RESHAPING TERTIARY CENTER PATHOLOGY AND LABORATORY SERVICES IN AN ERA OF PERSONALIZED MEDICINE

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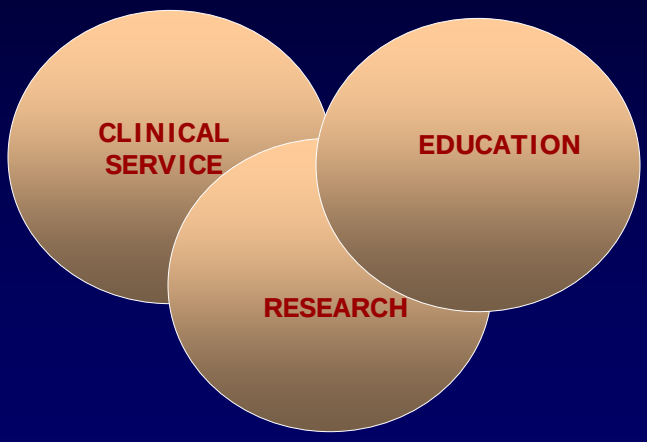
Dept. of Pathology & Laboratory Medicine at a Tertiary Medical Center



Pathology and Lab Medicine at CSHS Today

ANATOMIC PATHOLOGY
- Surgical Pathology (50,000)
- Cytopathology (17,000)
- Autopsy Pathology (105)

APPROXIMATELY 2.5 MILLION TEST RESULTS EACH YEAR

(30% outreach)

CLINICAL PATHOLOGY
- Core Laboratory (1.9 Million tests)
- Hematopathology (160,000)
- Transfusion Medicine (56,000 units transfused each year; 1,100 therapeutic apheresis)
- Microbiology (500,000)
- Molecular Pathology (26,000)
- Cytogenetics (5,000)

Pathology and Lab Medicine at CSHS Today

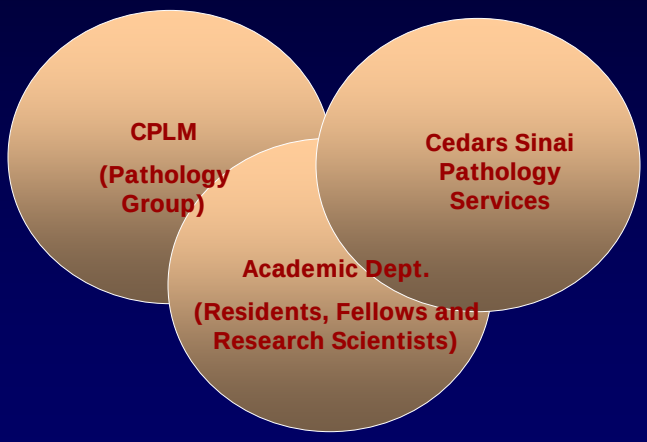
- **2.5 Million tests and 8 Million test results generated by / in**
  - 529 professionals
    - 41 M.D. and Ph.D faculty
    - 28 Residents and Fellows
    - 460 Laboratory Technologists and Assistants
  - 24/7 operation
  - 35,000 + sq. feet at multiple locations in Medical Center
  - Customer Service receives 125,000 calls per year

Pathology and Laboratory Medicine

Faculty and House Staff

Academic Year 2007-2008

Dept. of Pathology & Laboratory Medicine



Dept. of Pathology & Laboratory Medicine in Tertiary Medical Centers

- Traditional challenges:

- Multiple goals (clinical service, research and education) – often conflicting – Depts. looking for the elusive “triple threat pathologist”

- Leadership vision varies considerably between Depts. in the country

- Complex org. structures (Hospital, Group/Clinic, Academic enterprise/Med. School)

Dept. of Pathology & Laboratory Medicine in Tertiary Medical Centers

- Traditional challenges:

- Depts. most often fractionated (AP, CP, Experimental, Blood bank ….)

- Pathologists mostly salaried (not incentivised)

- Medical Centers are large and complex – lack agility to compete in the Lab. Market Space (Sales, Marketing, IT support, billing)

- “Real estate” in Medical Centers is a premium – more lucrative programs are competitors for space

Dept. of Pathology & Laboratory Medicine in Tertiary Medical Centers

- Newer challenges – Landscape is changing every day & every moment:

