The Power of the "Right" Biospecimens in Clinical Research and Care

David B. Agus, M.D.

Center for Applied Molecular Medicine

Westside Prostate Cancer Center

Keck School of Medicine

University of Southern California

Los Angeles, CA

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Cancer is a pretty common disease-

a lot of opportunity to obtain tissue??

US Mortality, 2001

Rank	Cause of Death	No. of deaths	% of all deaths
1.	Heart Diseases	700,142	29.0
2.	**Cancer**	**553,768**	**22.9**
3.	Cerebrovascular diseases	163,538	6.8
4.	Chronic lower respiratory diseases	123,013	5.1
5.	Accidents (Unintentional injuries)	101,537	4.2
6.	Diabetes mellitus	71,372	3.0
7.	Influenza and Pneumonia	62,034	2.6
8.	Alzheimer's disease	53,852	2.2
9.	Nephritis	39,480	1.6
10.	Septicemia	32,238	1.3

Source: US Mortality Public Use Data Tape 2001, National Center for Health Statistics, Centers for Disease Control and Prevention, 2003.

Clinical annotation – good for the paper business

Canada- 60,000 Physicians

The volume of patient information for Canadian doctors[43]

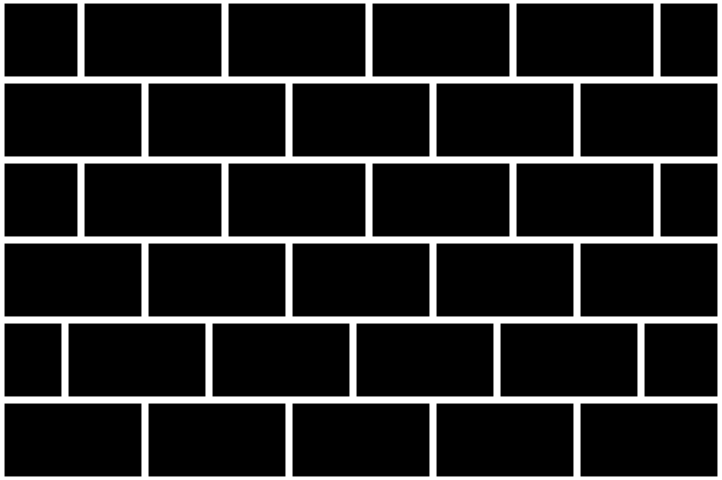
	Per doctor each year	Total each year
Office-based doctor visits	5,367	322,000,000
Diagnostic images	583	35,000,000
Laboratory tests	7,333	440,000,000
Prescriptions	6,367	382,000,000

1.8M new medical papers. In 20,000 journals and 300,000 clinical trials each year

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Biomedical Science is Built One Brick at a Time In a Sequential Fashion

Peer review Journals → Scientific Fact *"foundation"*



One bad brick, *especially in the foundation* . . . . .

USC UNIVERSITY OF SOUTHERN CALIFORNIA

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Example – gene expression studies

