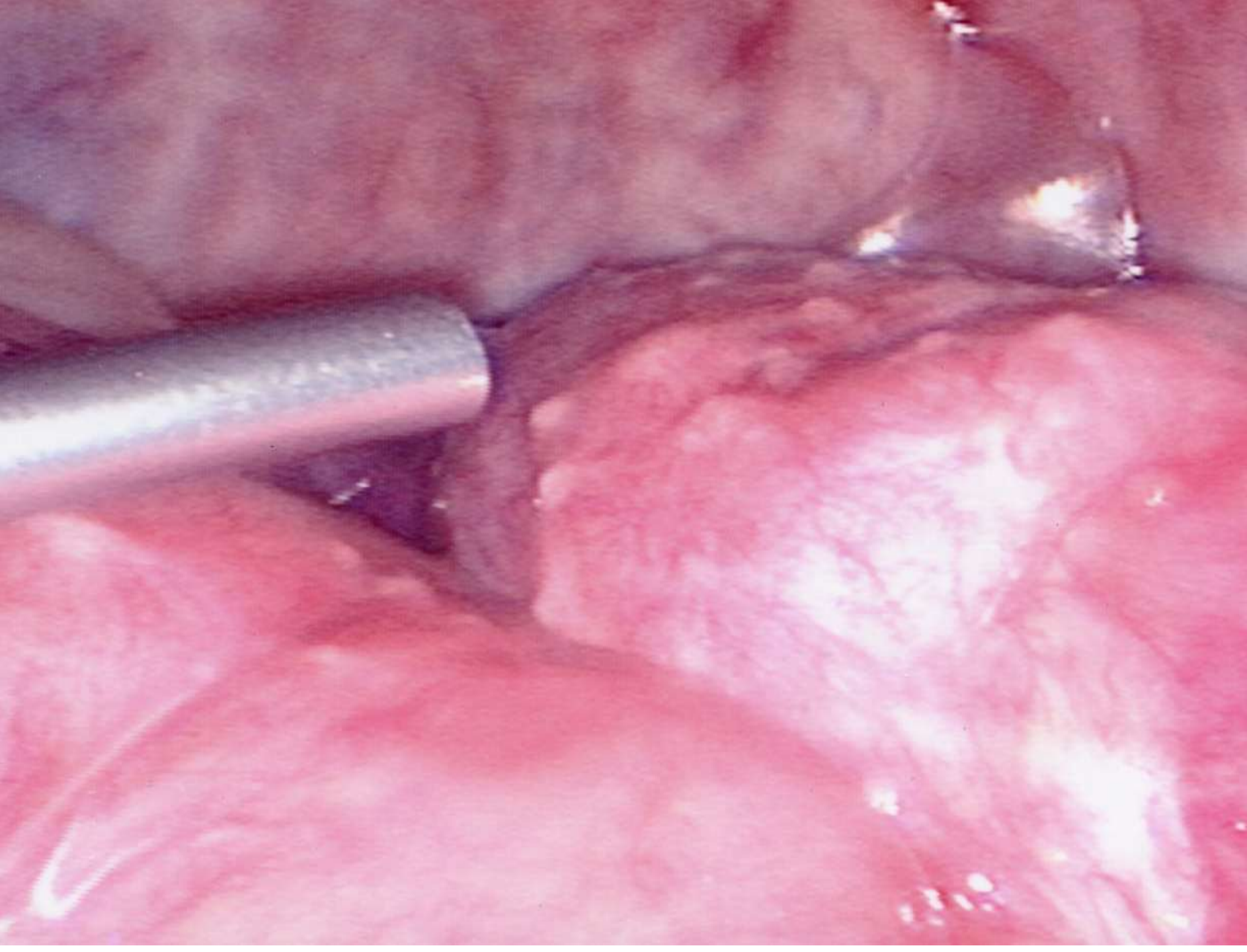
Why are we not making faster
progress?

Ovary Cancer-Initial Therapy

- Taxol and a platinum drug
- An operation to remove tumor
- Standard-Surgery with goal to remove all visible tumor and subsequently 6 treatments with carboplatin and paclitaxel every 3 weeks

Key Questions for Initial Therapy

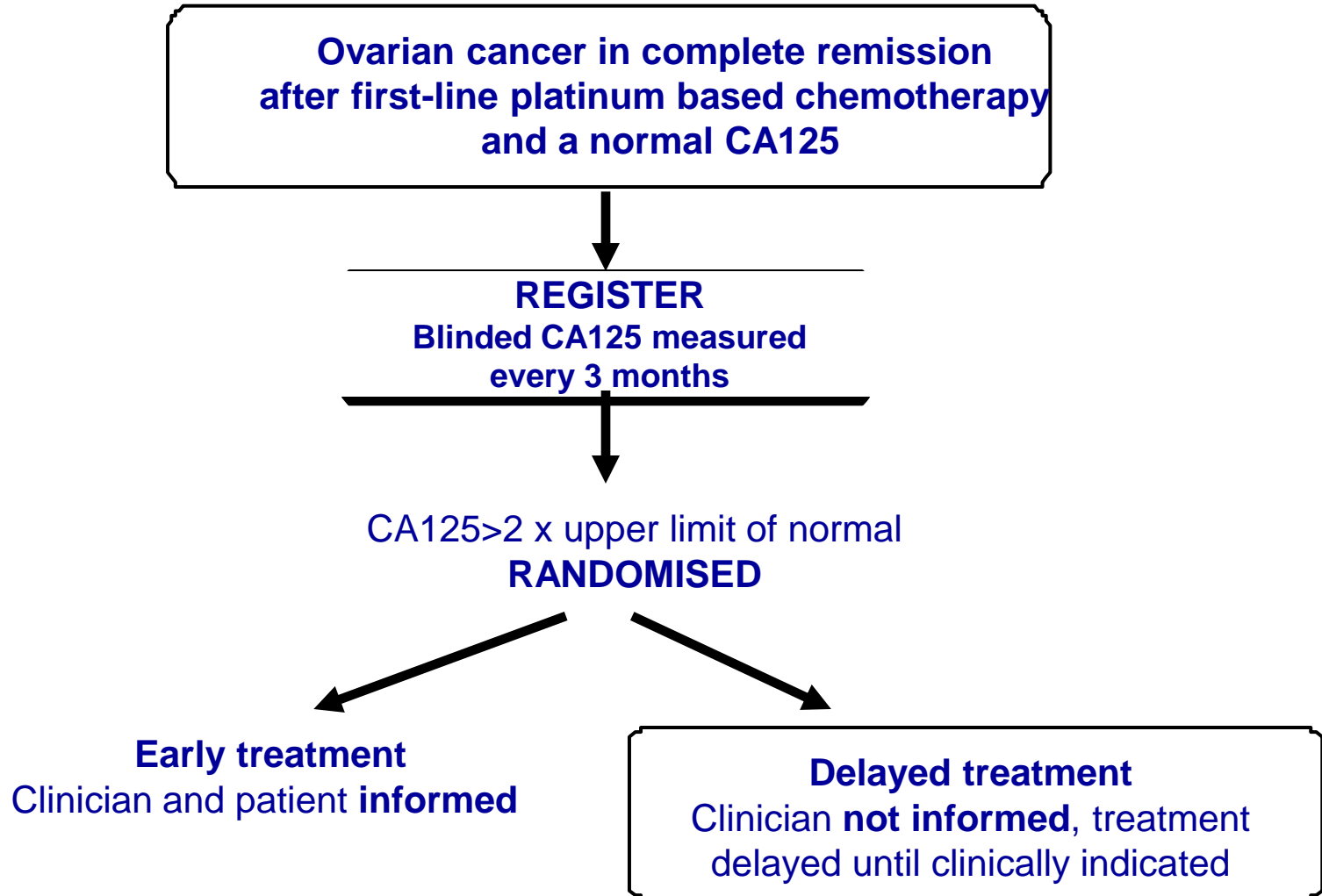
- Operation first than chemo or chemo first than an operation
- Drugs every 3 weeks or should the taxol be weekly?
- Should you add bevacizumab?
- Should some of the chemotherapy be given in the peritoneal cavity?



