University of California, Irvine and Children's Hospital of Orange County

Chao Family Comprehensive Cancer Center

An NCI-designated Comprehensive Cancer Center

Adolescent and Young Adult Cancers and the Ethical Challenges of Care

Leonard Sender, MD

Director of Adolescent and Young Adult Cancer Program

CHOC® CANCER INSTITUTE

UCI School of Medicine

Association for Ethics in Spine Surgery

Symposium

Ethics: "The Role of Industry and Academia"

June 28th 2008

Cancer in the USA

- **1.4 million Americans are predicted to be diagnosed in 2008 with cancer**

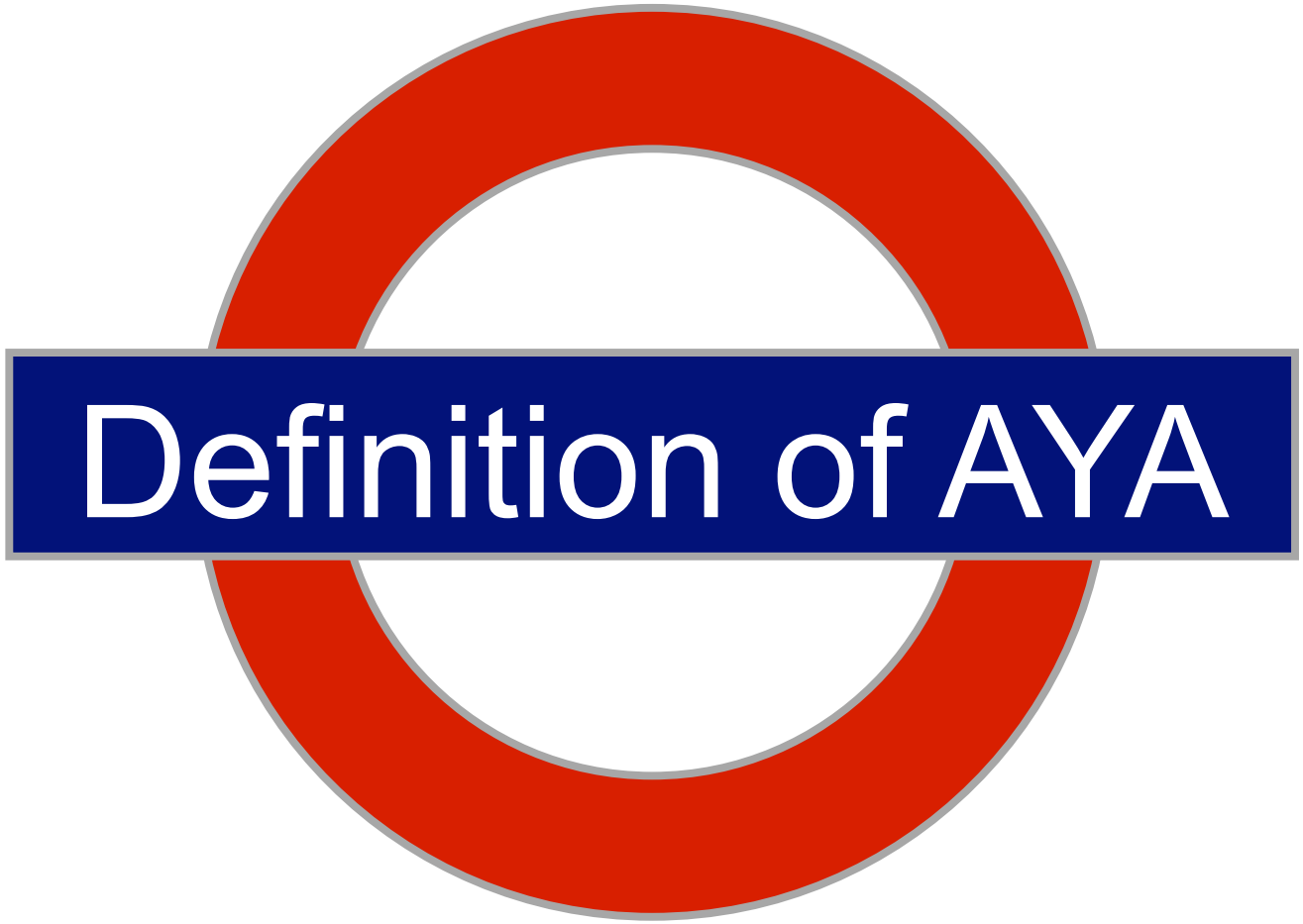
Old Thinking

Pediatric Oncology and Adult Oncology

New Thinking

Pediatric, **Adolescent and Young Adult** , Adult, and **Geriatric Cancer**

Adolescents and Young Adults with Cancer



Definition of AYA

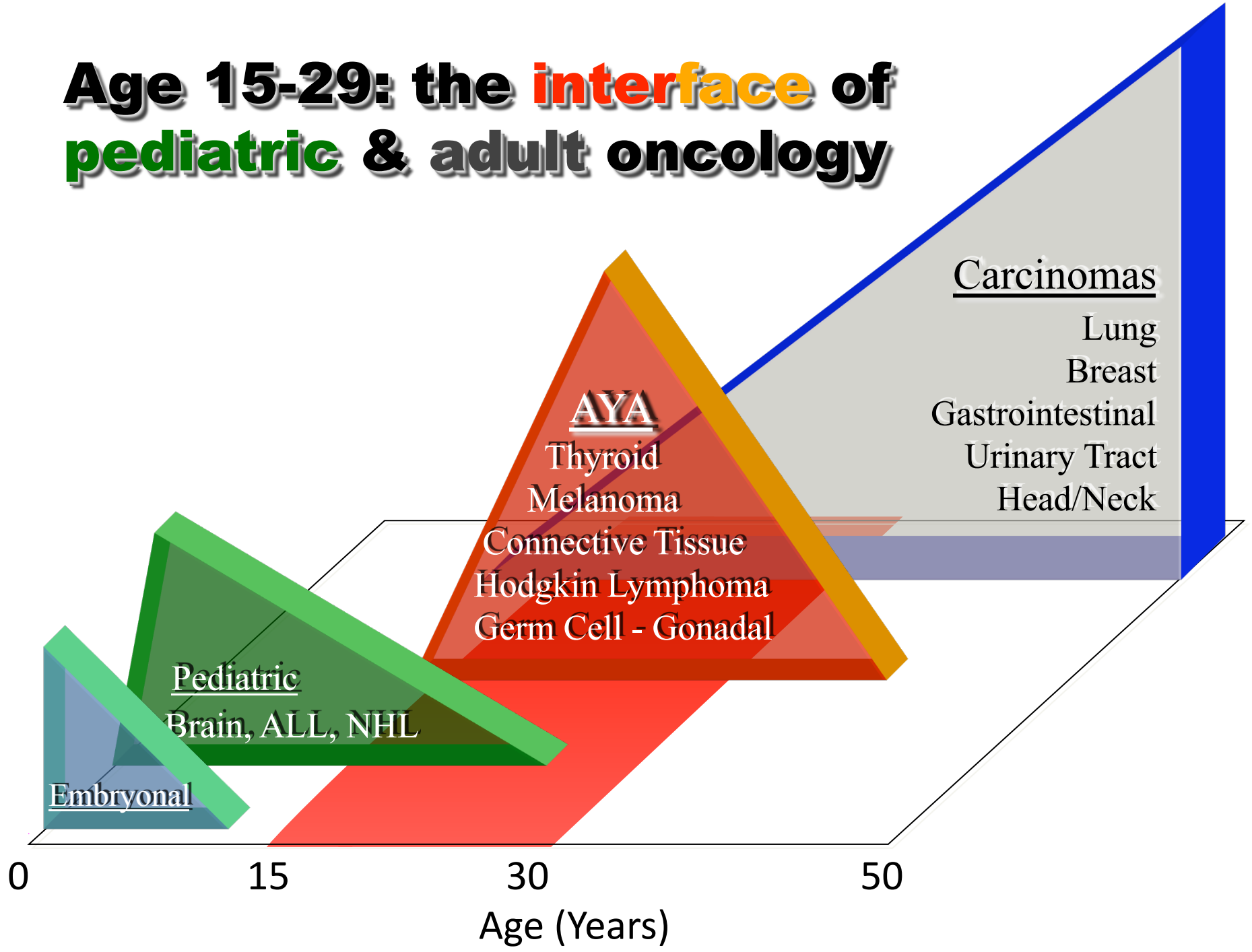
As defined by the NCI AYA Program Review Group 2006