Hypoxia = hundreds of genes

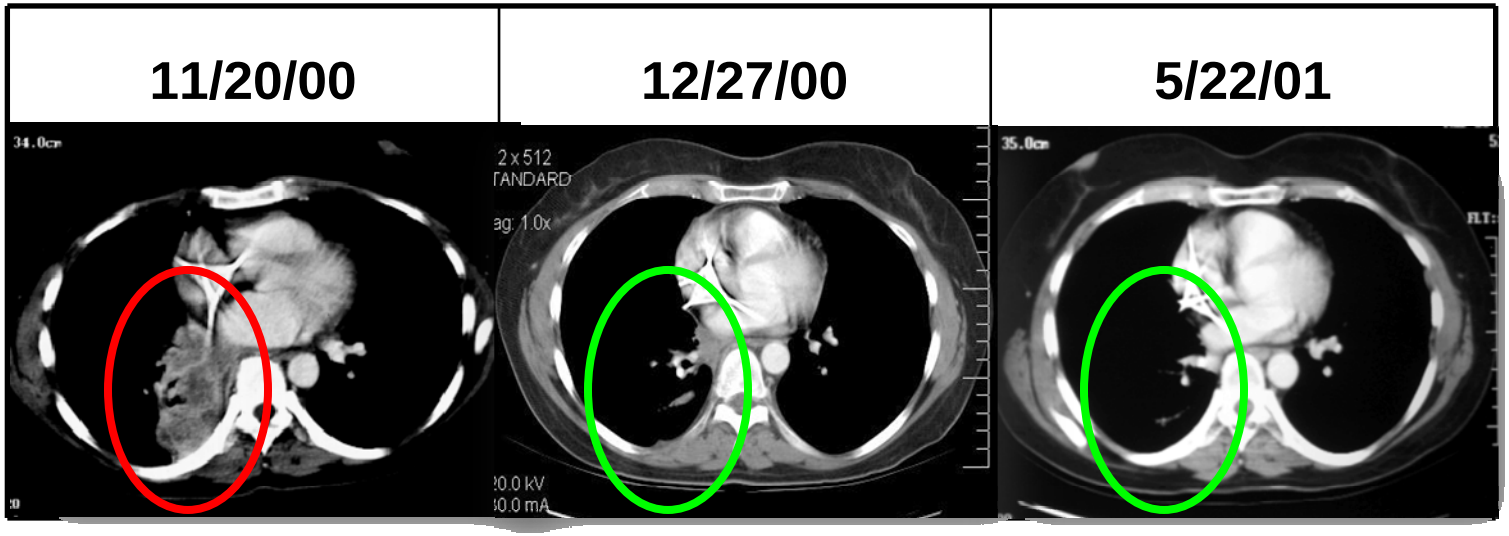
Artifacts are many times not random

- **We treat cancer surgically different based on extent of disease**
- **Difficulty of surgery, time of surgery – different tissue handling**

Clinical Annotation- sometimes straight forward

Patient 012

- 46 year old Female with Stage IV NSCLC S/P neurosurgery excision x 2 and SRS x 3 for recurrent brain metastases
- S/P Carbo/Txl – Carbo/Txtr, S/P Gem, S/P NVB
- Started on Gefitinib Trial 039 - 11/27/00



Source: Ron Natale, CSMC

Clinical Annotation- sometimes not straight forward

EGFR kinase inhibitor in advanced lung cancer

- Response rate: ~10%
- Advanced patients, failed three other chemotherapies
- Life expectancy = weeks
- Symptom improvement by 30% in greater than 30% of patients
- Little to no toxicity

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Clinical Annotation- sometimes not straight forward

Randomized trial of EGFR kinase inhibitor in advanced lung cancer

- Response rate: ~10%
- In treatment group, number of patients with survival advantage: ~70%
- How do we identify the patients who are 'clinically benefiting' from a therapy?
- Annotation would group refractory and clinical 'benefitors' the same

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Common Clinical Scenario

- 55 yo gentleman with metastatic lung cancer in lung, liver and bone
- Progressive disease after chemotherapy
- Starts molecular targeted drug
- After three months disease 15% larger
- What do you do?? If you biopsy patient what ***bucket*** does tissue go in??

Clinical Annotation- sometimes not straight forward

Example- glioblastoma – progression can depend on when you look

Very few binary clinical annotations – we don't have data elements for 'shades of grey'

With relatively small datasets, data readouts can be very misleading

NO COMMON DATA ELEMENTS USED – PATHOLOGY / IMAGING

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Improving Patient Management

- Combine electronic records
  - clinical **standardized** data
  - use outcome data for classification strategies
  - develop standards of care

  to facilitate delivery of high quality, consistent care (exportable)