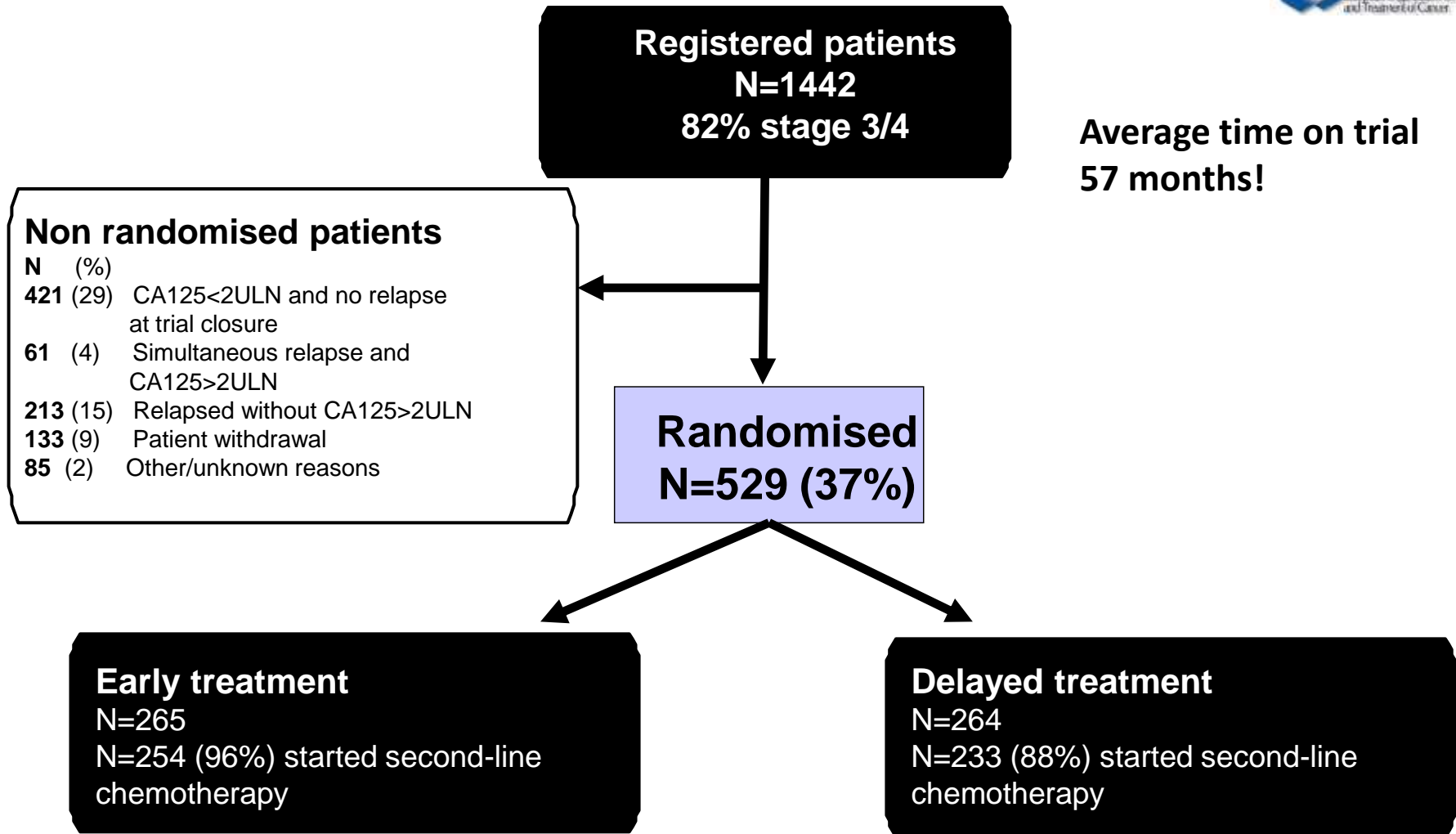
CA-125

- A mucin protein on the surface of cells
- Lots on the surface of most ovary cancers
- This protein can be shed into the bloodstream
- Normal is under 35
- In women with ovary cancer and serous cancer of the uterus the value and change in the value tends to predict changing tumor volume

MRC OV05 Trial



MRC OV05 Trial



MRC OV05 Trial Results

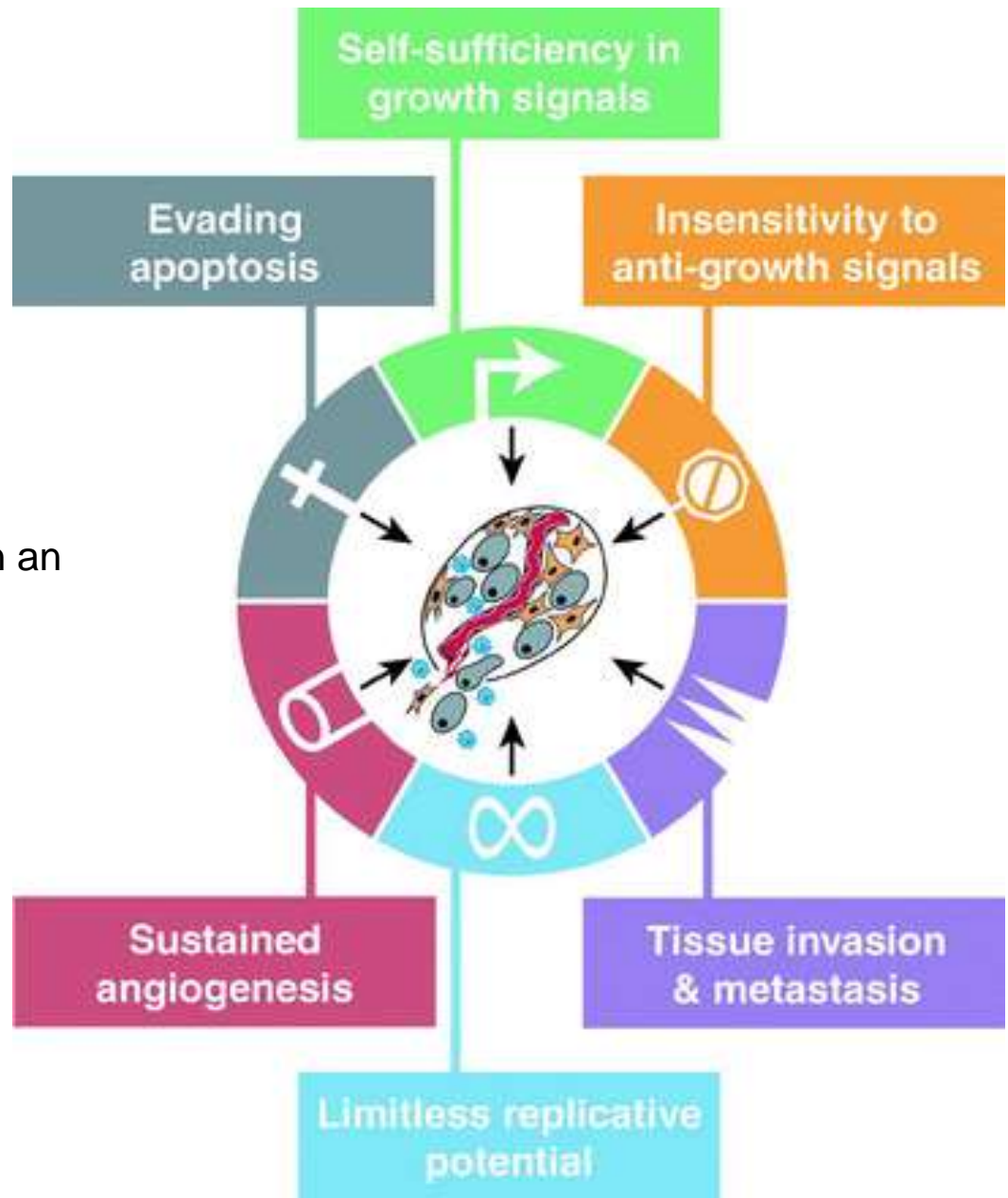
- In early treatment arm based on rise of CA125
 - Second-line chemotherapy started a median of 4.8 months earlier
 - Third-line chemotherapy started a median of 4.6 months earlier
- This early treatment did not improve overall survival
- Early chemotherapy does not improve quality of life

