

Cancer Pharmacogenomics: Setting a Research Agenda

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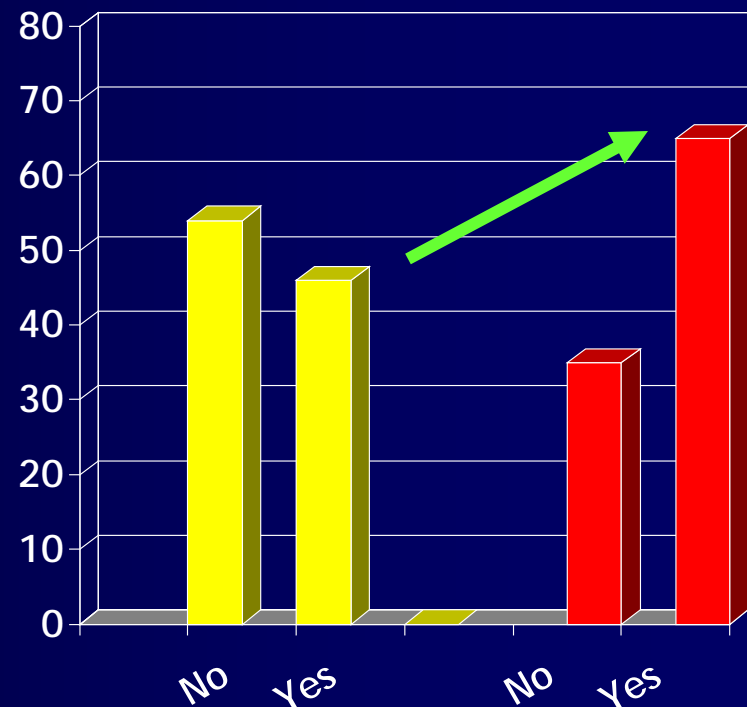
3 key discussion points

- Integration of Health Behaviors
 - Why we shouldn't ignore supplement use and other nutritional factors
- Necessity of a Transdisciplinary Approach to Cancer Prognosis
- Value of new Patient Cohorts