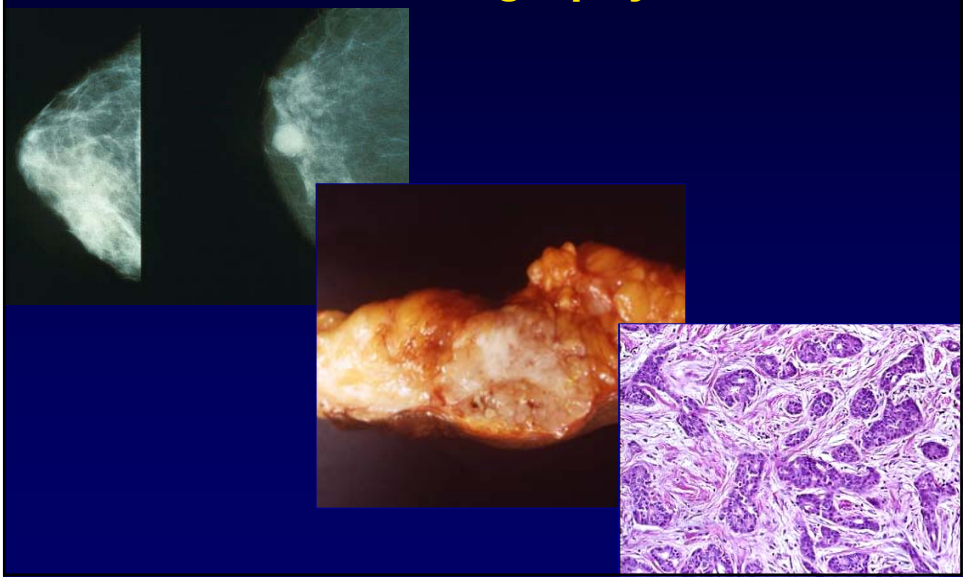
- Clinician owned Pathology Enterprises (POD labs) – Urology, GI…- reduced volumes
- For Profit labs with large customer service component, IT, sales forces and capital – competing for doctors office generated cases
- Diminishing research $s – offset from clinical income
- Ever expanding menu of esoteric tests – expensive and “outsourced”

RESHAPING TERTIARY CENTER PATHOLOGY AND LABORATORY SERVICES IN AN ERA OF PERSONALIZED MEDICINE

The Cedars Sinai Experience

What is Personalized Medicine

38 year old woman who underwent mammography



BREAST CANCER: Report- 1985

LEFT BREAST, MASTECTOMY:

-Infiltrating ductal carcinoma, Grade III, 1.2cm, upper outer quadrant resection margins free

-Eight lymph nodes, negative for carcinoma (0/8), axillary tail

-Background breast with fibrocystic changes with apocrine metaplasia, focal microcalcifications, adenosis, duct ectasia, focal atypical lobular hyperplasia and focal ductal hyperplasia

Evolution of Surgical Pathology

- Era of Autopsy Pathology – Curious physicians (1700 – early 1900s)
- Era of Surgical Pathology – Branched out from Surgery (early to mid-1900s)
- Era of Personalized Medicine – Integrated Anatomic and Clinical Pathology (turn of the century)

Symptoms vs. Genetic-based Medicine

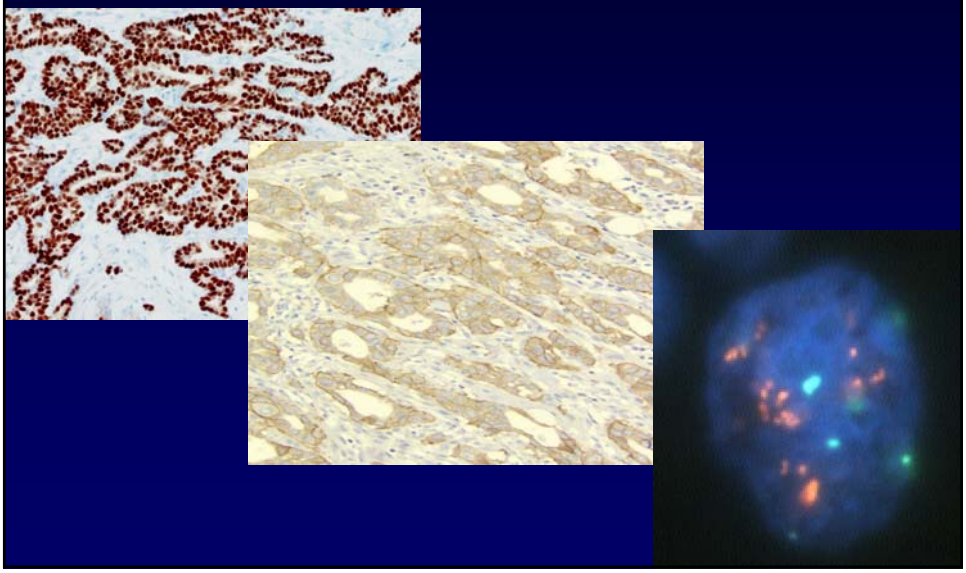
Symptoms-based

- Symptomatic diagnosis, prescription & monitoring
- Treatment Targets selected based on largest population
- Blockbuster drug for all patients effective in only 40-60% and c adverse drug (ADR)
- Reactive