Therapies

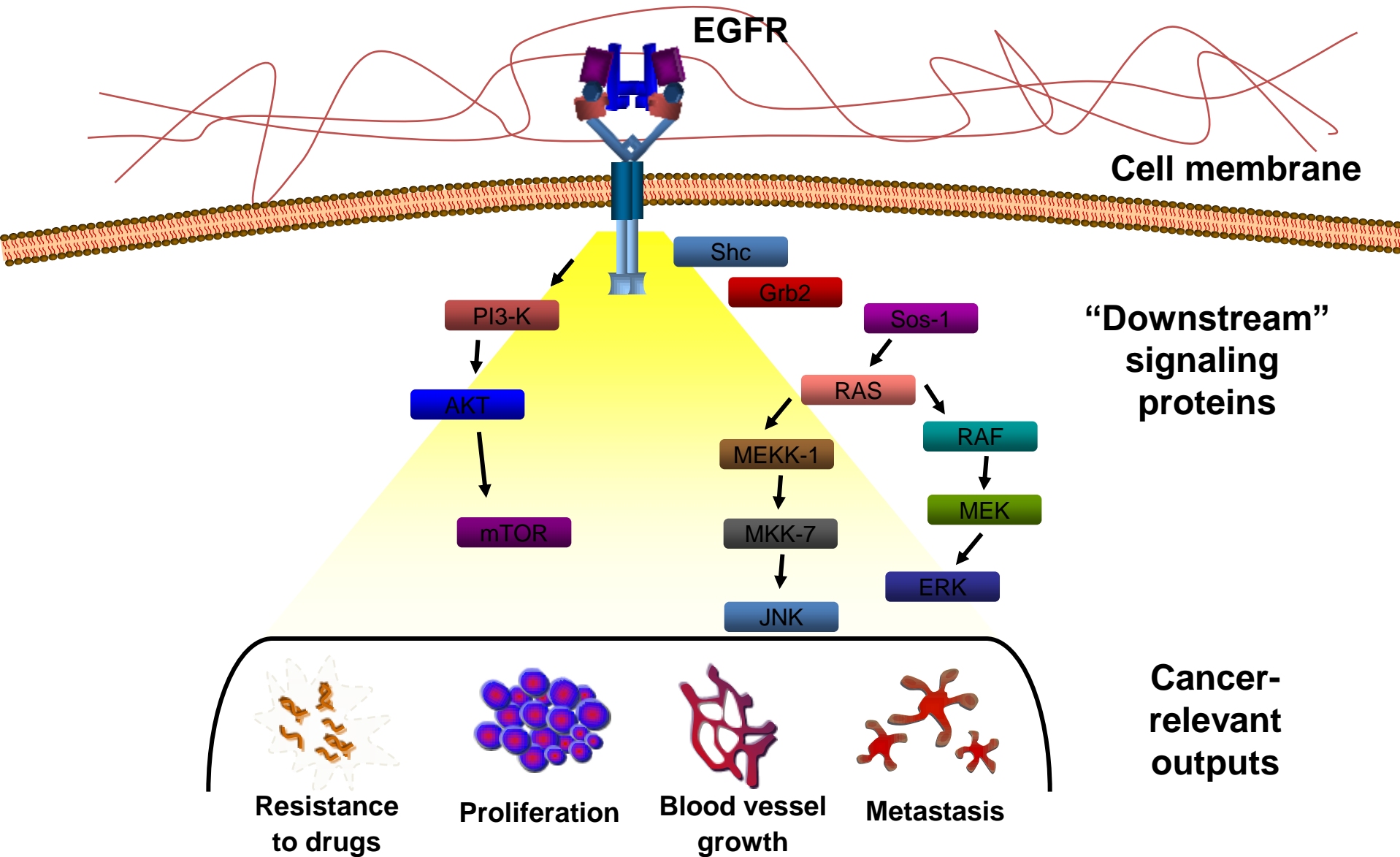
- Surgery-1950's-present
- Radiation-1960's
- Melphelan-1960's
- Cis-platinum-1970's
- Hexamethylene-1970's
- Paclitaxel-1980's
- Carboplatin-1990's
- Liposomal Doxorubicin-1990's
- Topotecan-1990's
- Gemcitabine-1990's
- Pemetrexate-2000's
- Bevacizumab (Angiogenesis inhibitors)-2000's
- *Olaparib (Parp inhibitors)-2010's?*

Acquired Capabilities of Cancer

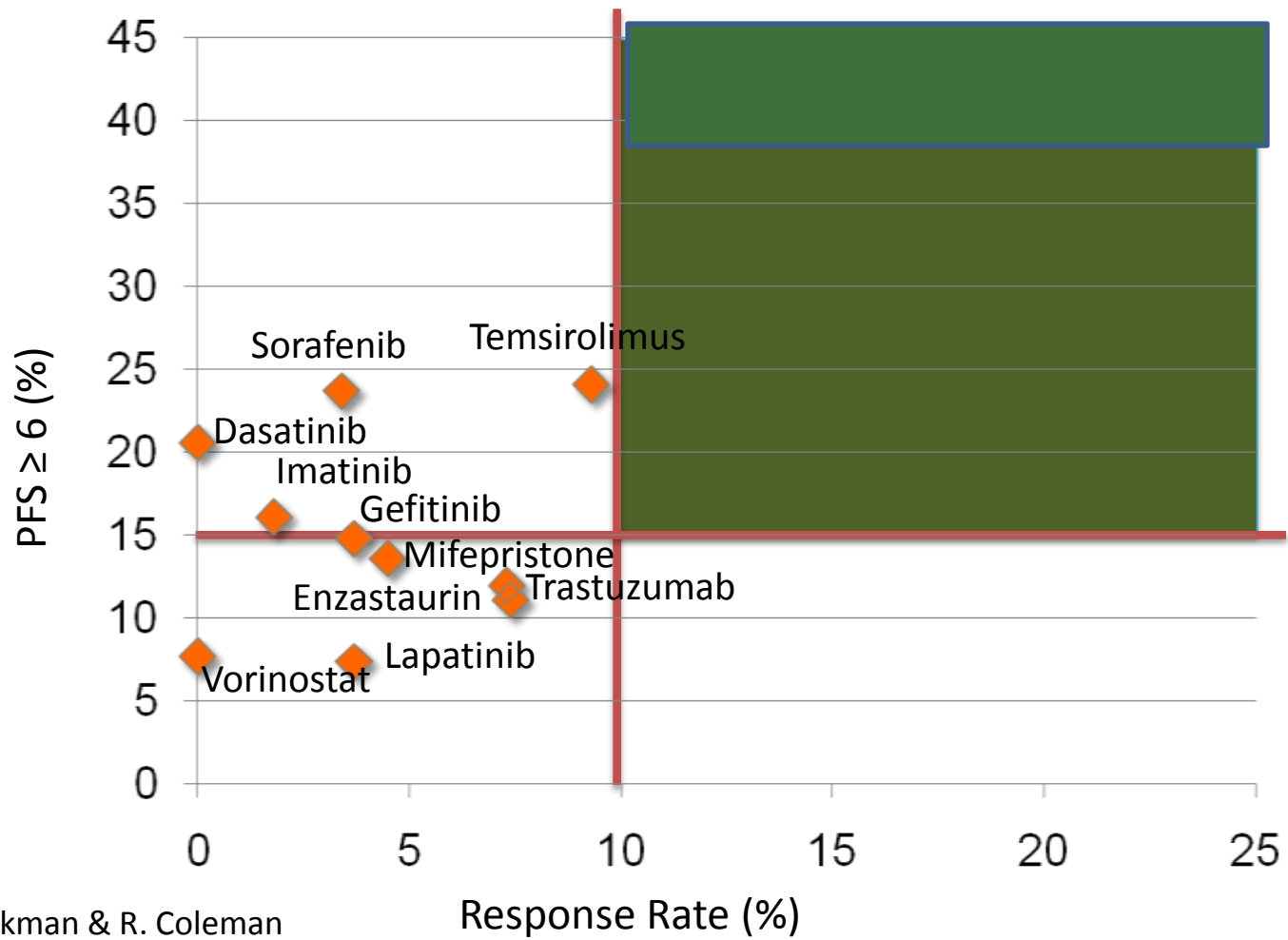
Defining addictive signals in an individual's tumor