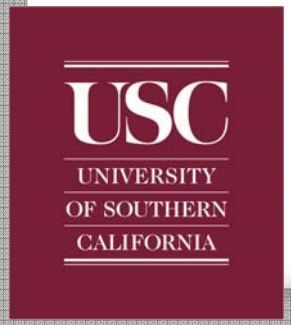
NEED STANDARDS AND HEROES TO DONATE THEIR CLINICAL INFORMATION AND TISSUE

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Application of IT to Healthcare

- Limitations
  - No standards
  - Not tied to reimbursement
  - No reason for adoption

  - Gonna change soon - $$$$



Improving Patient Management

- **Research example: Clinical Outcomes Project**

  Clinical Data/ Annotation

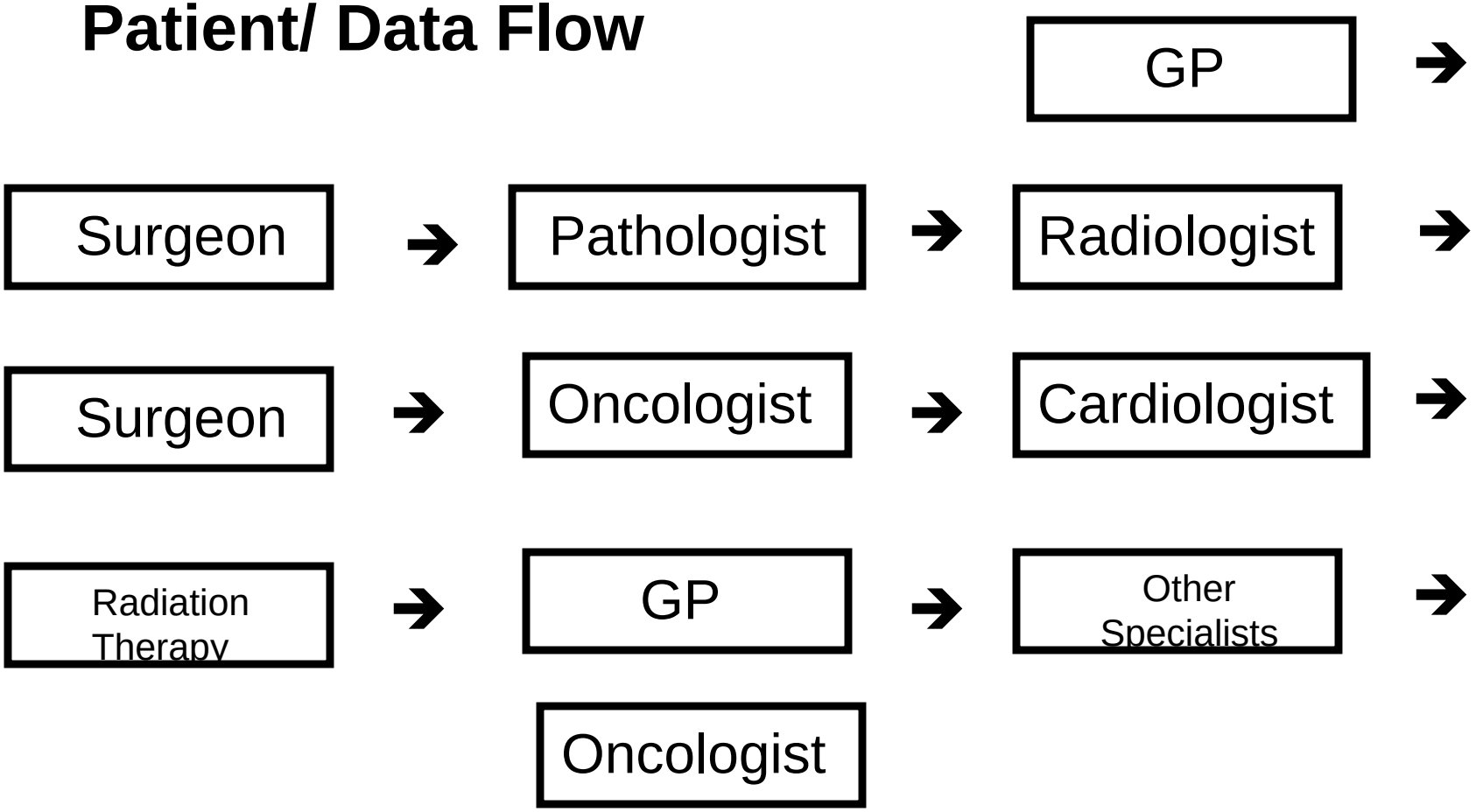
  + Technology (Proteomics, Genomics, others)