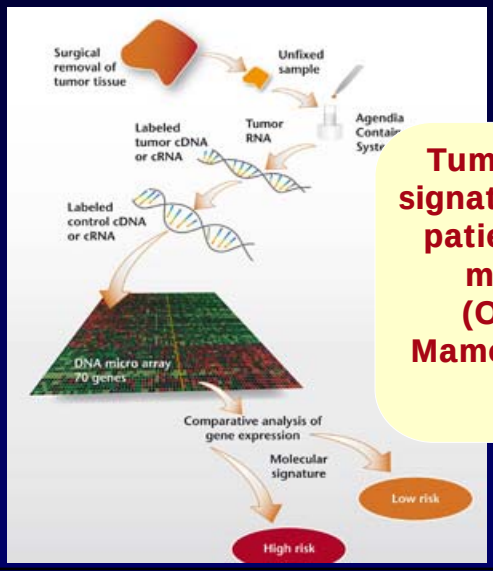
One size fits all

This patient
•Radical surgery
•Standard chemotherapy
•Prognosis based on population statistics

Molecular Testing on Breast Cancer



Molecular Testing on Breast Cancer Risk Stratification

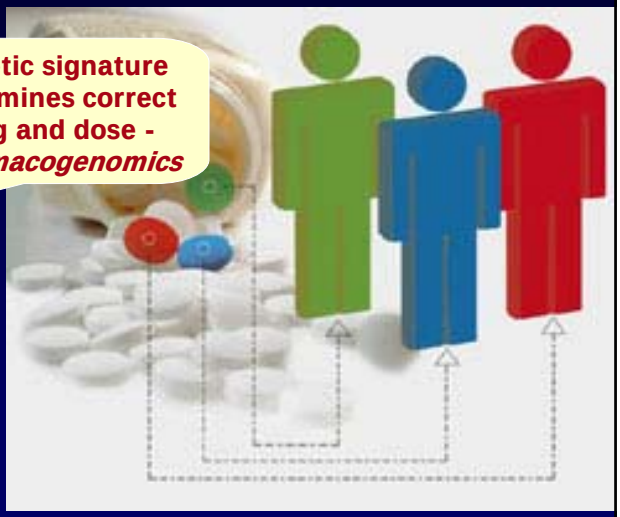


Tumors genetic signature stratifies patients risk for metastasis (OncodxTM, MamoprintTM etc)

Personalized Medicine

Genetic signature determines correct drug and dose - *pharmacogenomics*

Based on genetic testing and detection of variation in production of enzyme that metabolizes Tamoxifen



Personalized Medicine

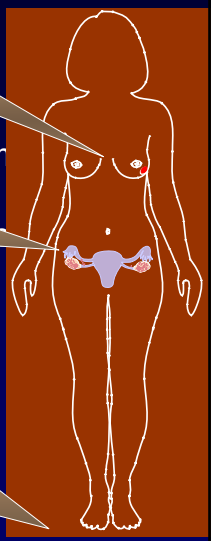
- Patient had family history of breast cancer
- Ashkenazi Jewish heritage
- Underwent sequencing for CA2 r
- Patient detected to be BRC

breast cancer (50%-85%)

ovarian cancer (10%-20%)

Increased surveillance in opposite breast with choices for chemo-prevention and prophylactic surgery

Increased risk of laryngeal, melanoma and pancreas cancers



BREAST CANCER – REPORTING 2009

RIGHT BREAST: INFILTRATING DUCTAL CARCINOMA

Macroscopic	
Specimen type:	Excision
Lymph node sampling:	No lymph nodes sampled
Laterality:	Right
Tumor site:	Upper outer quadrant
Microscopic	
Histologic Type:	Infiltrating ductal carcinoma, NOS
Tumor size (invasive):	3cm (maximum diameter)
Histologic Grade:	Grade III, poorly differentiated, total score 8 (Tubule formation 2; Nuclear grade 3; Mitotic count 3)
Necrosis:	Minimal
Associated in situ component:	Present, ductal carcinoma in situ, moderate
Architectural Patterns of in situ component:	Cribriform and Micropapillary
Nuclear Grade of in situ component:	Intermediate grade
Surgical Margins:	Surgical margins are negative.
Prognostic/Pathologic Stage	
Angio-lymphatic invasion:	Not identified
AJCC TNM Staging 6th edition, 2003:	pT1, Nx,
Primary Tumor (pT):	pT1: Tumor 2 cm or less in greatest dimension
Lymph node pathologic classification:	pNX: Regional lymph nodes cannot be assessed
Predictive Factors	
Estrogen Receptor (Immunohistochemistry):	Positive
Progesterone Receptor (Immunohistochemistry):	Positive
HER-2/neu (Immunohistochemistry-Pathway):	Negative
HER-2/neu (FISH – Path Vysion):	Negative
MIB-1 proliferation index:	<10% (Low)