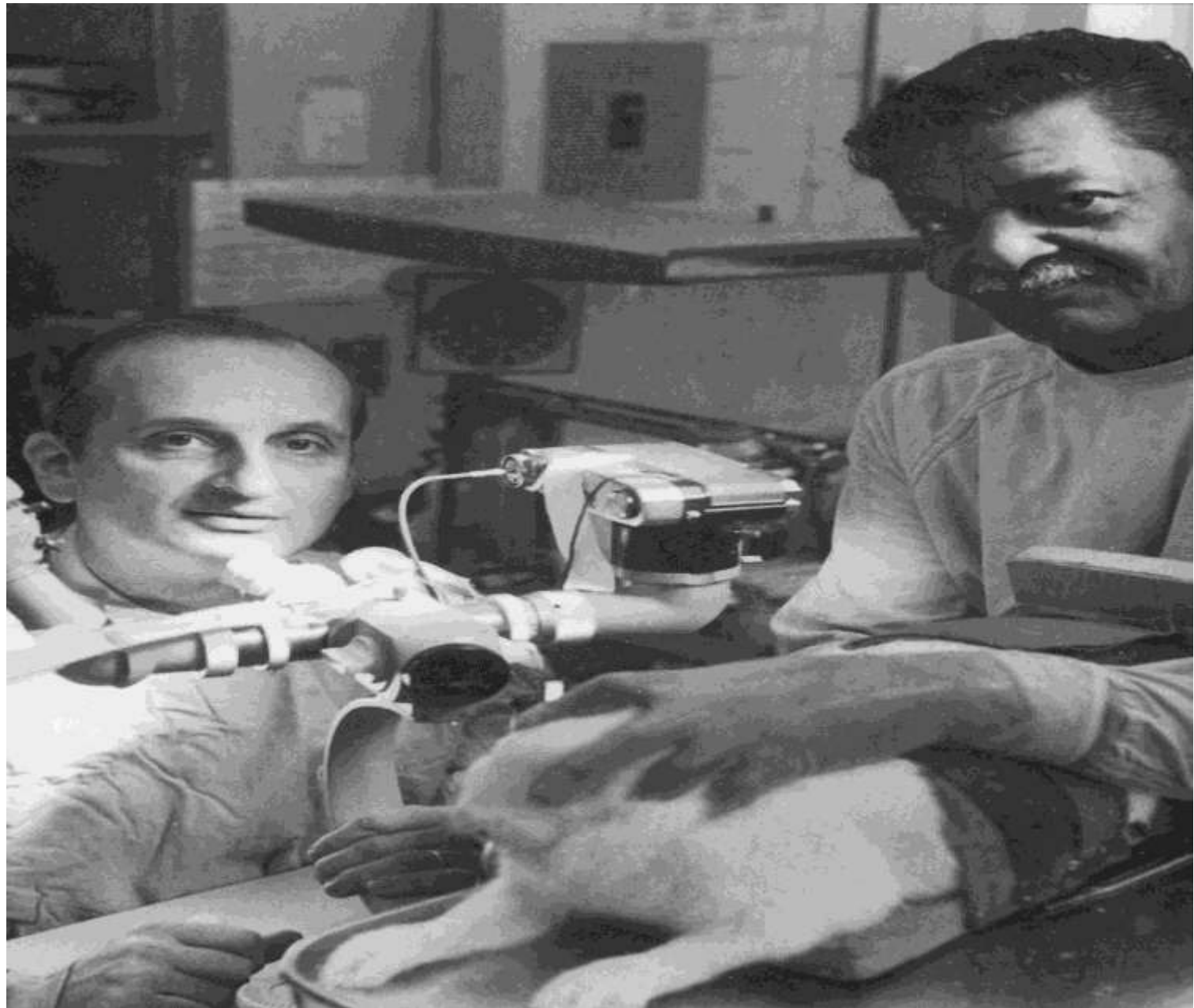
Targeting Pathways



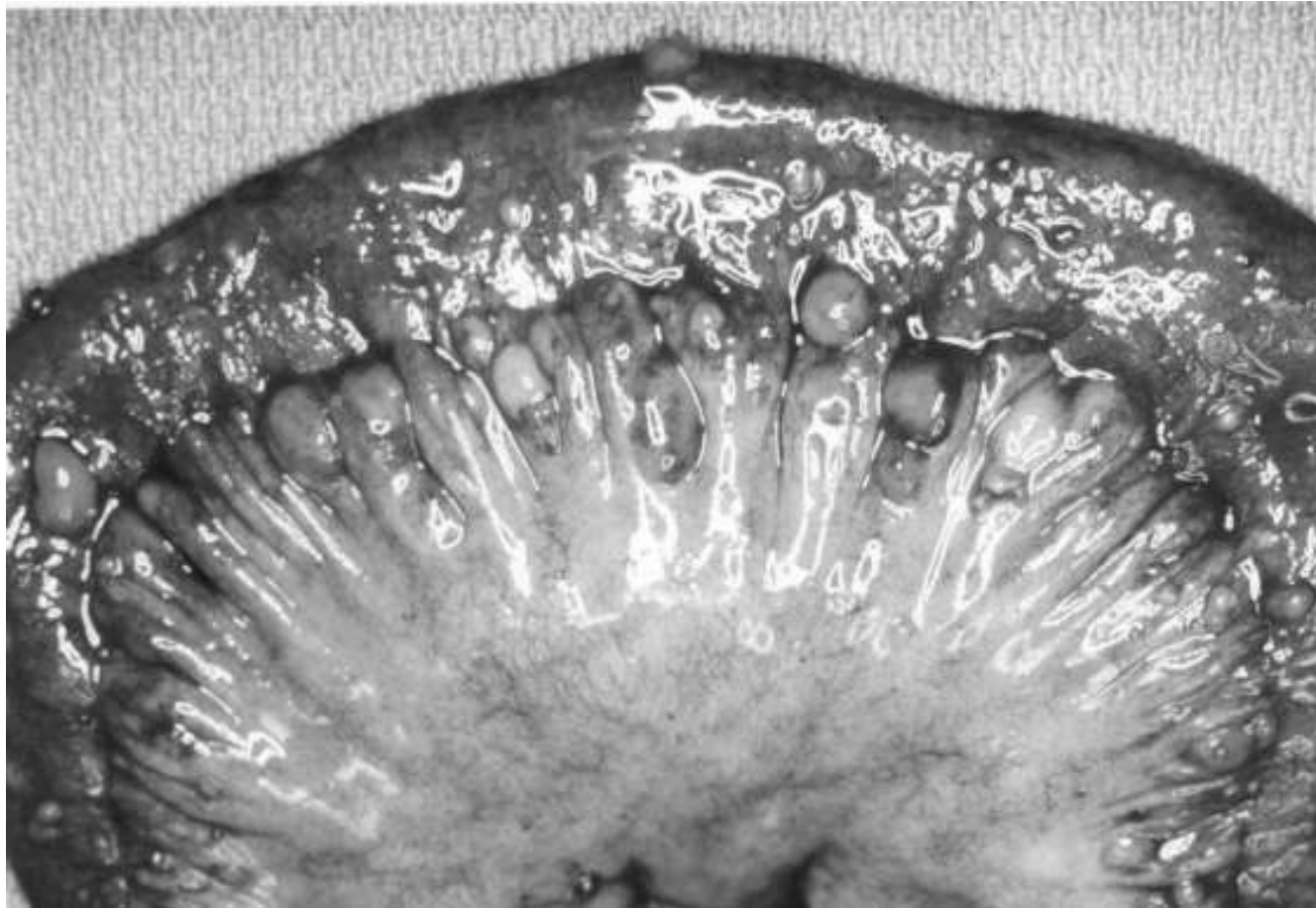
GOG 170 series: track record



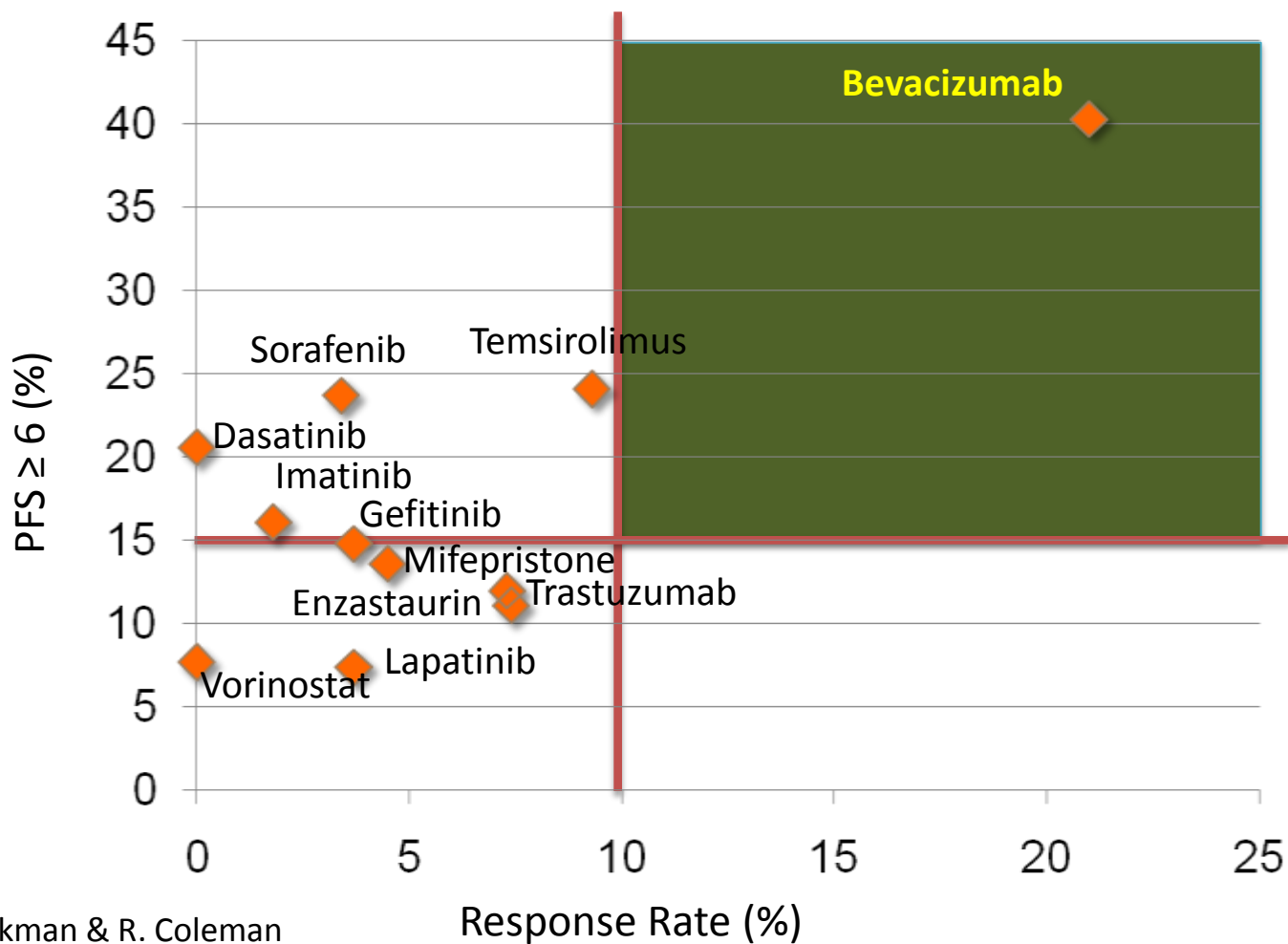