Cancer patients: Vitamin supplement use is high

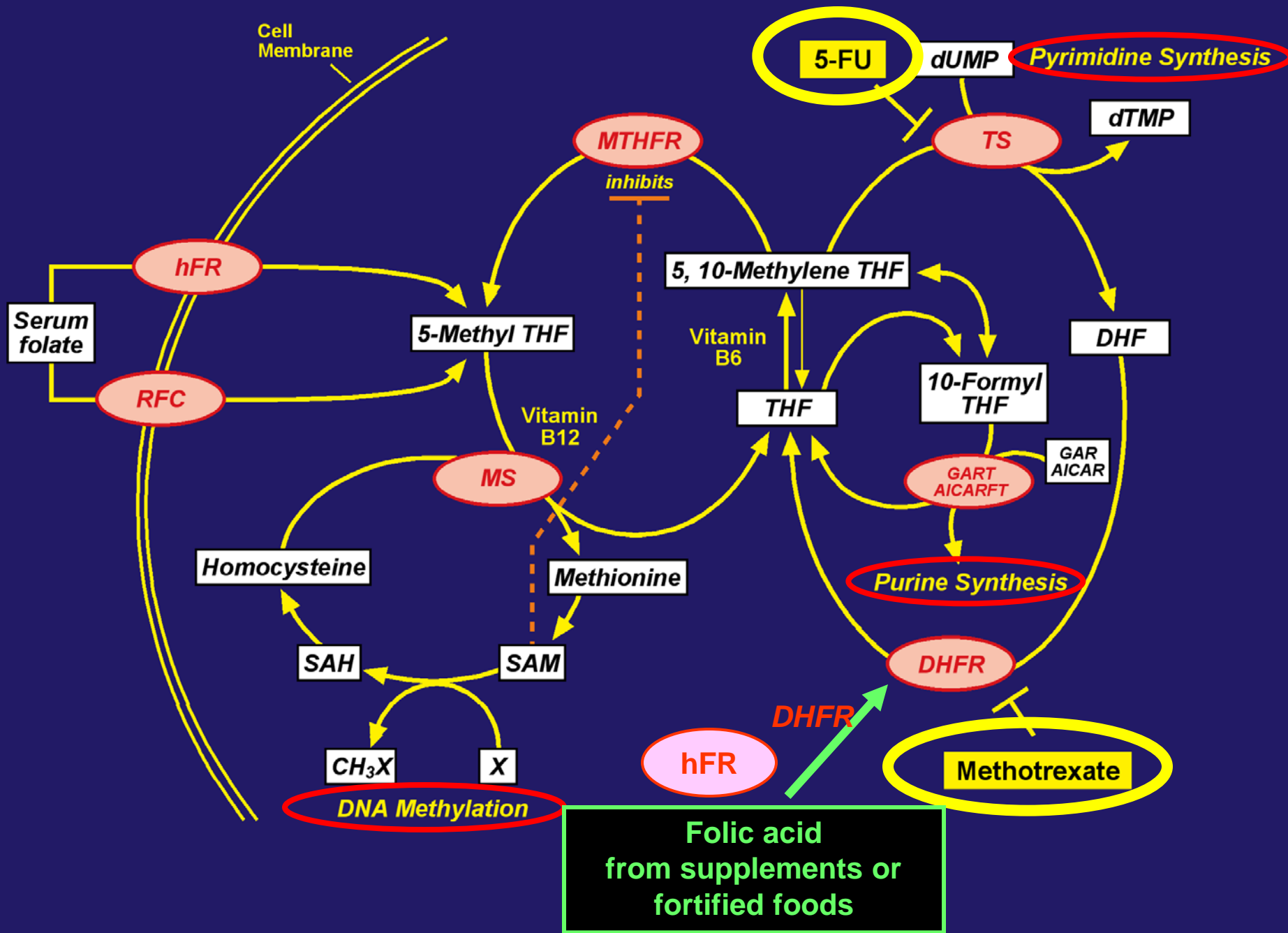
- Review of 32 studies addressing vitamin and mineral supplement use among US adult cancer patients:
 - 64-81% any vitamin or mineral supplements
 - 14%-32% of survivors initiate supplement use after diagnosis
 - Physicians commonly unaware of use

Increase in use of folic-acid containing supplements with diagnosis, Colon CCFR patients, n=971



Velicer & Ulrich. *JCO*. 2008; 26(4): 665-73.