Symptoms vs. Genetic-based Medicine

Symptoms-based

- Symptomatic diagnosis, prescription & monitoring
- Treatment Targets selected based on largest population
- Blockbuster drug for all patients effective in only 40-60% and can have adverse drug reactions (ADR)
- Reactive

One size fits all

Symptoms vs. Genetic-based Prospective Care

Genetic-based

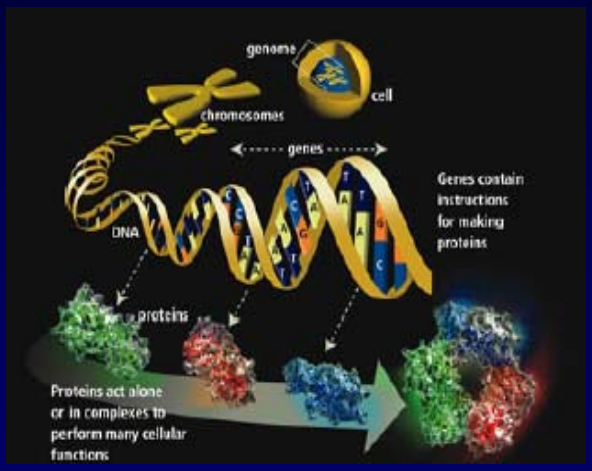
- Molecular Diagnosis
- Risk-stratification by molecular
- Drug-targeted therapy
- Less or no ADR
- Molecular monitoring of disease
- Preventive

Our patient

- **Local resection**
- **Personalized risk-stratification**
- **Targeted therapy**
- **Prevention and prophylaxis**

The right treatment for the right person at the right time with the right dose for right outcome and improved quality of life

Personalized Medicine



- Sequencing of the human genome (2003)
- New paradigm for medicine based on gene-based knowledge combined with health information technology: Personalized Medicine
- 3 billion DNA base pairs
- 30,000 genes
- 500,000 protein characterize the human genome

Personalized Health Care:
Opportunities, Pathways, Resources

- **Predict** our individual susceptibility to disease
- Provide more useful & person specific tools for **preventing** disease
- **Detect** the onset of disease at the earliest moments
- **Preempt** the progression of disease
- **Target medicines** and dosages more precisely and safely to each patient.

Genomics- health information technology-evidence/clinical delivery

THE HILL TUESDAY, JANUARY 20, 2009 15

THE HILL TUESDAY, JANUARY 20, 2009 15

The New President of the United States
on the future of personalized medicine and genetic testing…

"We've made so many achievements and come a long way in our understanding and application of genetics knowledge."

"And yet, we are just beginning to realize the full potential of this science to predict the onset of disease, diagnose earlier, and develop therapies that can treat or cure Americans from so many afflictions."

"We have used these research findings to pinpoint the causes of many diseases, such as sickle cell anemia, cystic fibrosis, and chronic myelogenous leukemia."

"Personalized medicine represents a revolutionary and exciting change in the fundamental approach and practice of medicine."

RESULTS *for* LIFE

LAB TESTING: BETTER HEALTH, IMPROVED OUTCOMES

For information about the value of laboratory medicine: *www.labresultsforlife.org* or 202.637.9466.

Those are the words of Senator Barack Obama on the Senate floor in March 2007. They capture this remarkable science and frame the opportunities that lie ahead. We look forward to working with him, the individuals in his Administration, and the Members of the 111th Congress in translating the promise of genetic testing and personalized medicine into reality.

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Obama to Broaden Role of Genetics in Medical Care

By RICARDO ALONSO-ZALDIVAR
The Associated Press
Friday, November 28, 2008; 1:57 PM

"The president-elect has indicated his support for both advancing personalized medicine and increasing (research) funding," said Rep. Patrick J. Kennedy, House that builds on Obama's.

Obama is also interested in the role that personalized medicine could play as an element of changes in the broader health care system.

"The issue of getting the right treatment to the right person goes with his whole emphasis on health reform," said Mark McClellan, a noted Republican heal Bush as Medicare director and head of the Food and Drug Administration. "If we're thinking about reforming the health care system, we should be thinkin when health care reform is fully implemented," McClellan said.

Although medical science is more technologically advanced than at any time in history, in some ways it is still strikingly old-fashioned. For example, most p percent of treated patients, leading to a trial-and-error approach to treatment that not only may be more costly, but can put some patients at risk.

Among patients, the varying responses to medications may be linked to differences in genetic makeup that affect how the body processes a drug. For exa for epileptic seizures may prompt a severe skin reaction in Asian patients because of a genetic trait. The practice of medicine could be streamlined if docto would work on which individuals.