  + Machine Learning

  Predictable Treatment Outcomes *('handicap the odds')*

USC UNIVERSITY OF SOUTHERN CALIFORNIA

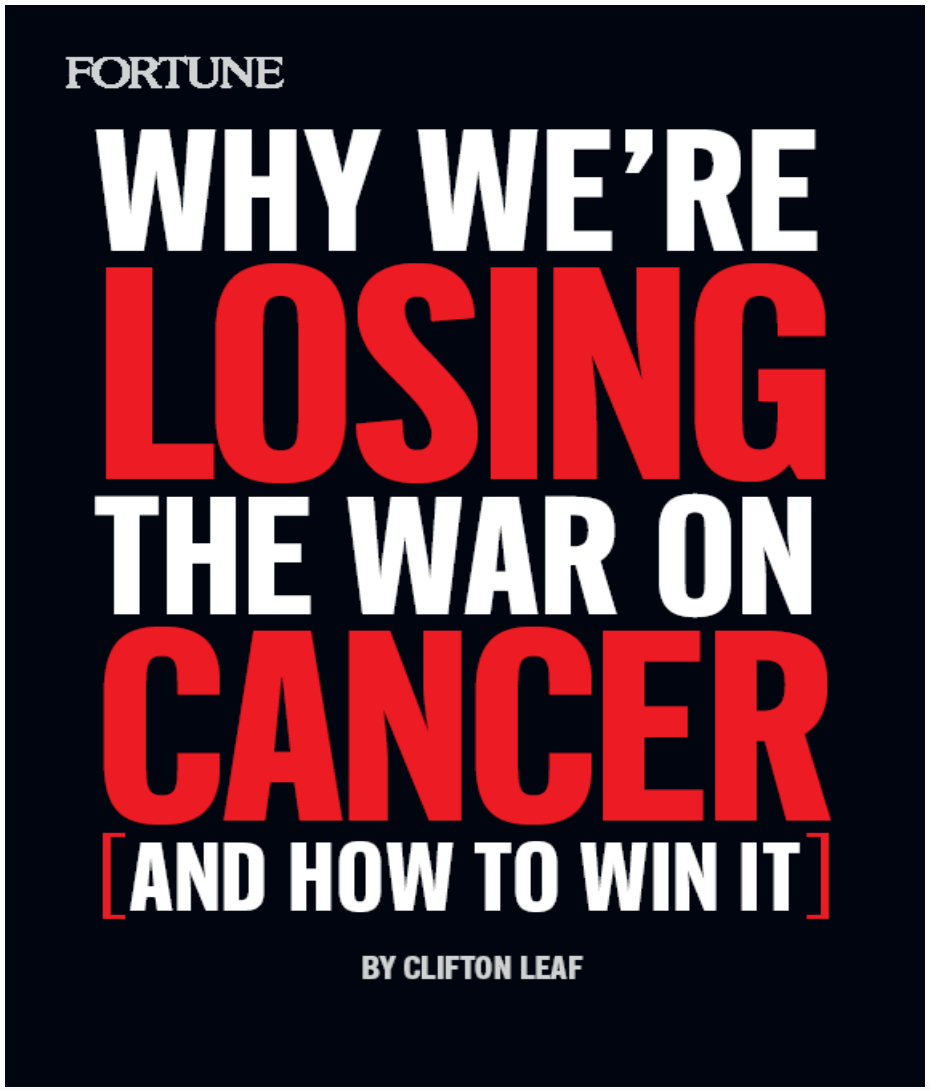
Patient/ Data Flow



A lot of boxes – especially with a small n!