Cancer patients between

15 and 39 years of age

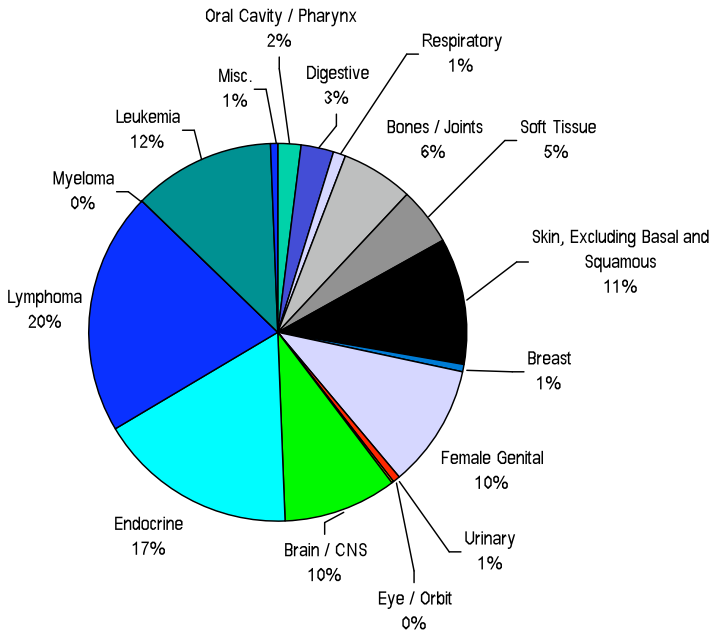
Adolescents and Young Adults with Cancer