Courtesy M.A. Bookman & R. Coleman



Development of Bowel Metastases

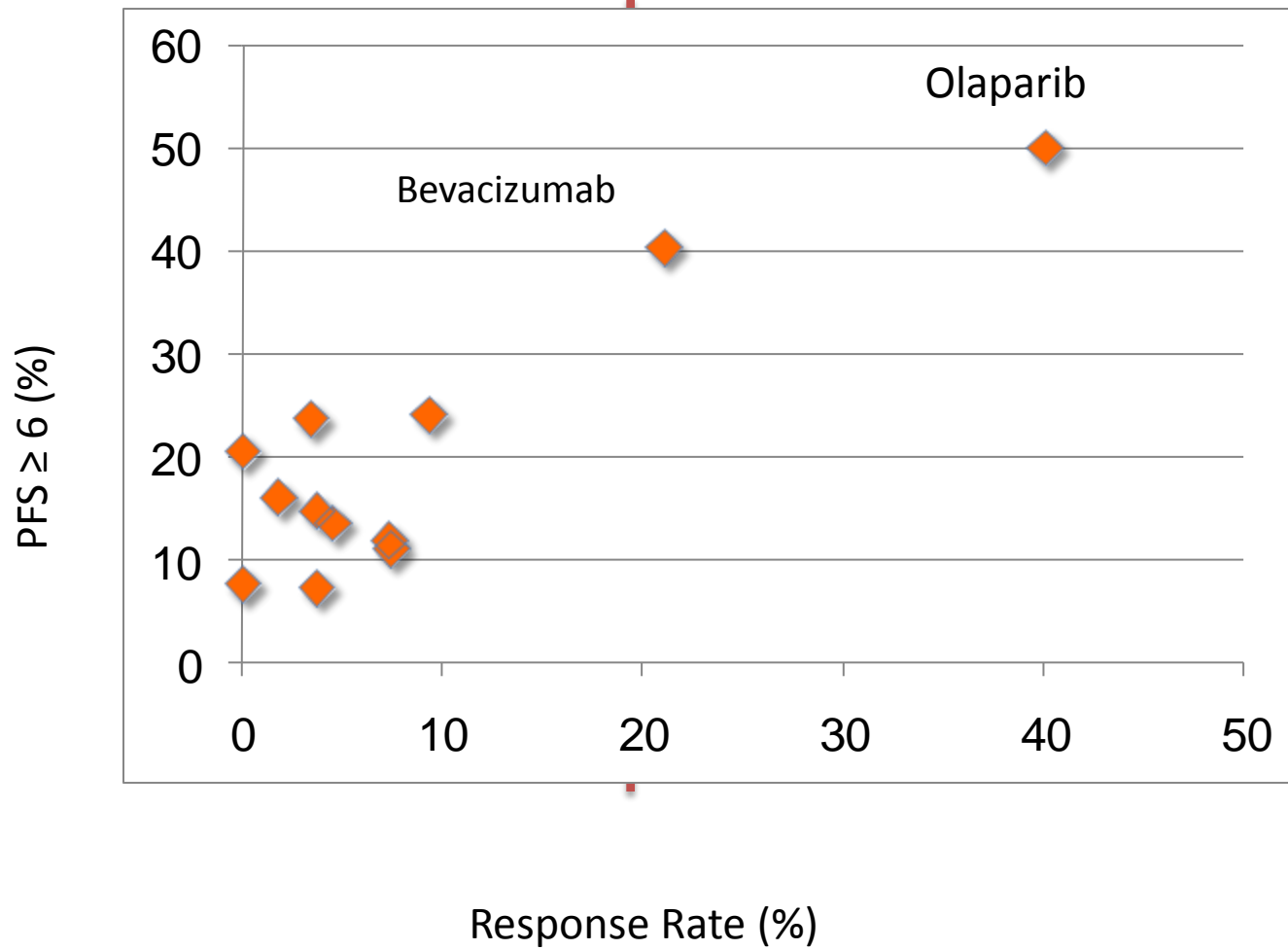


GOG 170 series: track record

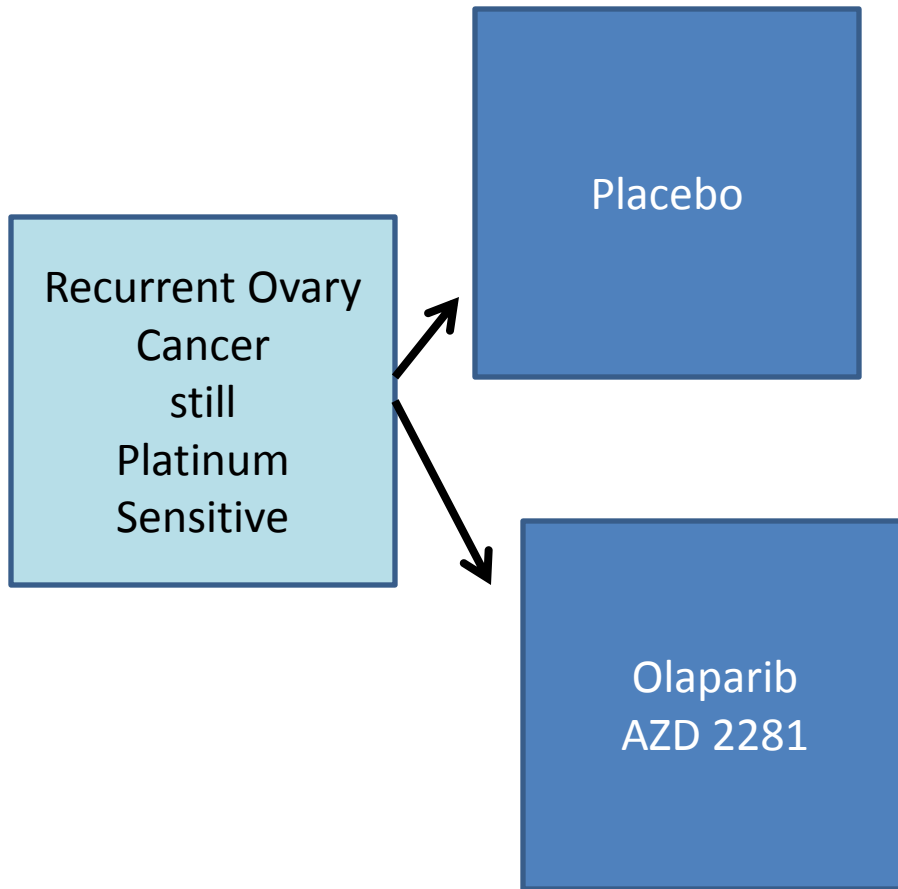