Folate-mediated one-carbon metabolism



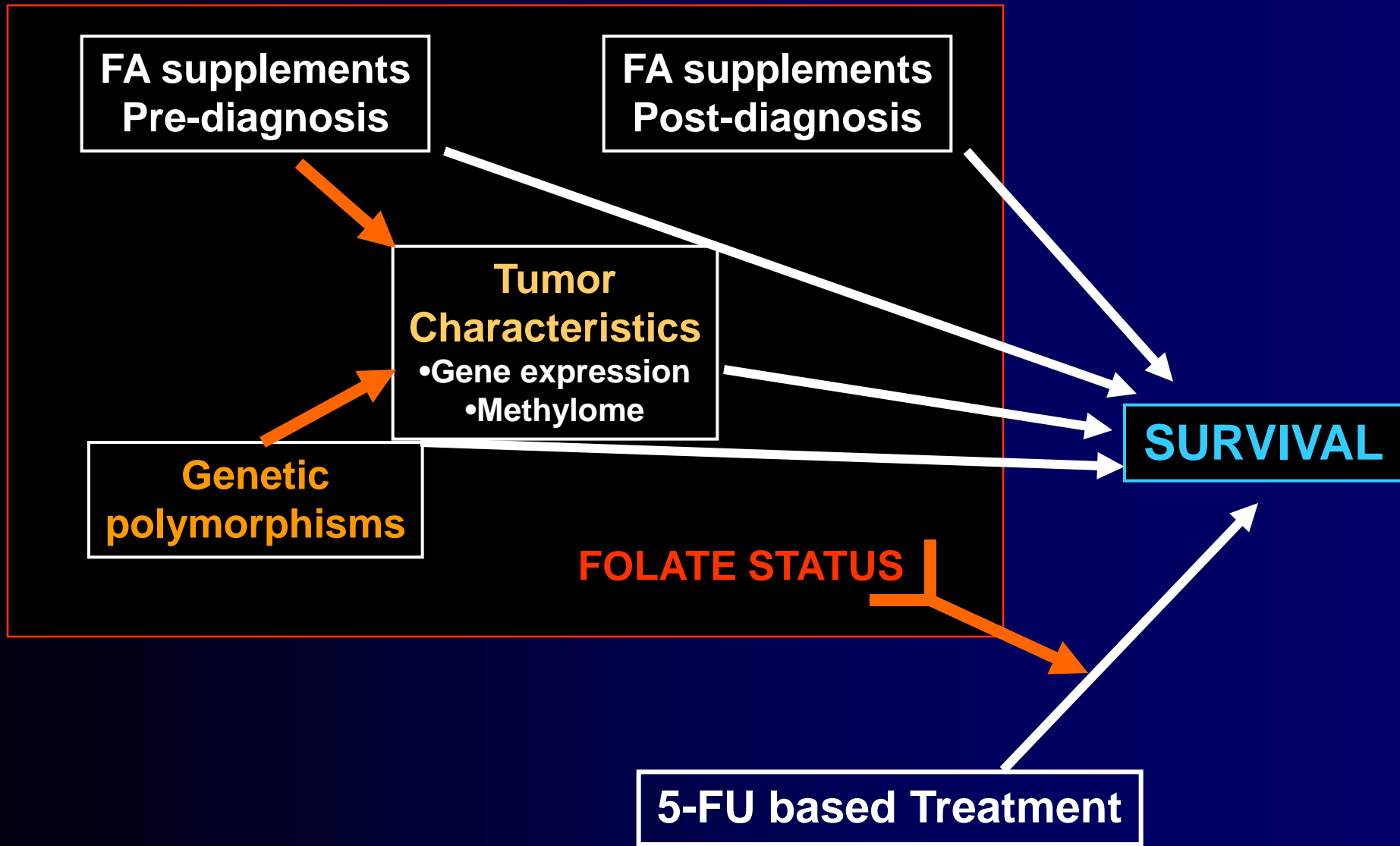
Can folate's role in providing nucleotides be harmful?

- Tumors have greater folate and nucleotide requirements to support their growth:
 - Antifolates are used in cancer chemotherapy
 - Tumors frequently upregulate folate receptors
- High folate intakes in rodents with early neoplastic lesions foster tumor growth (Kim 1996, Song 2000, Song 2000, Leu 2000)
- Aspirin/Folate Polyp Prevention Trial shows increased risk of advanced and multiple adenoma with folic acid administration (Cole 2007, Ulrich 2007)