Age 15-29: the interface of pediatric & adult oncology

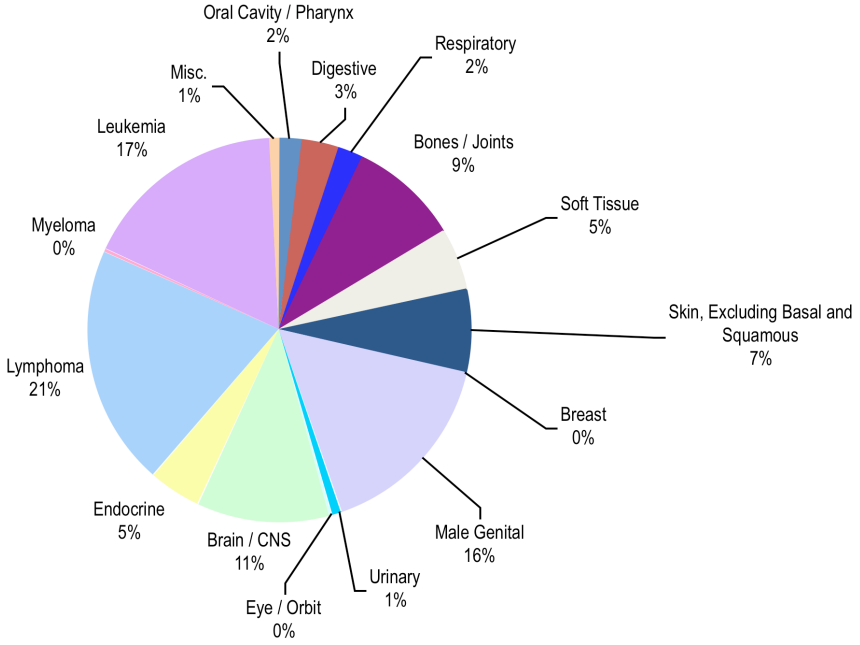


Cancer in Persons 15-19 Years Old

CA Cancer Registry, 1988-2004



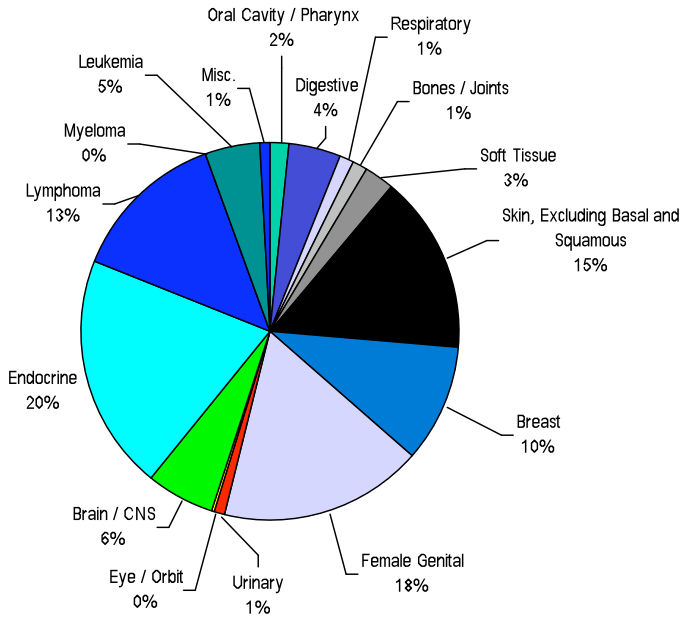
Females



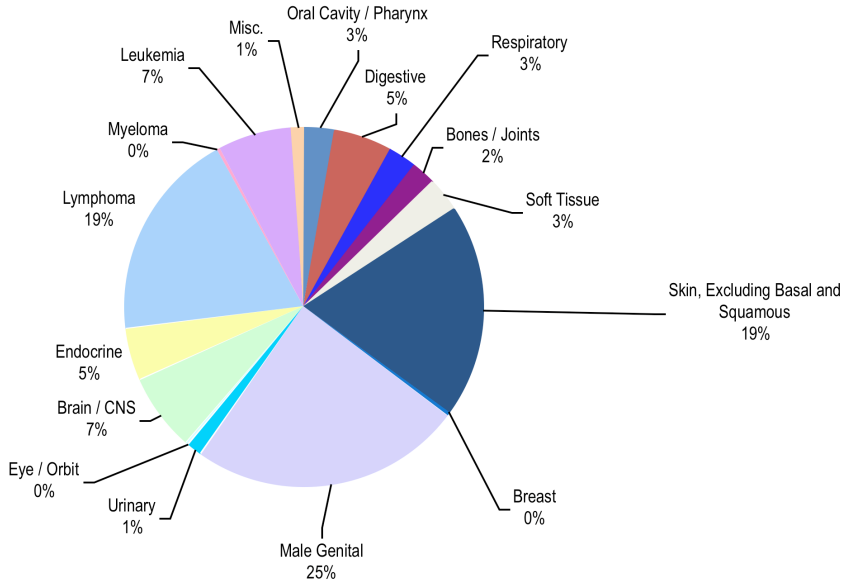
Males

Cancer in Persons 20-29 Years Old

CA Cancer Registry, 1988-2004



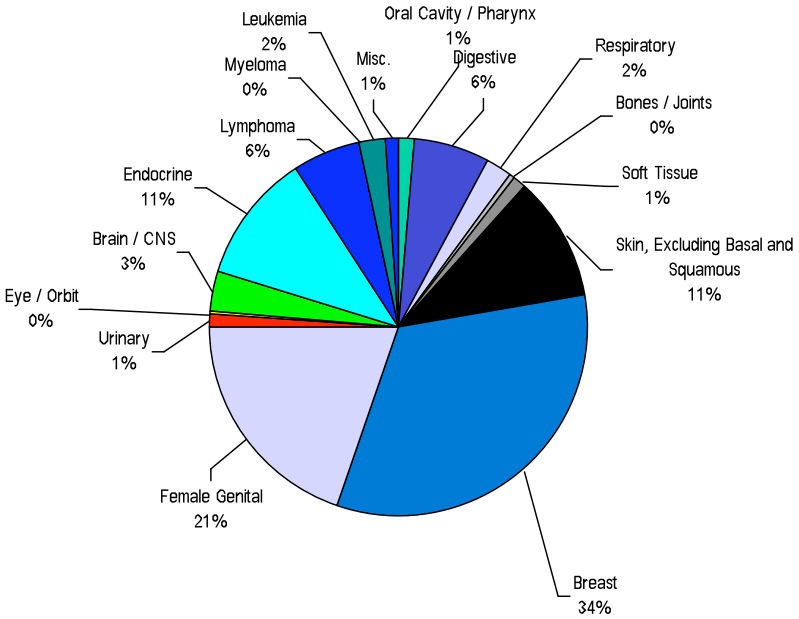
Females



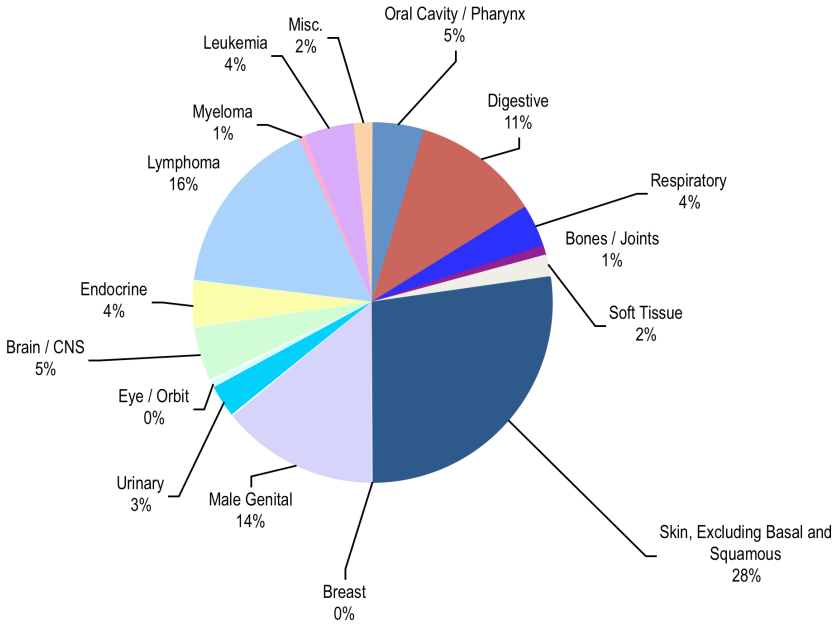
Males

Cancer in Persons 30-39 Years Old

CA Cancer Registry, 1988-2004



Females