Courtesy M.A. Bookman & R. Coleman

Rational Therapy in Ovary Cancer

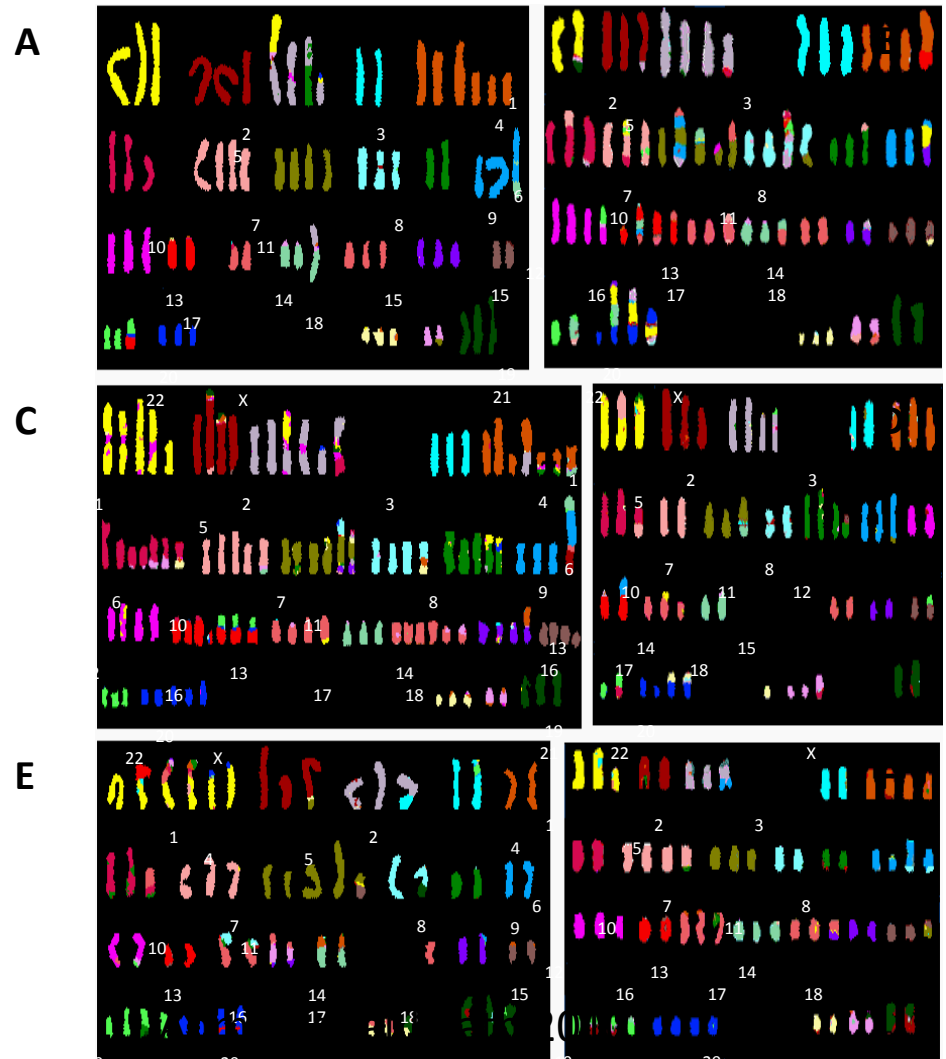
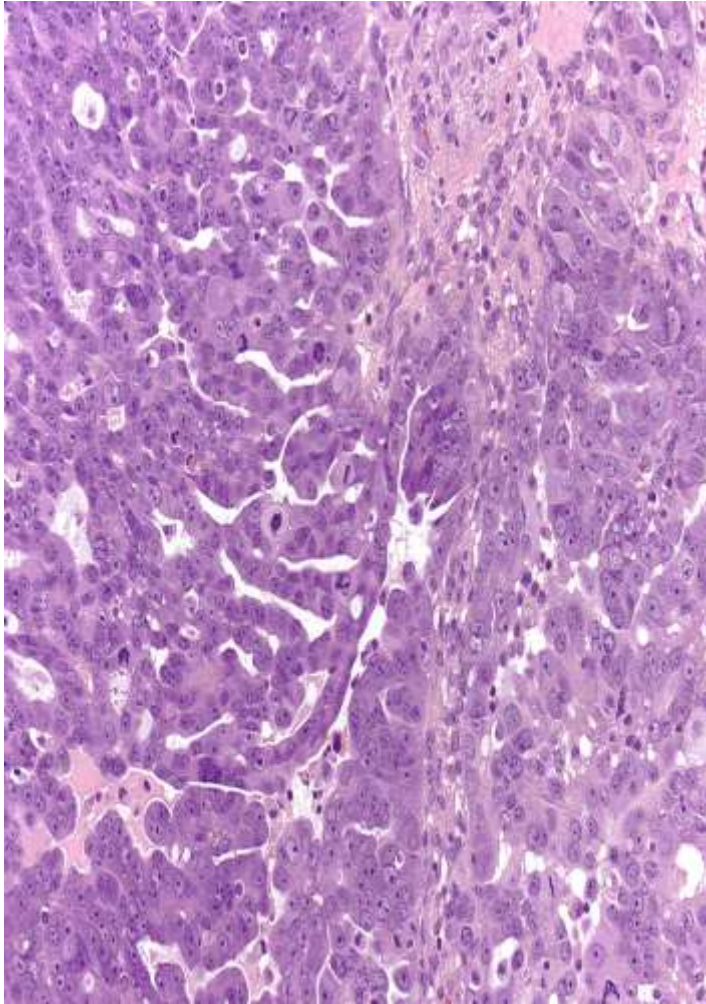