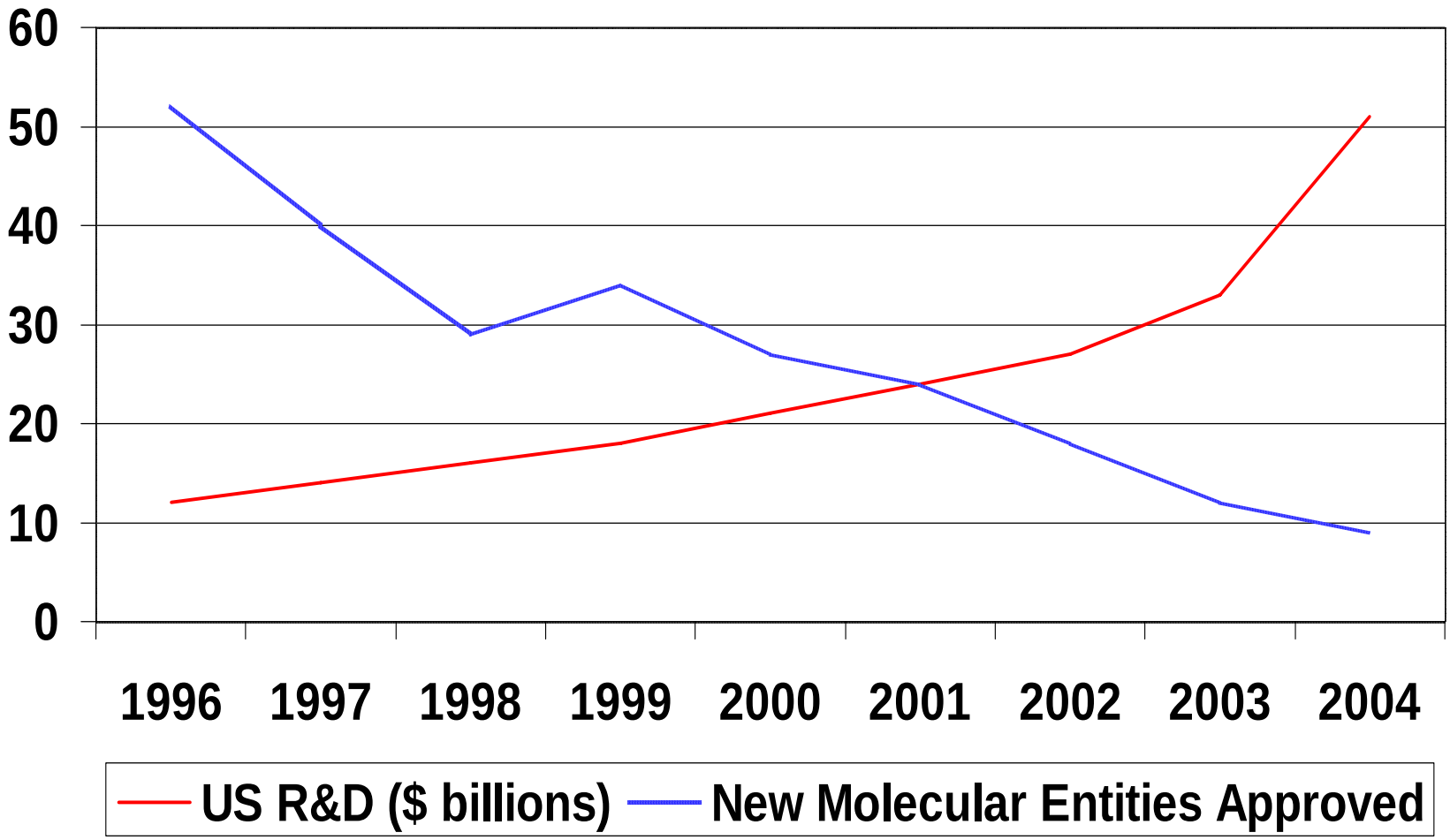
USC UNIVERSITY OF SOUTHERN CALIFORNIA

Fortune Magazine, March 22, 2004



USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Troubling Trends- *all* therapeutic areas