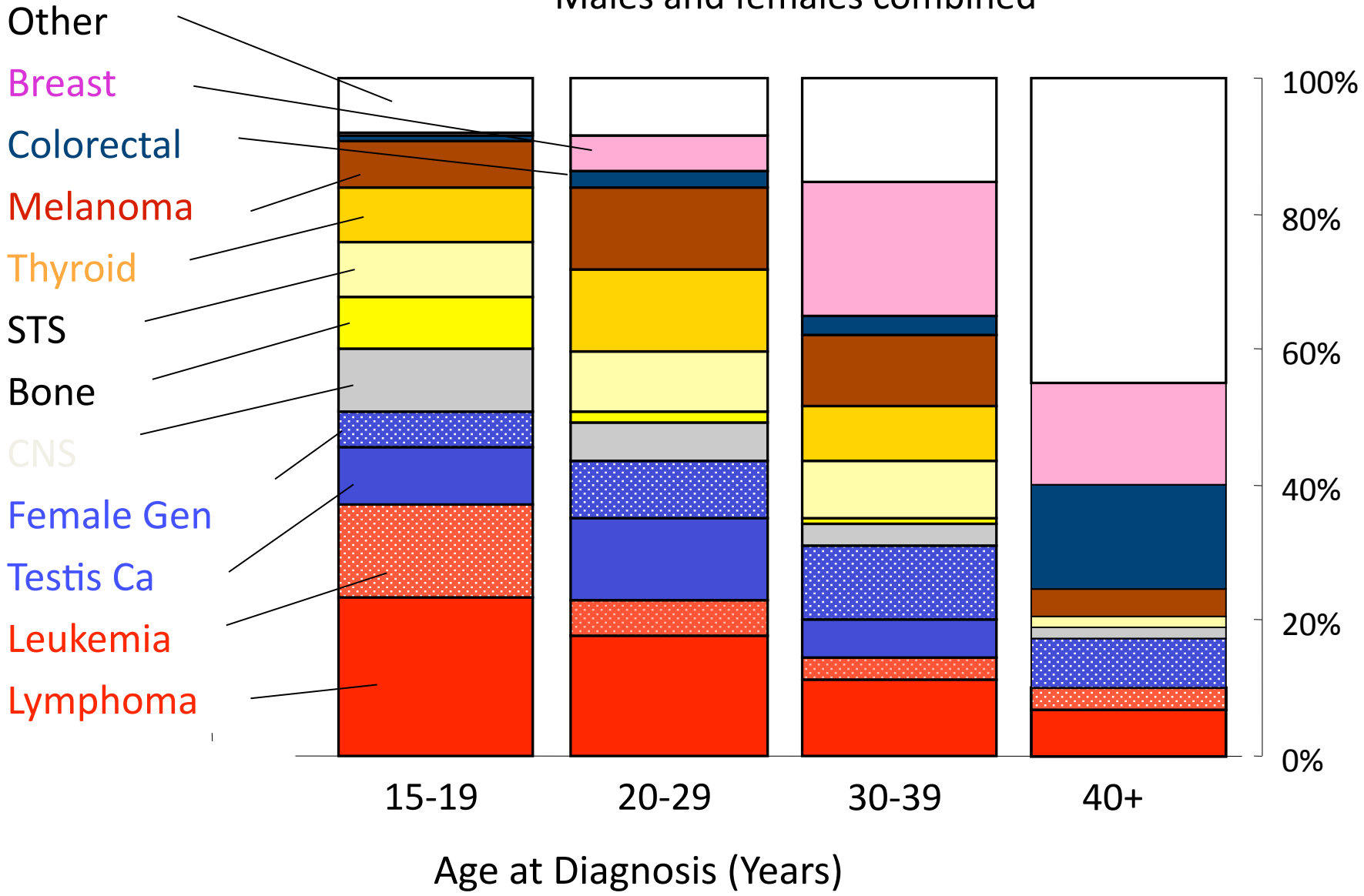


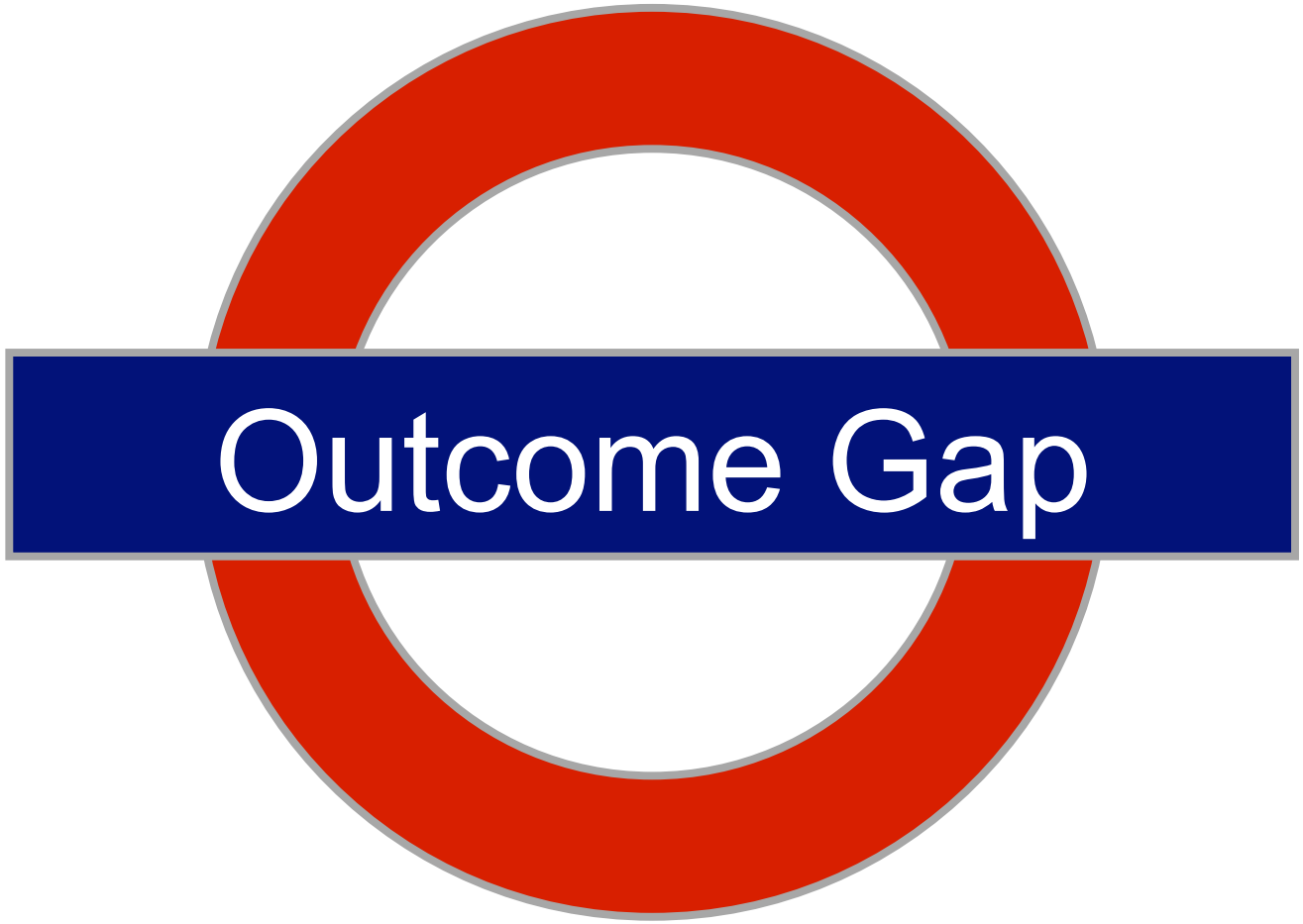
Males

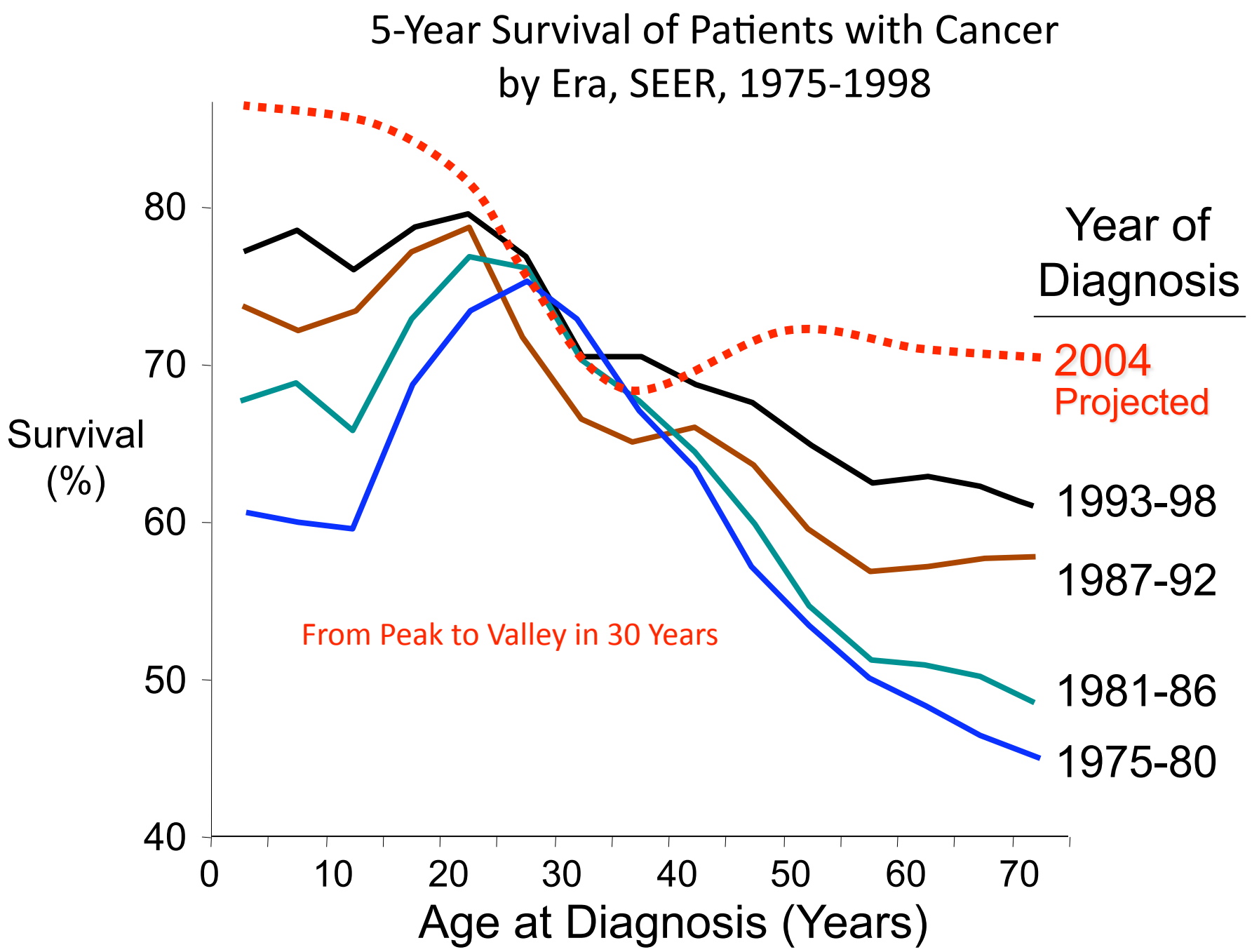
Relative Incidence of Types of Cancer by Age

Age 15+, U.S. SEER, 1992-2002

Males and females combined




Outcome Gap

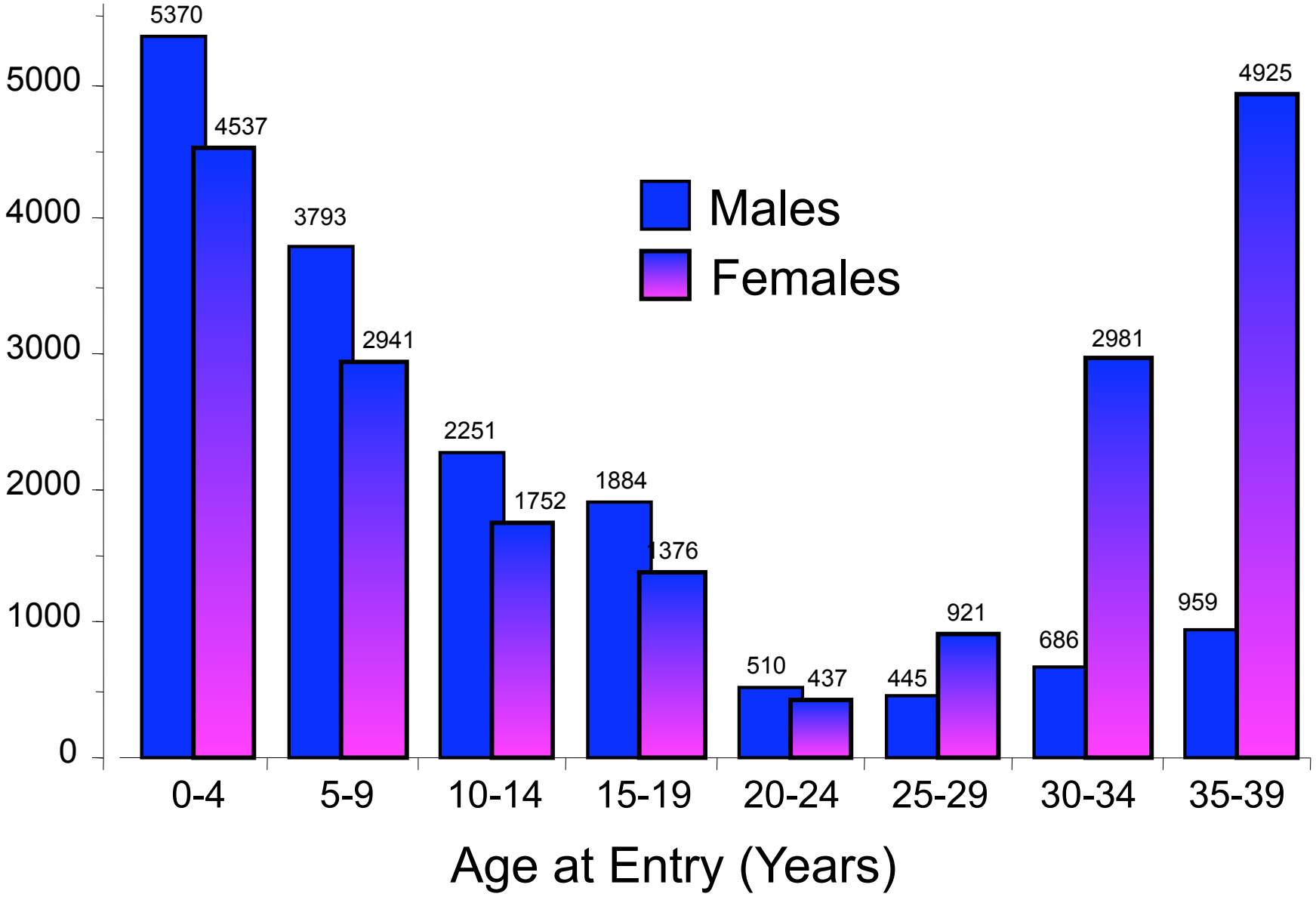

5-Year Survival of Patients with Cancer
by Era, SEER, 1975-1998
Survival
(%)
80
70
60
50
40
0
10
20
30
40
50
60
70
Age at Diagnosis (Years)
Year of
Diagnosis
2004
Projected
1993-98
1987-92
1981-86
1975-80
From Peak to Valley in 30 Years