Parp Inhibitor Maintenance Trial

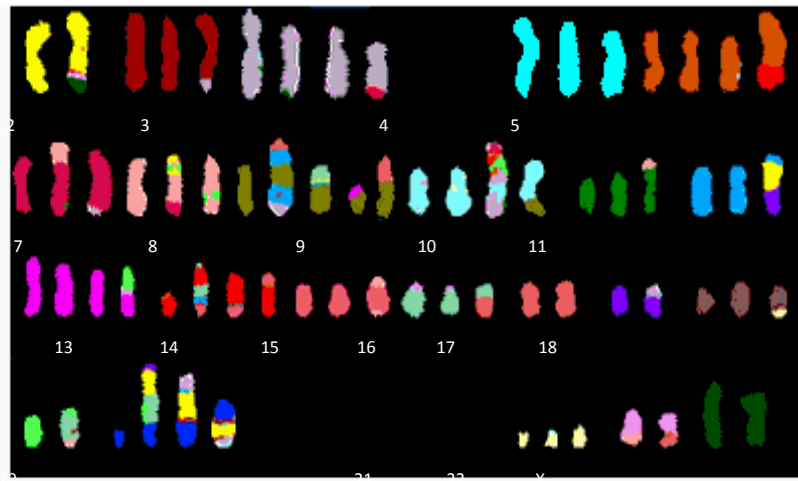
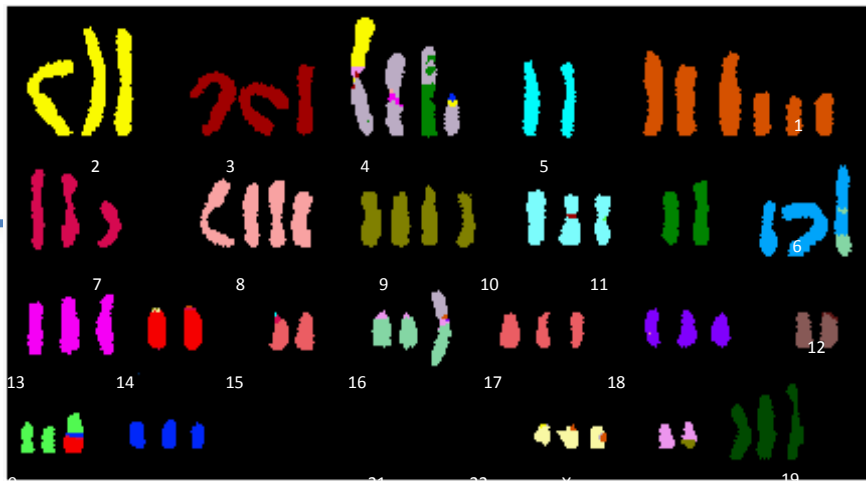
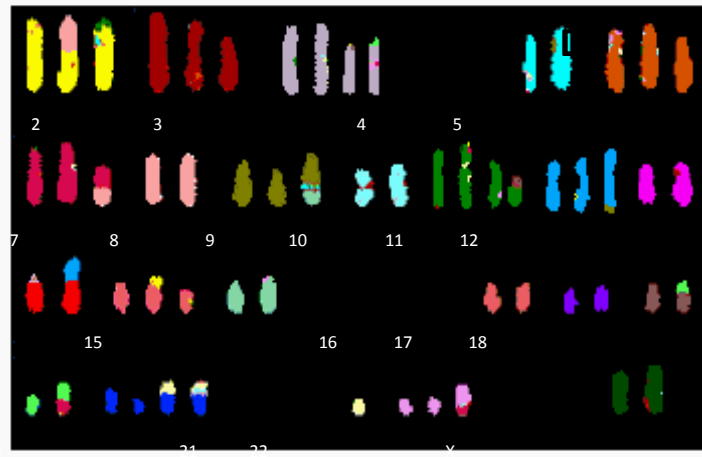
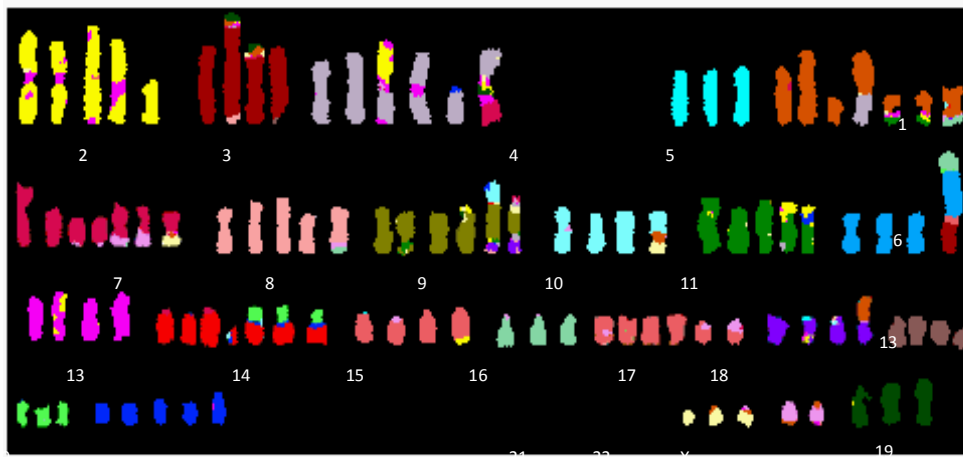
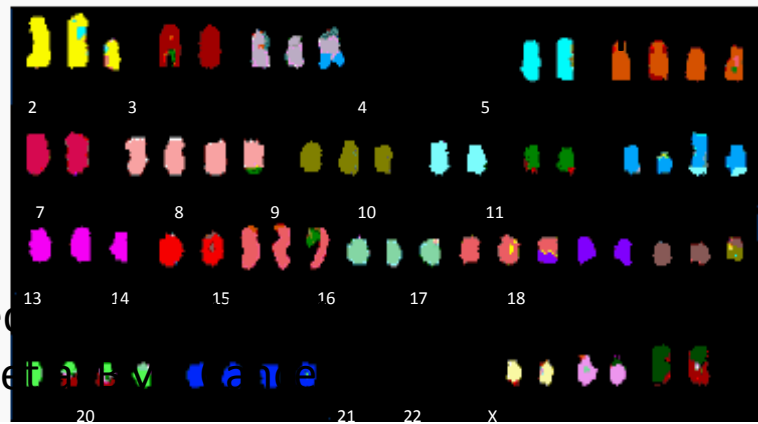
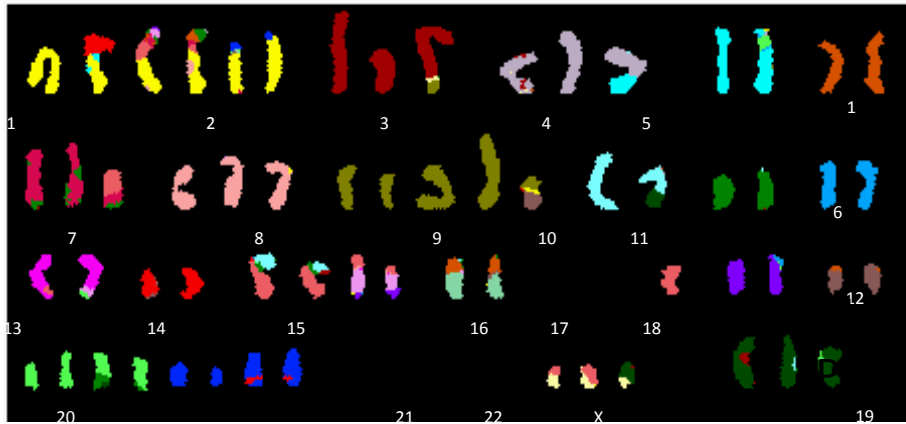


- 265 patients, high grade, papillary serous
- Randomized 1:1
- Olaparib 400mg twice a day or placebo
- Progression
 - Olaparib-8.4months
 - Placebo-4.8 months
- Toxicity
 - Nausea, fatigue, anemia