Unanswered questions - folic acid in cancer patients

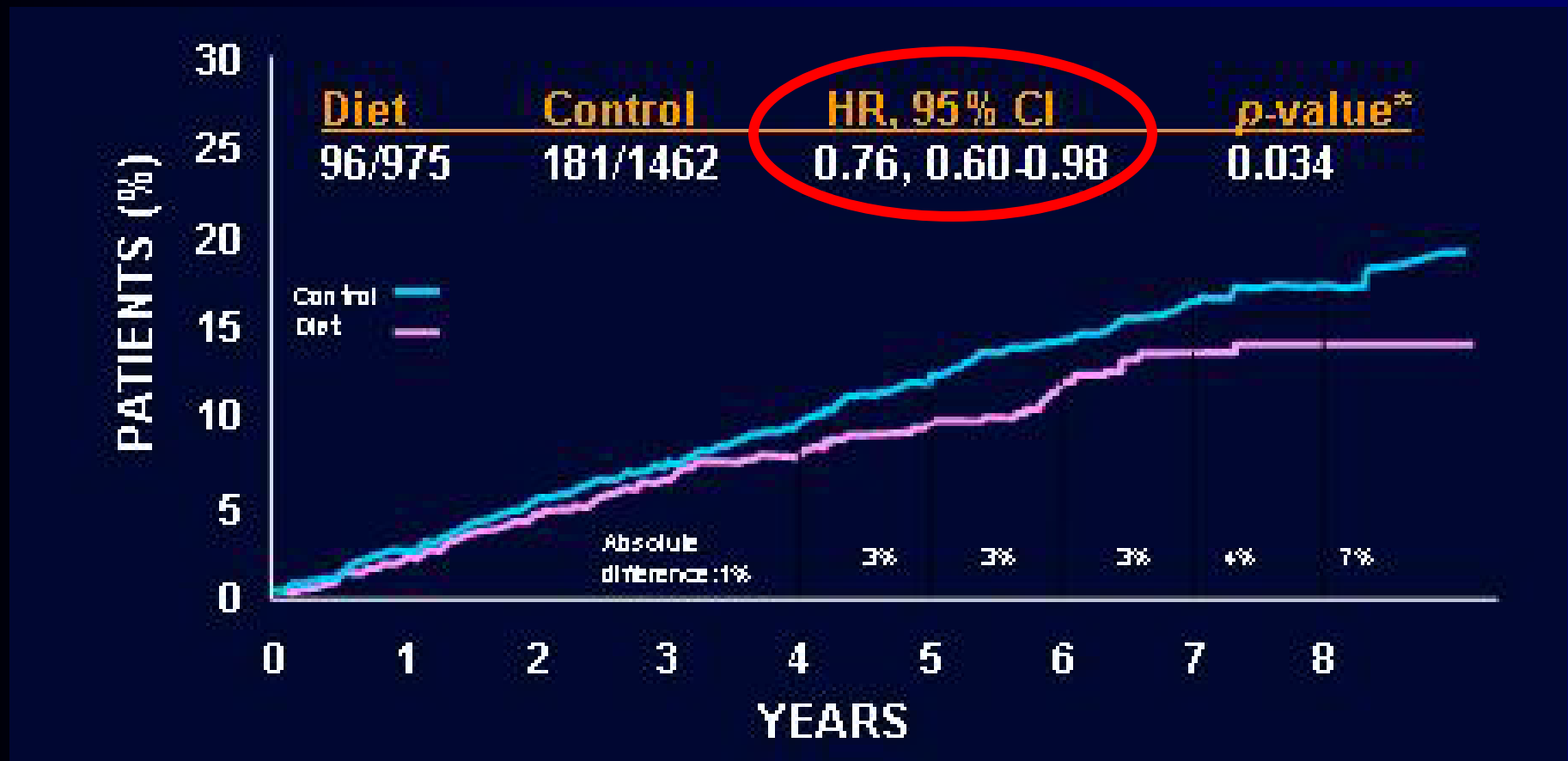
- Do tumors differ depending on folic acid supplementation?
 - Differences in folate receptors, or gene expression? → altering treatment efficacy?
- Do treatment effects (5-FU, MTX) differ with folic acid supplementation?
- Are there gene-diet interactions in determining response?
- Does growth of micrometastases and risk of recurrence differ with folic acid supplementation?

Folate status and colon cancer prognosis -- a paradigm for transdisciplinary research



Women's Intervention Nutrition Study (WINS) Trial

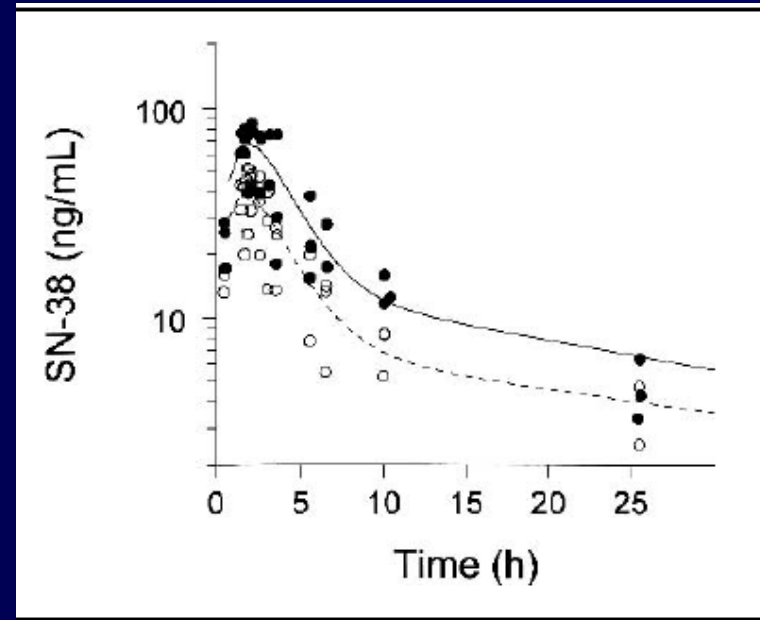
- * n=2437 women with resected early stage breast cancer
- * low-fat diet intervention reduces relapse events