Adolescents and Young Adults with Cancer

London Underground Station

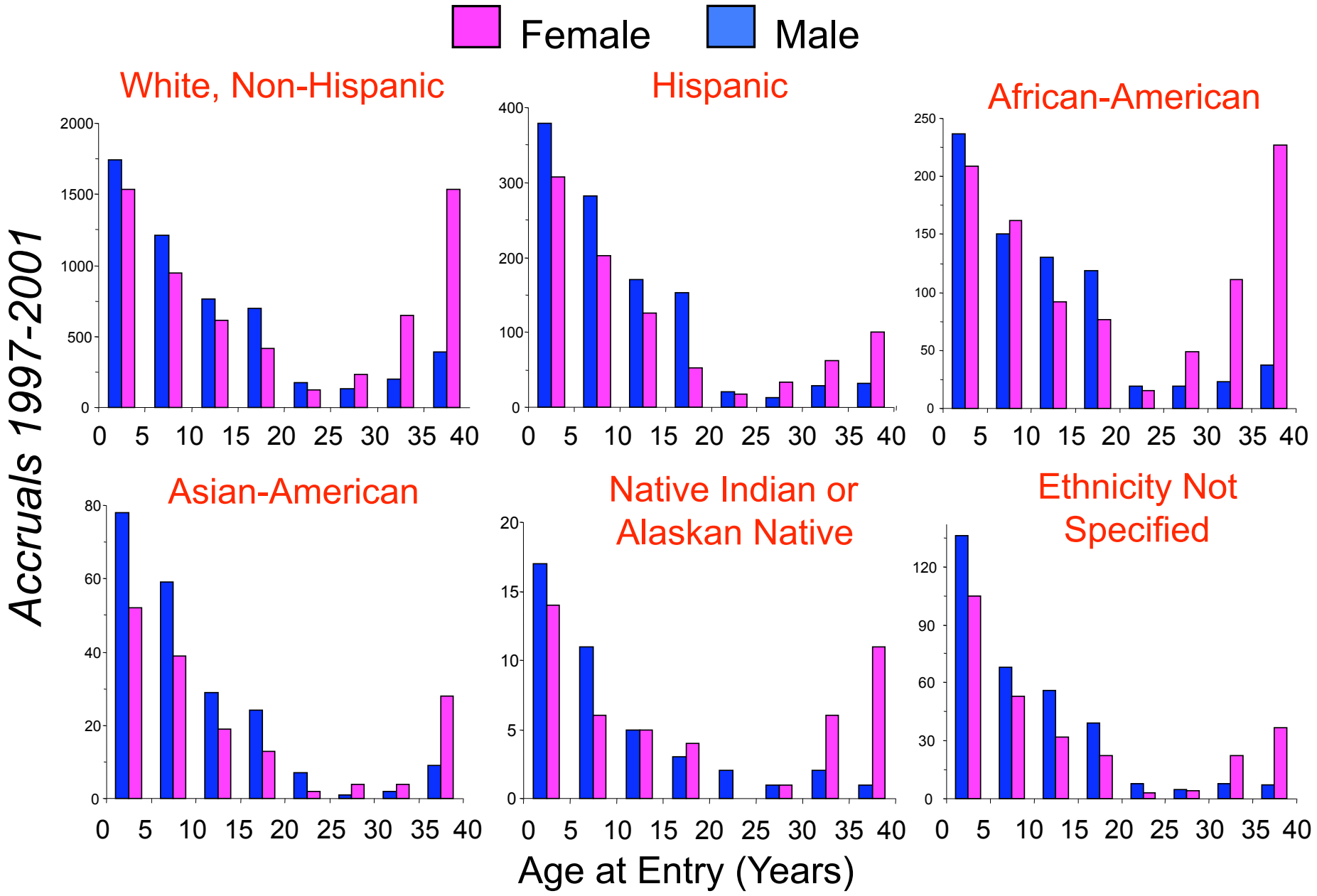
Data Courtesy M Montello, T Budd, CTEP, NCI

National Treatment Trial Accruals, 1990-1998



National Clinical Trial Accruals, 1997-2001

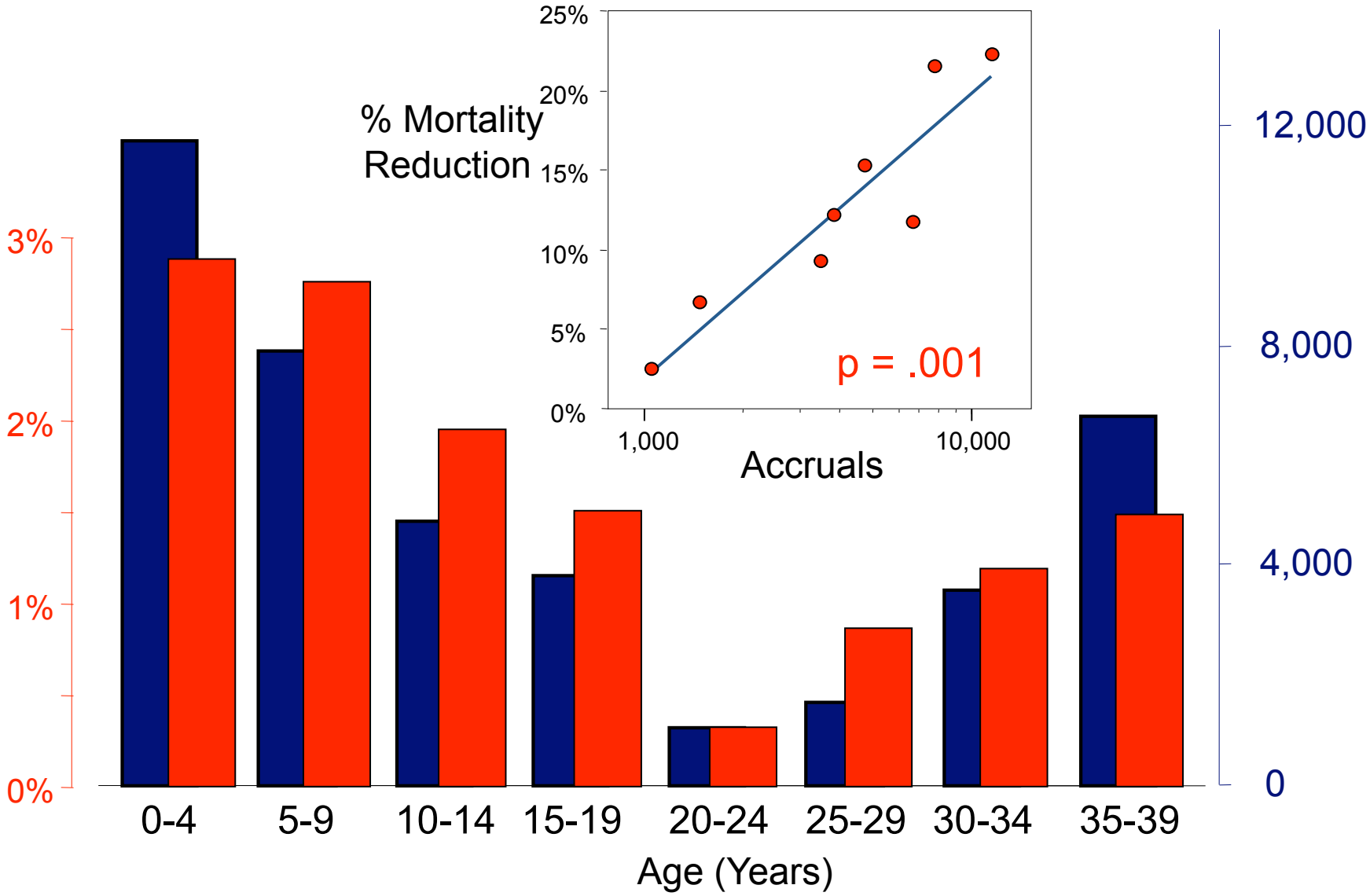
Bleyer A, Budd T, Montello M: POGO News, Fall 2002, pp. 8-11