Source: MIT Tech Review, Oct 2003, Stephen S. Hall

The Playing Field

- Current therapy for many cancers "works" (potentially can make some patients live longer or better)
- Not optimized
- Don't know how or why most drugs work
- Tissue correlates to outcome rare
- 'Educated guessing' of biomarkers hasn't worked well
- Many targets, many drugs in the pipeline- few new therapeutics in past 5 years

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Hope for field ➔"Bio-Markers"

Biomarkers = measurable molecular phenotypic parameter(s) that characterize an organism's state of health or disease, or a response to particular therapeutic intervention- *(Negm et al. Trends Mol Med 2002)*

Biomarkers are sought as instruments to help in:

- disease risk assessment
- early disease detection
- as surrogate endpoints in clinical trials (or in some cases as surrogates for environmental and other exogenous factors such as diet)

**Markers may be, but are not necessarily causal (directly or indirectly)

**Markers may be, but are not necessarily effects (directly or indirectly)

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Biomarker confusion

- Lack of biopsy of advanced disease
- Difficulty studying primary disease fresh tissue
- Multi-clonal disease – which cells are informative?
- Lack of concordancy between pathologists
- Lack of standardization of nomenclature
- Tissue processing differences
- Need open source software and hardware, a normalization/ control standard
- Need established standards distributed by neutral group

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Example: Prostate Cancer

- Problems multiplied
- Double edge sword of PSA
- Difficulty of bi-dimensional measurements
- Heterogeneous clinical outcome
- Multiple diseases under one name
- Lack of tissue correlates/standards
- New disease to the oncology world

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Example: PC - Early Detection

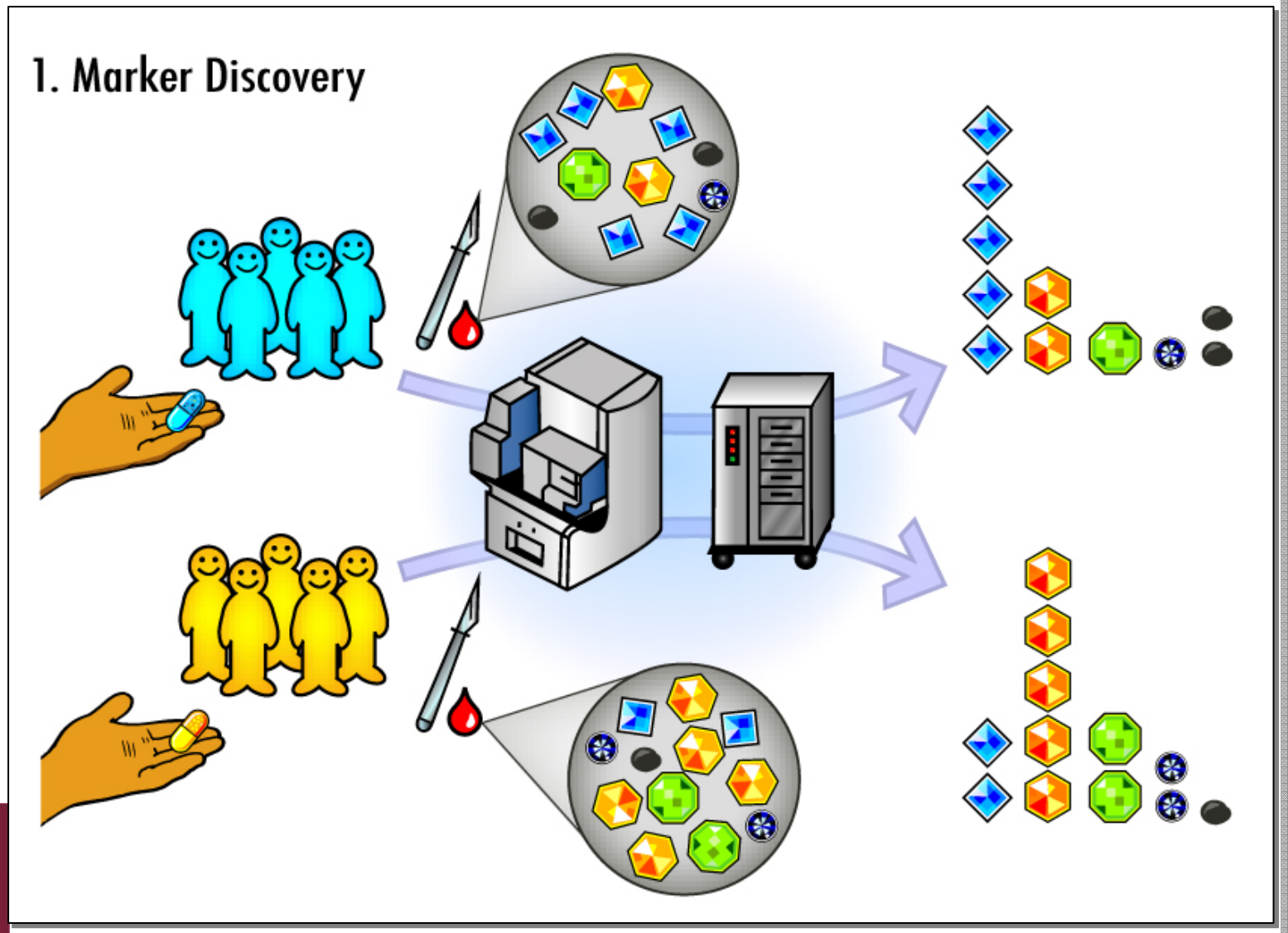
- How often does it help?
- Do we need another PSA?
- Develop biomarkers for outcome, not disease identification
- Early detection programs change disease biology and clinical behavior of disease