Government funding for research helped make possible many of the scientific gains in genetics, and Congress has passed landmark legislation outlawing di information.

But the mundane decisions, such as whether or not to pay for some genetic tests, have not progressed that smoothly.

PERSONALIZED HEALTH CARE

- Need a system that profits from wellness NOT treatment
- Pay for value NOT volume

Secretary Leavitt

Coll[illegible]an Pathologists

Perso[illegible]ed Health Care

AUGUST 2008

White Paper

Personalized Healthcare White Paper

College of American Pathologists

Personalized Health Care Committee Members

Louis D. Wright, Jr. MD, FCAP, (Chair)
Mahul B. Amin, MD, FCAP
J. Robert Beck, MD, FCAP
W. Stephen S Black-Schaffer, MD, FCAP
Samuel K. Caughron, MD, FCAP
Rajesh Chandra Dash, MD, FCAP
Jeffrey A. Kant, MD, PhD, FCAP
Debra G.B. Leonard, MD, PhD, FCAP
Ronald B. Lepoff, MD, FCAP
James A. Robb, MD, FCAP
Gail Habegger Vance, MD, FCAP
David L. Witte, MD, PhD, FCAP

PERSONALIZED HEALTH CARE COMMITTEE (2009) :
new CAP committee

PERSONALIZED HEALTH CARE

Stakeholders

Patients
Physicians
Third party payers
Federal Government – *NIH /NCI/ FDA*
Scientists
Pharmaceuticals (targeted therapy)
Pathologist

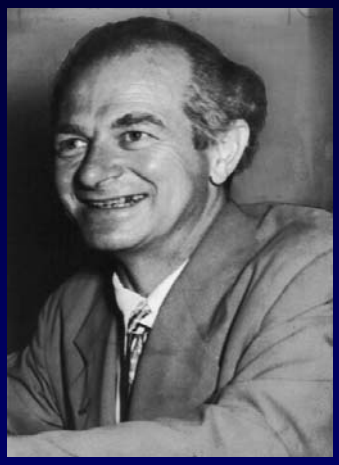
PERSONALIZED HEALTH CARE

- ***Change must be transformative and disruptive***
- ***Commitment to change must be embraced as an inner core value from top down & bottom up***
- ***Disruptive technologies***
  - ***Multiplexing of biomarkers***
  - ***Digital pathology***
  - ***Nanotechnology***
  - ***In vivo imaging – convergence of pathology & radiology***

BEFORE WIDESPREAD SCREENING OF PROSTATE CANCER

1991: diagnosed with prostate cancer

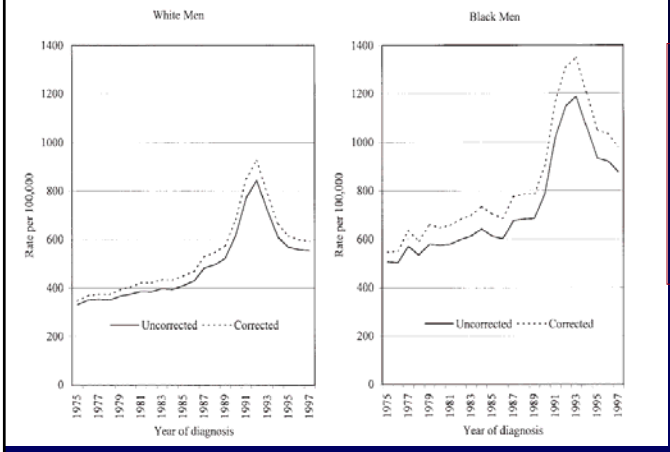
1994: died of advanced prostate cancer with spread to the intestines



(1901-1994)