→ Major improvement (42%) in relapse-free survival with low-fat diet among ER- patients

Herbal drugs can affect chemotherapeutic pharmacokinetics

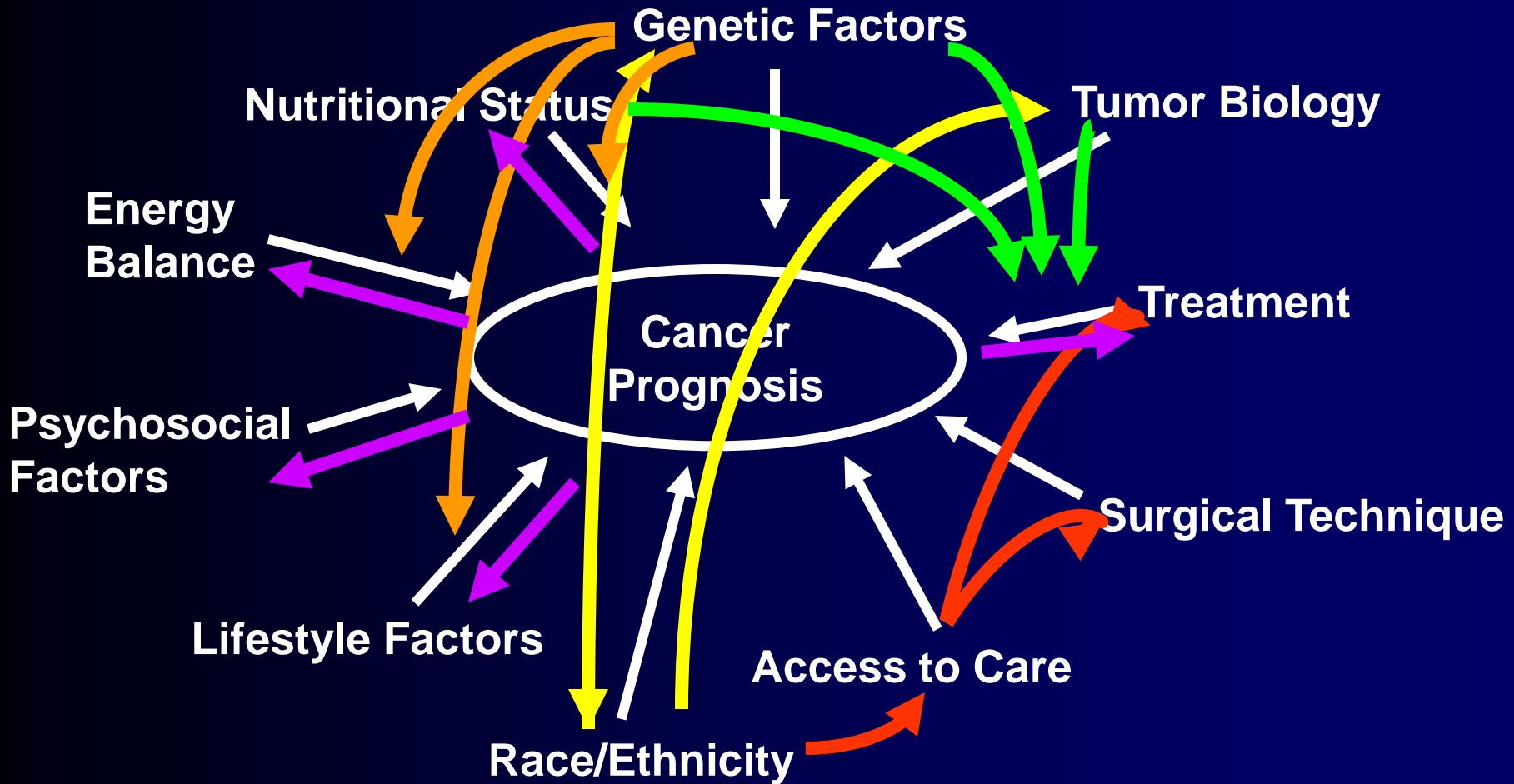
- St. John's wort:
 - Widely used herbal supplement for mild forms of depression
 - Can induce the expression of CYP3A4
- Irinotecan is eliminated via CYP3A4 and has a narrow therapeutic range
- St. John's wort for 18 days significantly reduced plasma levels of SN-38 and drug efficacy