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Patients Need Individualized Treatment Information

- Will my cancer spread?
- Do I need chemotherapy after surgery for my cancer type?
- What are the benefits and side effects of chemotherapy for me?
- Are there any new drugs targeted for my type of cancer?
- Will I survive?

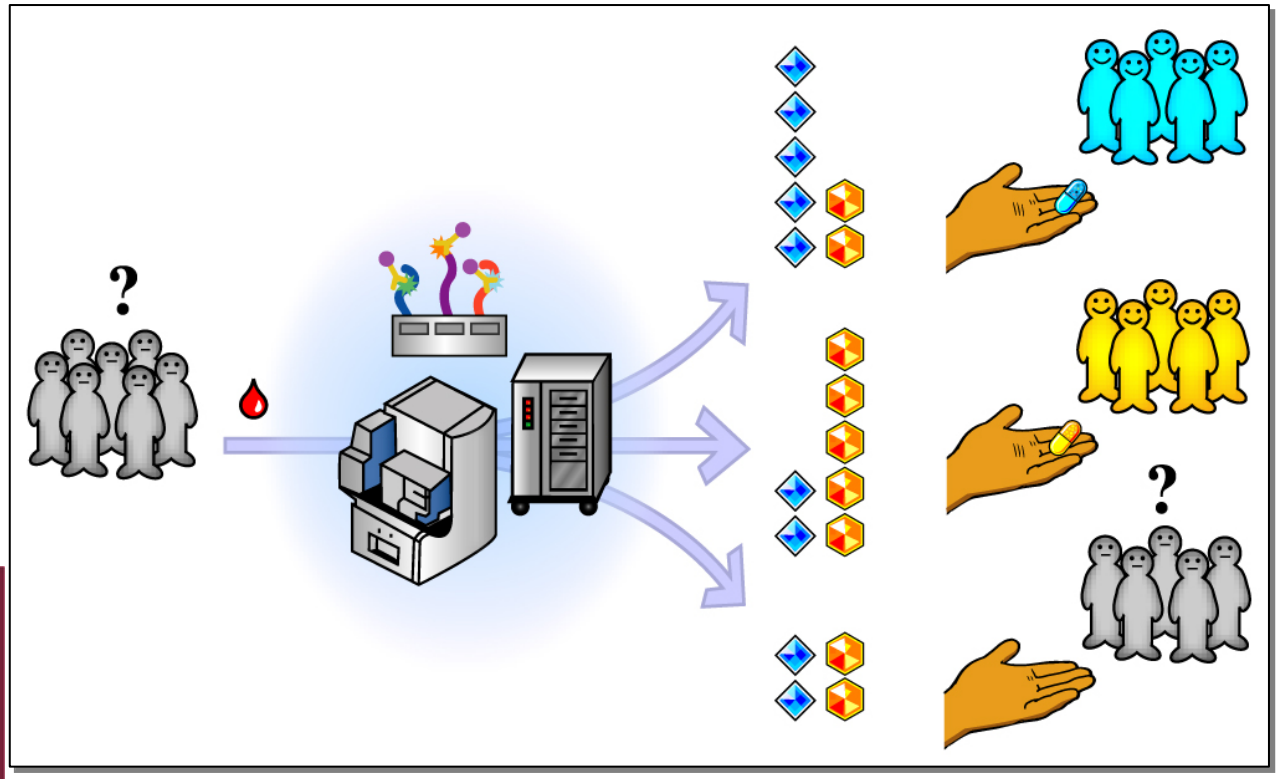
USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA



USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

The Grand Vision: Personalized Medicine Realized

Delivering the right treatment to each patient through proteomic profiling



USC UNIVERSITY OF SOUTHERN CALIFORNIA

Quality Assurance in Biomarker Discovery

- Differentiate variation in process/platform from variation in patient
- Identify sources of variation within a process for optimization
- When a process is complete, assess if the data was ‘good’ or ‘not good’ before interpreting it

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Personalized Medicine

- Predictive medicine
- Pharmacogenomics
- Molecular diagnostics
- Biomarkers

- CAUTION: don’t become a reductionist

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

U.S. Physicians' Primary Careers

1980 and 2003Comparison

Primary Career	1980	2003	% Growth (1980-2003)
Research	15,377	6,589	-57%
Patient Care	376,512	713,526	90%

Unfortunately, what we presently do is an art, not yet a science --- need physician scientists!!

USC UNIVERSITY OF SOUTHERN CALIFORNIA

Scalable technology: Estimated Cost of Sequencing a Gene

Year	Cost
1974*	$150,000,000
1998	$150
2004	$1.50

Average gene is about 27,894 base pairs

* Monsanto Annual Report Estimate, 1974

Not all tissue equivalent

DNA / PROTEIN / RNA / OTHER

Not all technologies have require the same tissue specs

Not all clinical annotation equivalent

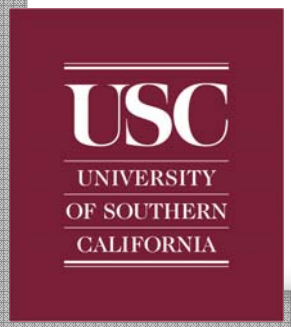
Not all technologies have require the same clinical annotation specs

KNOW YOUR STUDY / LIMITATIONS

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Not all data are equal

- Answers a question that matters
- Decision tree
- Drug development
- Audited dataset



Example – VISA

Late 1960s – Bank Americard

1966 Mastercard – 5 CA banks

1968 BofA licensee meeting in Columbus, OH

highly decentralized, highly collaborative

Dee Hock

Largest currency system in the world

USC
UNIVERSITY
OF SOUTHERN
CALIFORNIA

Summary

- No technology will 'win' in biomarker game
- Technology itself will win, thus patients will win
- Emphasis on quality
- Only way to achieve – volunteerism, team work

USC UNIVERSITY OF SOUTHERN CALIFORNIA