2 Nobel prizes for Peace and Chemistry

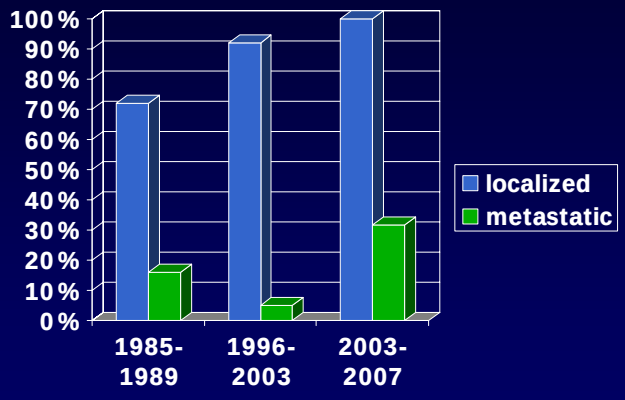
THE ERA OF SCREENING



Incidence of Prostate Cancer 1975-1997

- Serum PSA
- Transrectal ultrasound
- 18 gauge needle biopsy

Survival in Prostate Cancer

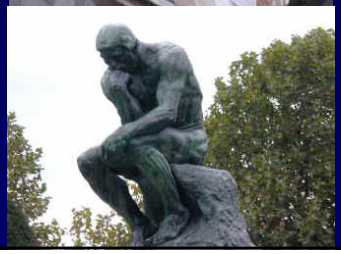


Therapeutic Options

RADIATION

SURGERY

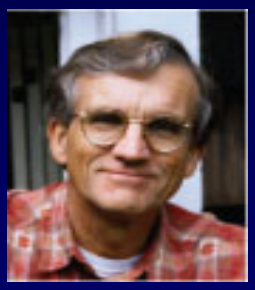
HORMONE THERAPY



WATCHFUL WAITING

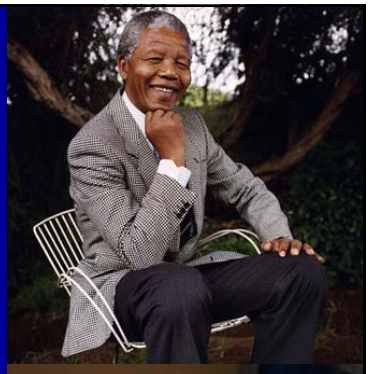
Rationale for Therapeutic Options

"I talked it over with my wife and son. I chose radiation therapy because we thought that it had the best potential for my situation."



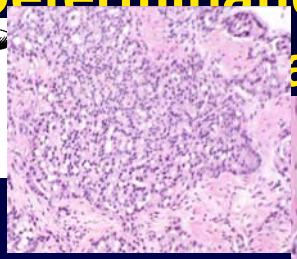
"My wife and I looked at the pros and cons of each treatment. In talking with several doctors who specialize in prostate cancer, we concluded that surgery was the best option for me."

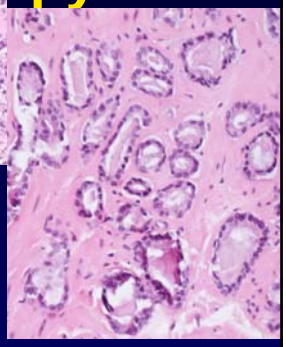
Radiation



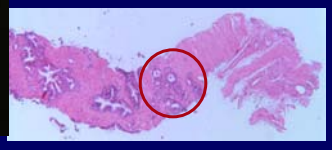
Surgery

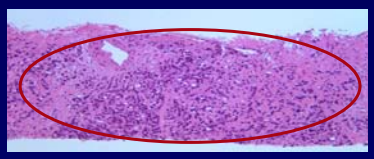
Current Determination of apy



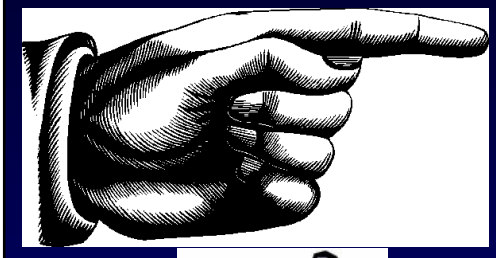


- Digital Rectal Exam
- Serum PSA
- Amt. of tumor in biopsy
- Gleason score





Limitations of Prognostication & Therapy Selection



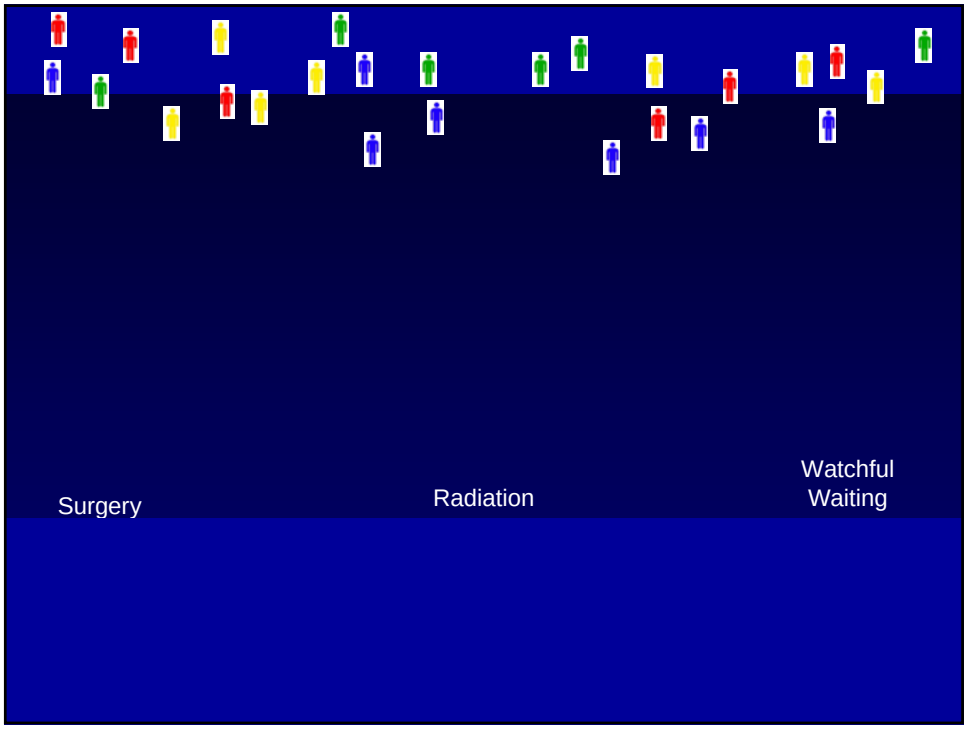
- Subjective assessment
- Broad distinctions
- Lack of predictive power at the individual level