Markowitz JS et al. *JAMA*. 2003; 290 (11): 1519-20.

Mathijssen R et al. *JNCI*. 2002; 94(16): 1247-9. Reprinted by permission of Oxford University Press.

Cancer prognosis - a multifactorial outcome



What research designs are needed?

- Cancer patients change health behaviors after their diagnosis & during treatment
- Assessments prior to diagnosis are inadequate to draw conclusions
- Randomized trials are not appropriate when harm is a possibility
- Potential for confounding in observational cohorts

→ What is needed?

- Both observational patient cohorts, with exposure assessment at diagnosis and afterwards at defined intervals
- Randomized trials where possible

Clinical trial vs prospective patient cohort

Clinical Trial

- Select population & treatment
- Uniform treatment
- Excellent outcome assessment
- Limited assessment of health behaviors
- Multicenter (many)
- Logistic challenges?
 - Many sites, COG setting

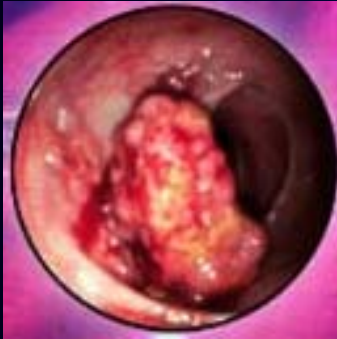
Population-based patient cohort

- General population & real-world Tx
- Heterogenous Tx
- Variable outcome assessment
- Excellent assessment of health behaviors
- Single or multicenter
- Logistic challenges?
 - HIPAA regulations
 - Multiple hospitals

New patient cohorts can “get it right”

- Collect data and biospecimens in a **high-quality, standardized** manner
- Obtain ***all*** transdisciplinary pieces of information
 - Health behaviors and epidemiologic data
 - Clinical exposures & outcomes
 - Biospecimens (tumor, blood, urine, stool...)
- Get data and specimens **repeatedly at critical time intervals**
 - What happens after diagnosis and during treatment?
 - Understudied and not feasible in existing cohorts

ColoCare Study Design



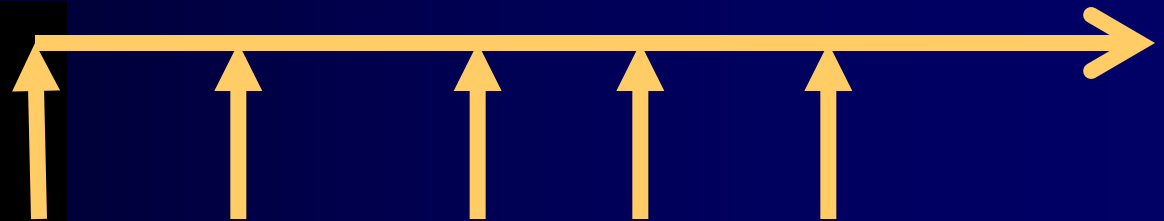
Treatment
Information

Outcomes:

- Treatment toxicity
- Survival
- Recurrence

Diagnosis

- Tumor & normal tissue
- Pre-surgery blood
- Urine collection
- Stool collection
- Questionnaires



3m

6m

12m

24m

Symptoms

- Blood draws
- Urine/Stool collection
- Questionnaires on current health habits