Outcome Improvement vs.
Clinical Trial Participation

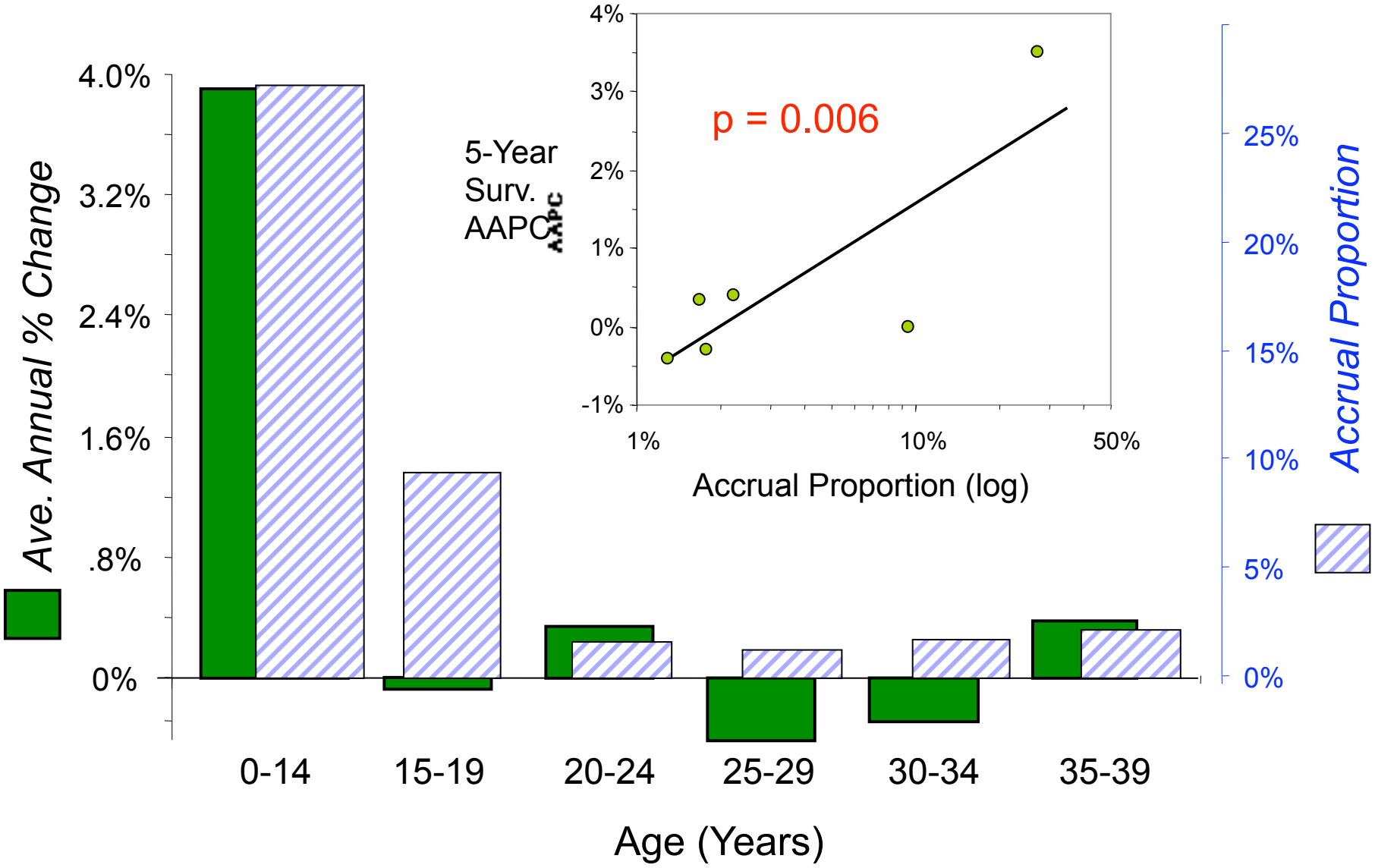
National Treatment Trial Accruals, 1990-1998

National Cancer Mortality Reduction, 1990-1998



Change in SEER 5-Year Survival from 1985-1992

vs. Accrual Proportion on National Treatment Trials, 1990-98



Clinical Cases

Highlights of two different cases

MELANOMA

OSTEOGENIC SARCOMA
(OSTEOSARCOMA)


Melanoma

MELANOMA

- 17 year old with Stage IV disease with liver metastasis
- Not eligible for clinical trials because he is younger than 18 years old
- Requested compassionate approval, to date not received
- So he waits….tumor grows
- Median survival is 8 months for Stage IV Melanoma

MELANOMA

- So I ask, what are the ethics of not having studies for patients less than 18

We need the FDA and Academic community to demand that young melanoma patient have equal access to care -- remember 10% of the adolescent and young adults (between 15-21 years old) with cancer have melanoma