High grade serous carcinomas



Press et al BMC Cancer 2008

A**C****E**

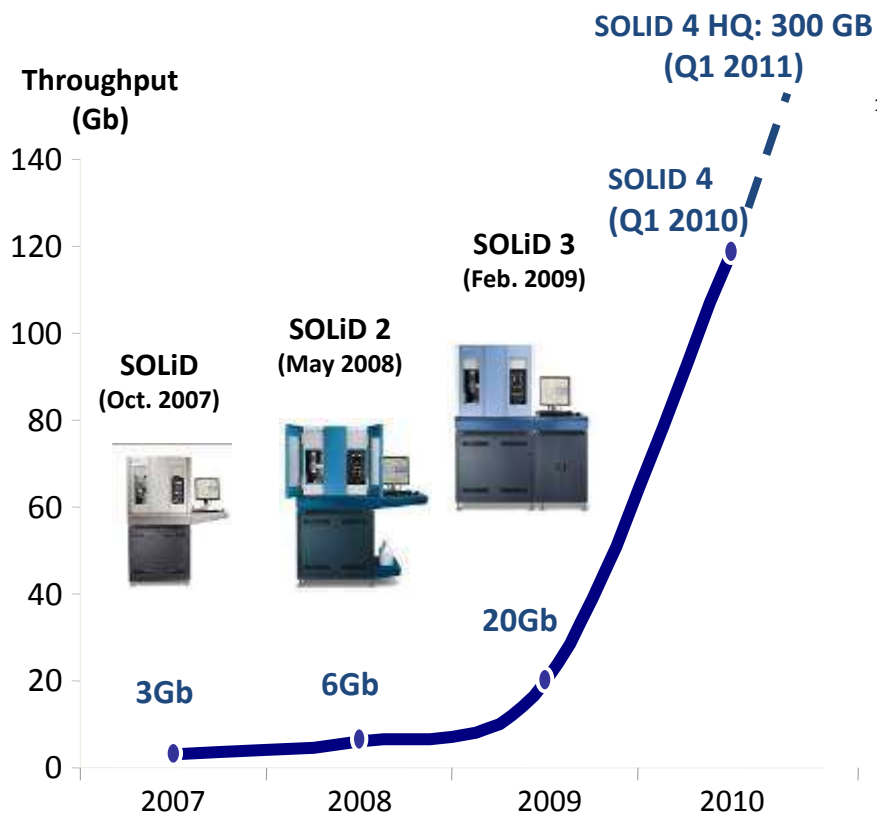


The Human Genome

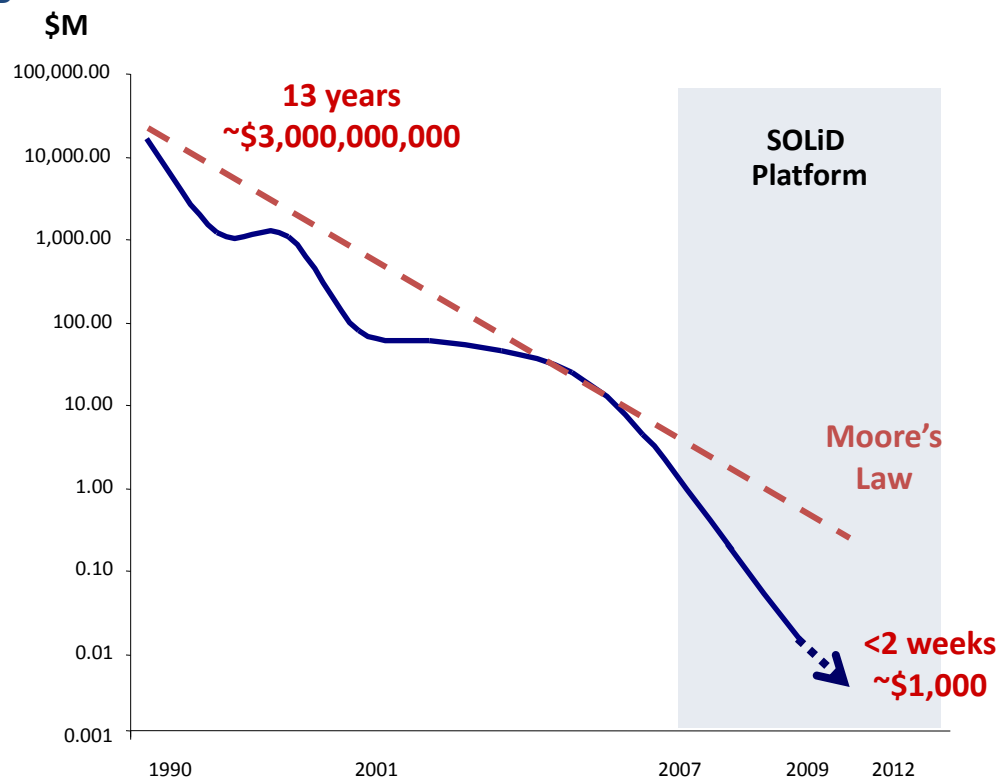


Whole Genome Sequence Analysis Is Becoming Affordable

Innovation of SOLiD throughput

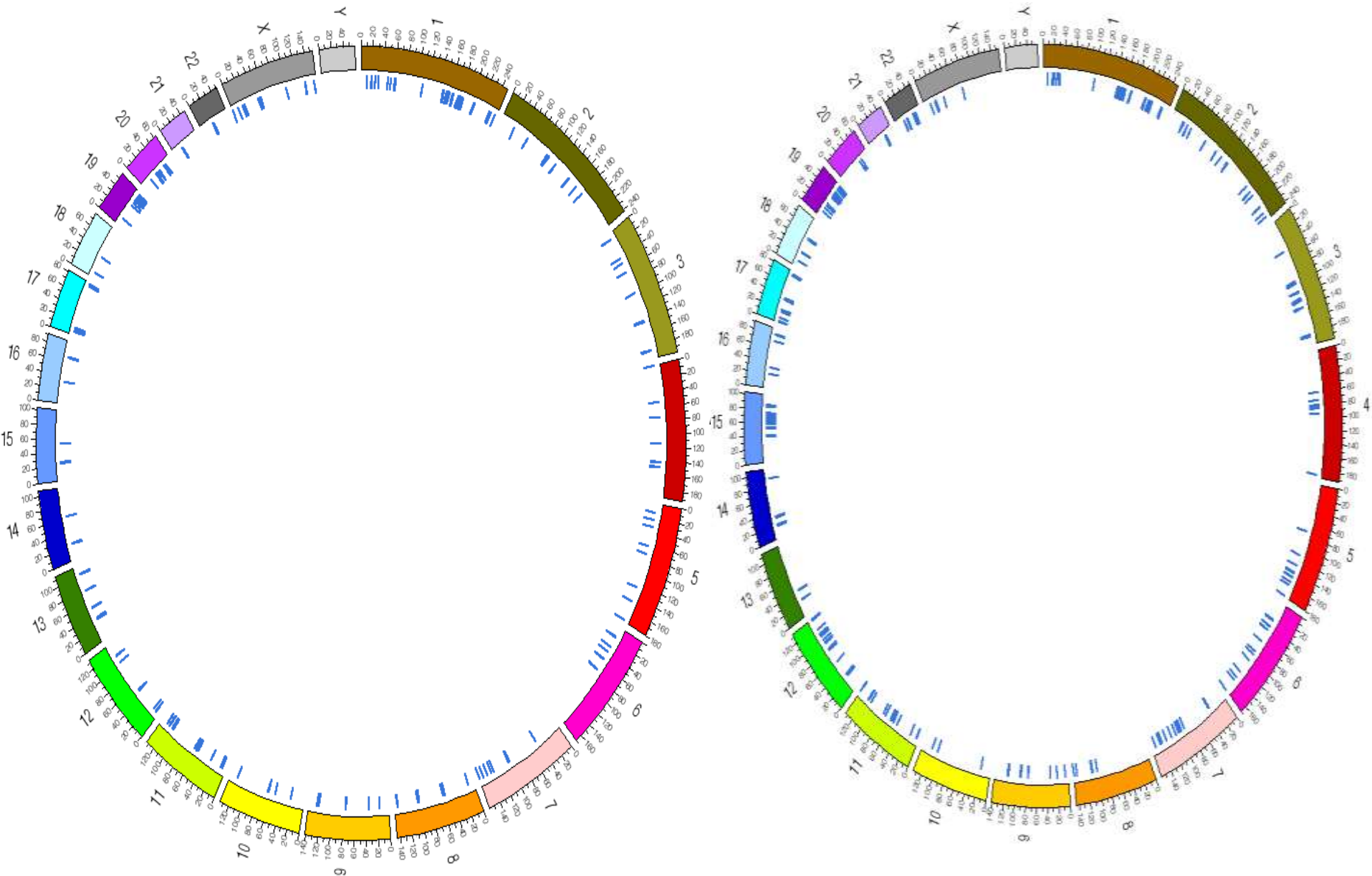


Cost per Human Genome



Capability, ease of use, and cost improvements make life science tools realistic for applied use

Gene Mutations in Serous Cancer



Opportunities and Challenges

- Opportunities-Whole gene sequencing will be available very soon!
 - Will provide new insights for individuals with family histories of ovary cancer but who are not BRCA-1/2 mutations carriers
 - Will provide a very personal signature of the mutations involved in your ovary cancer

Progress is Guaranteed

- In 1961-Survival for stage III/IV ovary cancer averaged less than a year
- In 2011-Survival is now averages 5 years which was accomplished largely in the dark!
- With a doubling of genetic data every year this translates into a 1000-fold increase in knowledge!
- This will lead to better outcomes!

FOX CHASE CANCER CENTER

West Building

West Building