Traditional approach- One size fits all

Challenges in Prostate Cancer 2009

- 218,890 new cases of prostate cancer **(1 in 6 men)**
- 27,050 will **35 men)**
- 9 out of 1 alized disease/
- 5 year re dy 100%

?



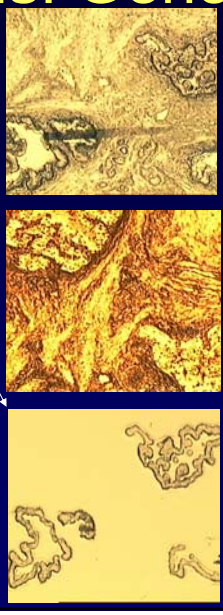
Challenges in Prostate Cancer 2[illegible]

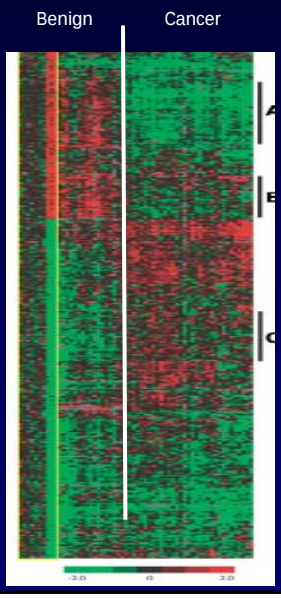
- 1 out of 10 patients will develop metastatic [illegible]
- 5 year relative survival rate is 32%