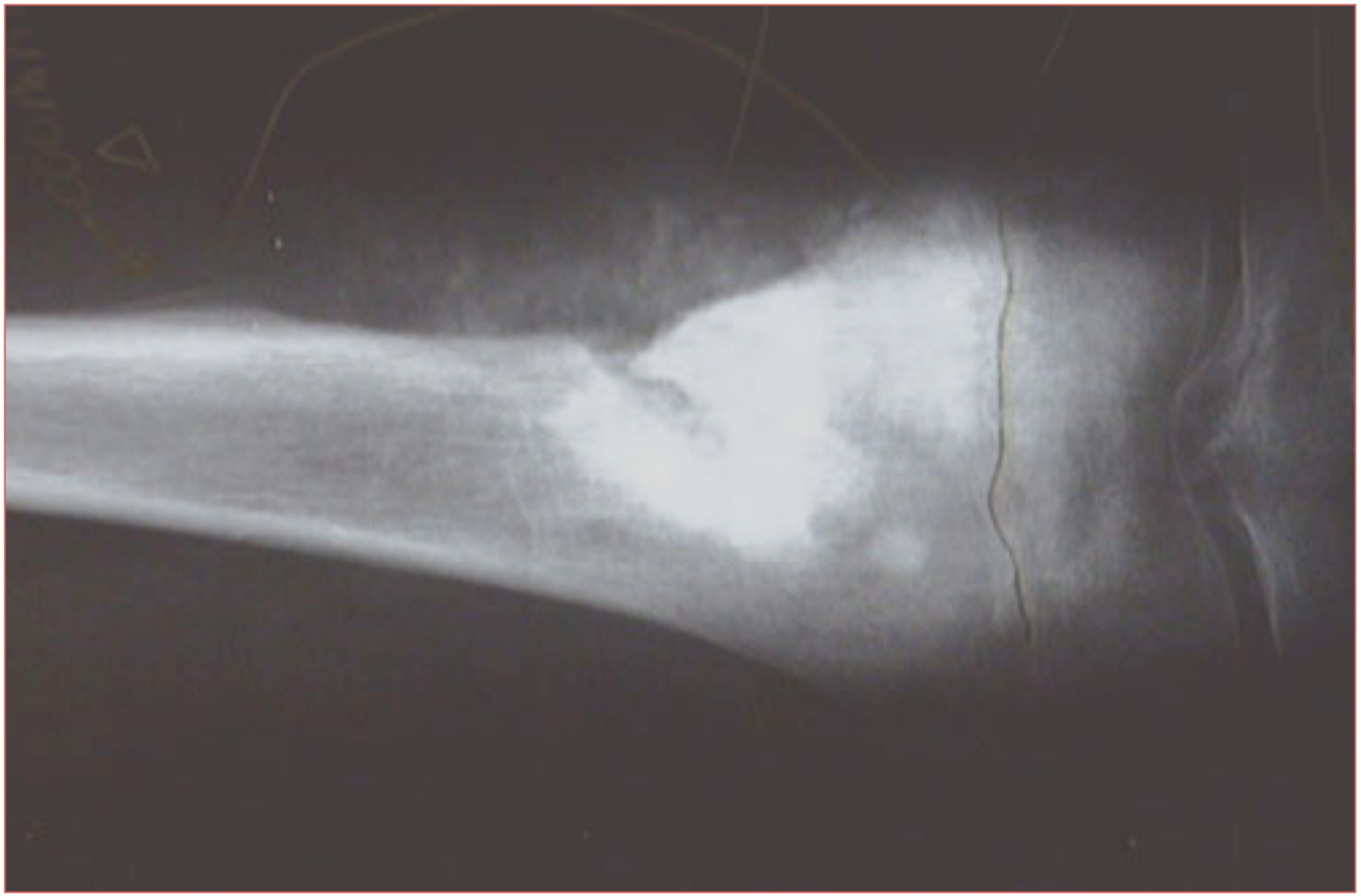

Osteosarcoma

OSTEOSARCOMA

Incidence

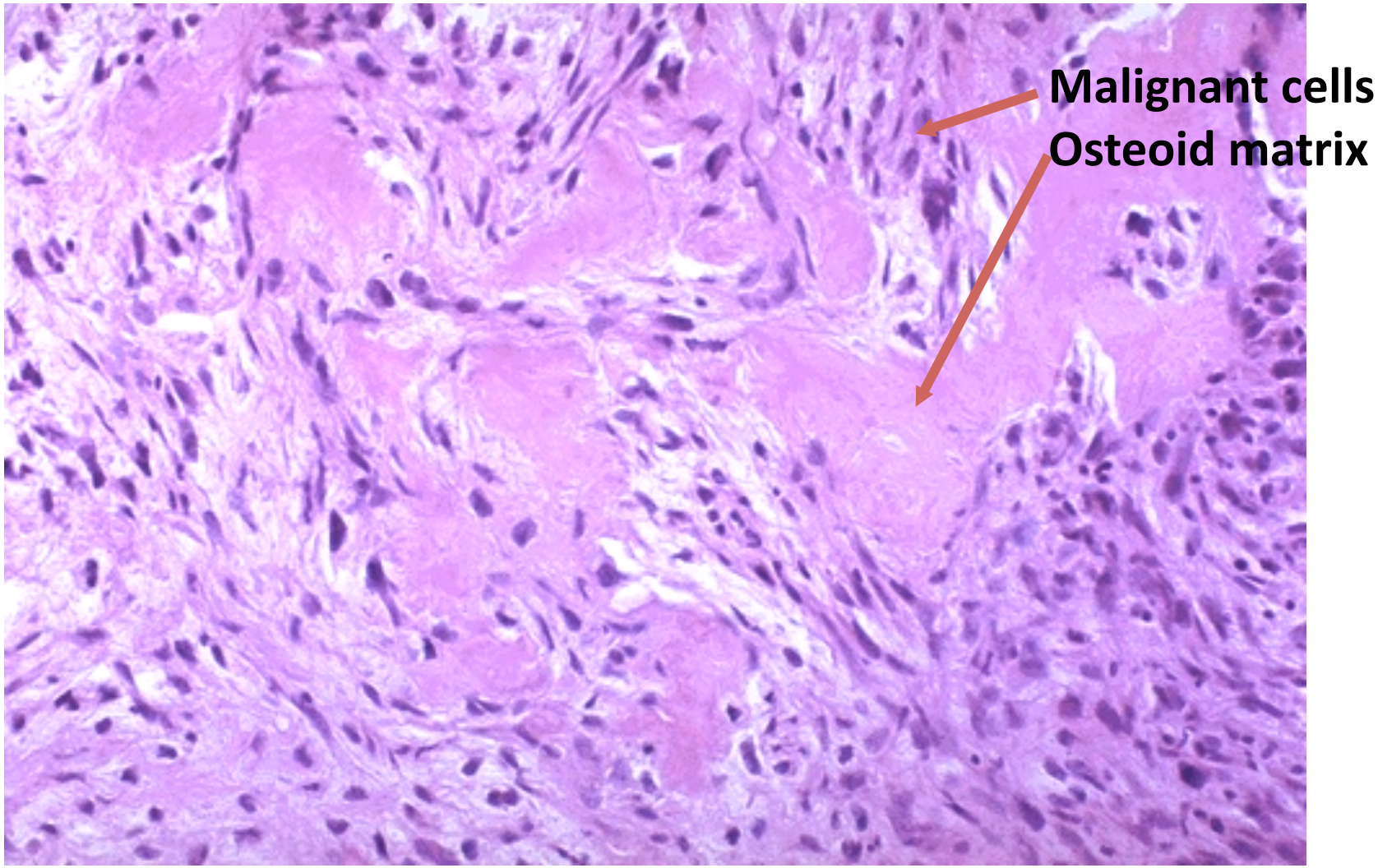
- The third most common cancer in adolescence, occurring less frequently than only lymphoma and brain tumors
- Accounts for 60% of malignant bone tumors during the first two decades of life
- Approximately 150 new cases each year in children under 15 and 400 cases in children and adolescents under 20

OSTEOSARCOMA – Radiograph



OSTEOSARCOMA – Gross

OSTEOSARSOMA - Microscopy



OSTEOSARCOMA

- In the 1980's controversy existed whether adjuvant chemotherapy was beneficial

- Then a "break-though" study showed benefit

Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. *N Engl J Med* 314:1600-6, 1986

OSTEOSARCOMA

- Randomized controlled trial
- **N=36** patients
- Two-year actuarial relapse-free survival was **17 percent in the control group** (similar to that found in studies before 1970) and **66 percent in the adjuvant-chemotherapy group** ($p < 0.001$)

OSTEOSARCOMA

- Now we now have a new controversy regarding the role of an adjunct to conventional chemotherapy

OSTEOSARCOMA RESEARCH 2005

VOLUME 23 · NUMBER 9 · MARCH 20 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin, and High-Dose Methotrexate

Paul A. Meyers, Cindy L. Schwartz, Mark Krailo, Eugenie S. Kleinerman, Donna Betcher, Mark L. Bernstein, Ernest Conrad, William Ferguson, Mark Gebhardt, Allen M. Goorin, Michael B. Harris, John Healey, Andrew Huvos, Michael Link, Joseph Montebello, Helen Nadel, Michael Nieder, Judith Sato, Gene Siegal, Michael Weiner, Robert Wells, Lester Wold, Richard Womer, and Holcombe Grier

OSTEOSARCOMA RESEARCH 2005

- In 2005 Meyers et al showed that there was a significant interaction with ifosfamide, but this had no significant impact on event free survival (EFS)

OSTEOSARCOMA RESEARCH 2008

VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Osteosarcoma: The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival—A Report From the Children's Oncology Group

Paul A. Meyers, Cindy L. Schwartz, Mark D. Krailo, John H. Healey, Mark L. Bernstein, Donna Betcher, William S. Ferguson, Mark C. Gebhardt, Allen M. Goorin, Michael Harris, Eugenie Kleinerman, Michael P. Link, Helen Nadel, Michael Nieder, Gene P. Siegal, Michael A. Weiner, Robert J. Wells, Richard B. Womer, and Holcombe E. Grier

OSTEOSARCOMA RESEARCH 2008

- In 2008 Meyers et al and the Children's Oncology Group reported on largest ever completed randomized trial in osteosarcoma (INT0133)
- N=662 localized, resectable osteosarcoma, randomly assigned to high-dose methotrexate, cisplatin, and doxorubicin plus ifosfamide in a 2 x 2 factorial design with a randomization to muramyl tripeptide ethanolamine (MTP), an immune modulator
- Liposomal MTP was shown to improve the overall survival for patients with this disease
- The addition of ifosfamide neither enhanced EFS nor overall survival

OSTEOSARCOMA

- But life gets complicated…
- In the 2008 study, cisplatin was omitted from preoperative chemotherapy in the ifosfamide-containing arm
- So it is difficult to evaluate its role as compared to previous studies

OSTEOSARCOMA

- In 2008 Meyers et al only reported a trend for better EFS (P =.08) and improved overall survival (P =.03) for the MTP arm.
- The previously observed interaction was no longer apparent
- The 2008 paper did not prove statistically that there was interaction, and therefore an improved EFS, and thus no efficacy of MTP, at least in this combination
- In letters to JCO some authors state, and I agree, that "decisions with such wide-ranging implications should never be based on a single trial"

“ACADEMIC DETAILING”

- The pharmaceutical industry wants the FDA to approve the drug (MTP), but the data is not convincing
- There is a lot of pressure to approve MTP because it has been the only new drug for osteosarcoma in the last 10 years

“ACADEMIC DETAILING”

- What is our ethical duty to patients?
- What do we know about the authors? Do they have a stake in the company? Do they speak for the company? Does their institution benefit from the study and having the drug approved? The answer is we don’t know and we ought to
- I call this “academic detailing” and it should counteract what the pharmaceutical industry calls “medical detailing”


Research Ethics

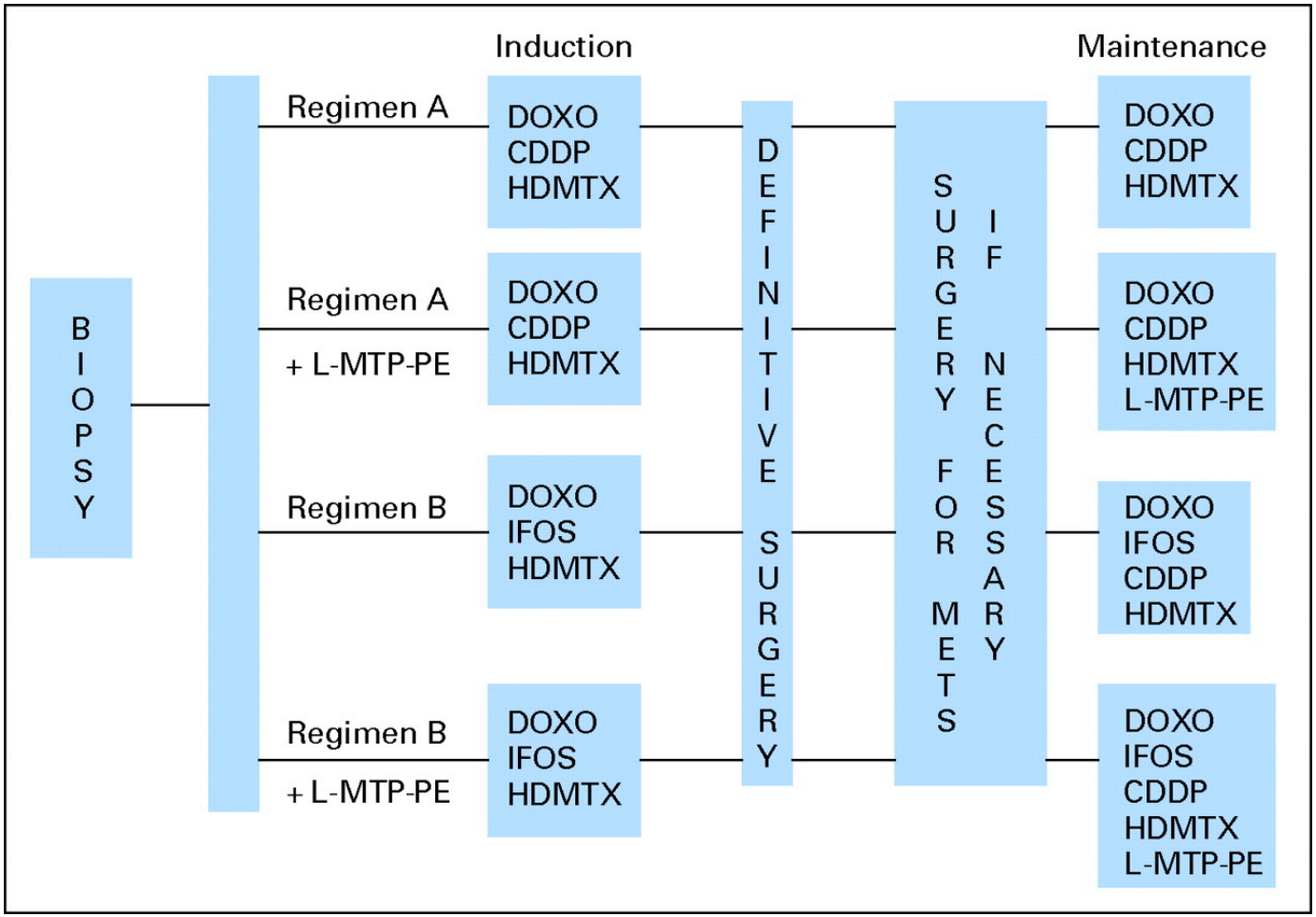
RESEARCH ETHICS – Pediatric and Adolescent Cancer Patients

- Approximately 60% of all pediatric cancer patients are enrolled on clinical trials
- However up to 80% of patients will go on a trial if offered
- Nearly all parents give consent, but can we say that “true consent” was given?

RESEARCH ETHICS – Informed Consent

- There are a number of factors that influence the informed consent process
- Capacity to understand
- Use of complex language (e.g. “limb salvage,” “randomization,” “necrosis,” “chemotherapy responsiveness”)
- Obtaining assent
- Distinguishing between treatment/doctor and research/investigator
- Voluntariness

Fig A1. Protocol road map



Meyers, P. A. et al. J Clin Oncol; 26:633-638 2008

RESEARCH ETHICS – Informed Consent

- Principle of Distributive Justice means neither an unfair burden nor an unfair exclusion from the potential benefits of research
- Those not competent to consent, shall not automatically be excluded from research that is potentially beneficial to themselves as individuals, or the group they represent
- So all this being said what do we know about the AYA population?

RESEARCH ETHICS – Access to Studies

Types of Protocols

- When treated according to a pediatric protocol, an acute lymphocytic leukemia patient (16-29 years) has a 70% 5 year survival
- If treated according to an adult protocol, that same patient has a 38% 5 year survival

Enrollment to Protocols

- There were no ALL patients (21-29 years) treated on protocol at UC hospitals in the last 10 years -- in fact, most patients of this age in the country were not on study
- There were only 8 patients with melanoma under the age of 30 who were treated on study in the U.S. in the last 5 years

RESEARCH ETHICS

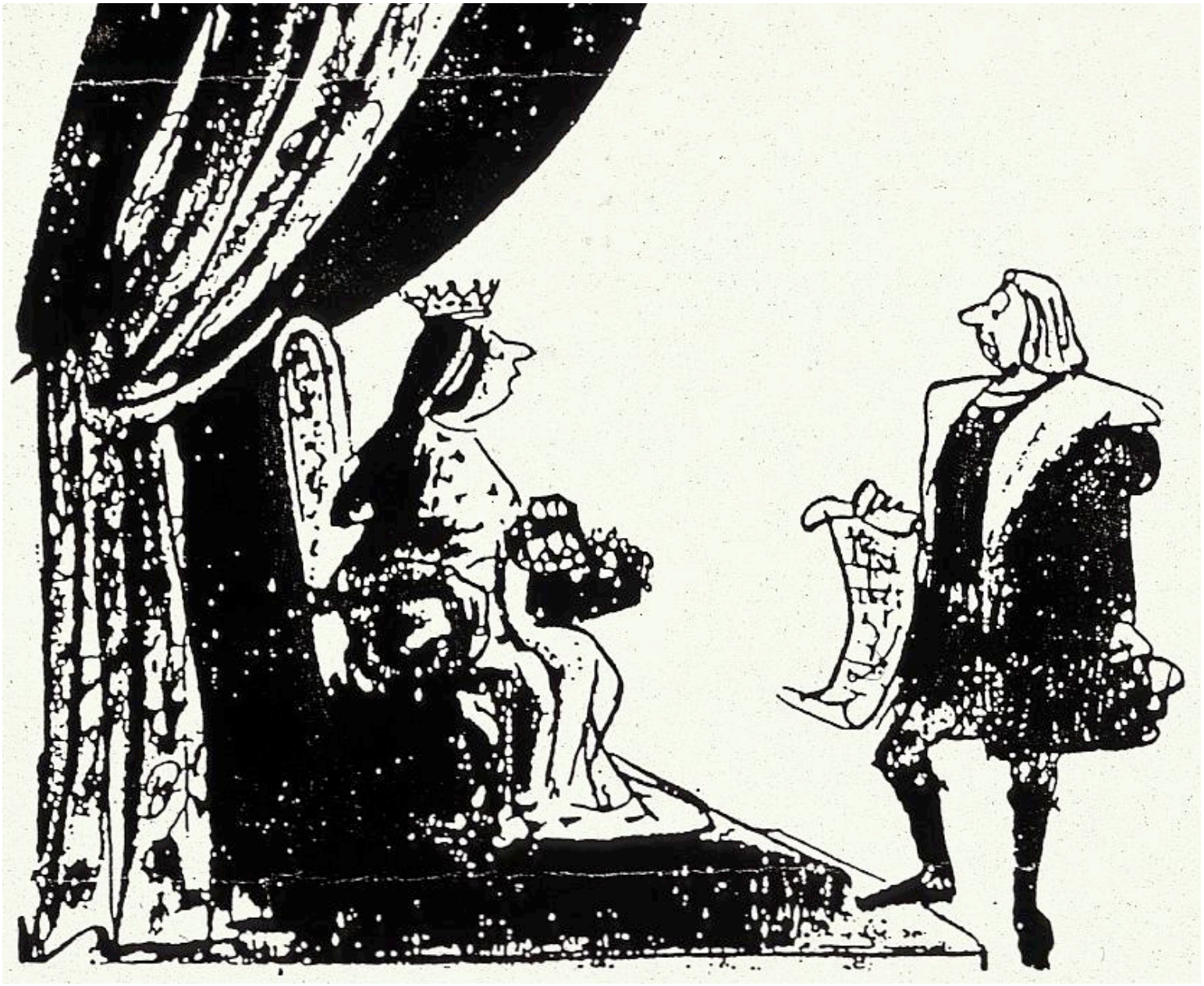
- So why is this discrepancy? My hypothesis is that academics has experienced an ethical lapse
- Excuses I have heard:
  - The disease or condition is too rare
  - It is too expensive to keep low-accruing protocols open
  - There are bigger fish to fry -- old men with prostates
  - Not an academic mission of the institution

RESEARCH ETHICS

- So lets quickly recall the Mission of the School of Medicine at UC Irvine…
  - Clinical Care
  - Education
  - Research

IN CLOSING

- Let's do the ethical thing and start changing how we interact with pharmaceutical companies; start academic detailing; and put our money where our mouth is and do the right thing
- UC Irvine is one of the few institutions that is developing an Young Adult Cancer Program to improve access to health care and increase cure and meaningful survival
- And this takes money and commitment



“Three ships is a lot of ships.
Why can’t you prove the world is round with one ship?”

Adolescent and Young Adult Cancer Bill of Rights

Advocacy

www.SeventyK.org

Adolescent and Young Adult Cancer Bill of Rights

We are neither pediatrics nor geriatrics,
we have unique needs- medically, socially, and economically.

However, the rights and dignity of adolescent and young adults are equal and vital to all individuals.

We deserve to have our beliefs, privacy,
and personal values respected.

Access to care is a right,
not a privilege.

Our rights, as we perceive them to be and intend to preserve them, are:

1. The right to be taken seriously when seeking medical attention to avoid late diagnosis or misdiagnosis, and entitlement to separate and confidential discussions regarding our own care.

2. The right to affordable health insurance and early detection tests, unhindered by insurance or socioeconomic status.

3. The right to be offered fertility preservation, as well as current information and research, regarding ongoing and potentially lifelong effects of cancer treatment that would affect our fertility.

4. The right to be informed about available clinical trials and given reasonable access to them.

5. The right to untethered access to adolescent and young adult cancer specialists and, when requested, a second opinion regardless of insurance or geographic location.

6. The right to access a social worker or caseworker who is well-versed in adolescent and young adult cancer specifics.

7. The right to “generationally applicable” psychosocial support.

8. The right to have our insurance, and position as a student or employee, protected by law while dealing with our cancer in order to minimize discrimination.

10. The right to clear explanations regarding the long-term side effects of our disease and its treatment, and to be offered all available and applicable physical reconstruction and rehabilitation options.

11. The right to have all of our treatment options explained to us in full detail, to have our questions answered, and to receive clarification when requested, so that we can be an active part of our own care.

Preserve our Potential.