Currently there is no treatment- Painful death

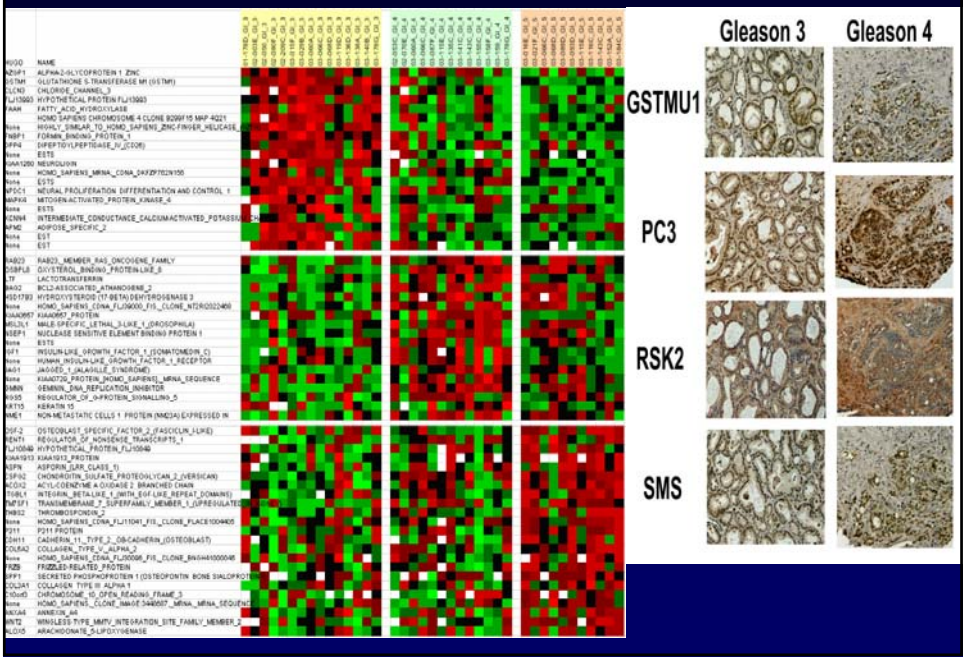
Hope: targeted therapy

Prognosis: Genomic Profiling

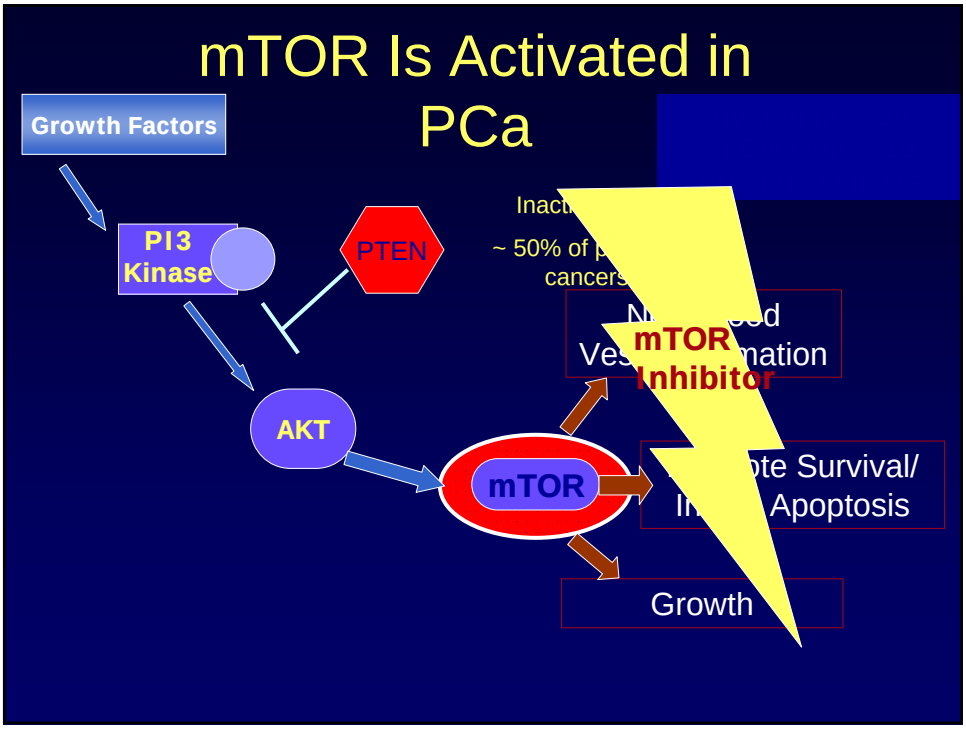




Towards a Molecular Gleason Grade

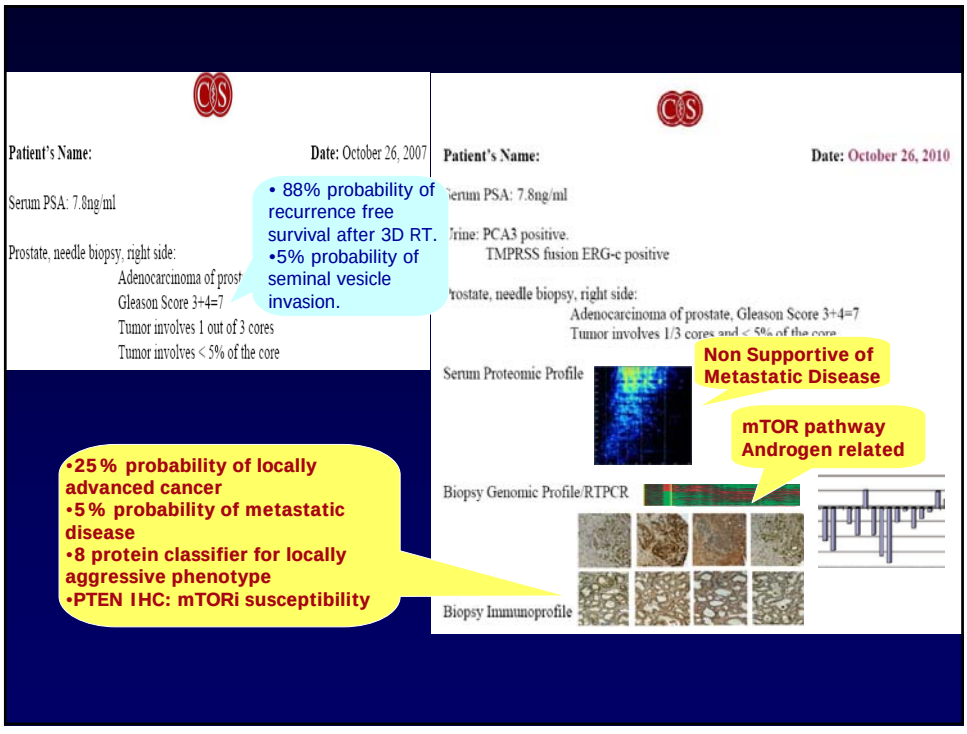


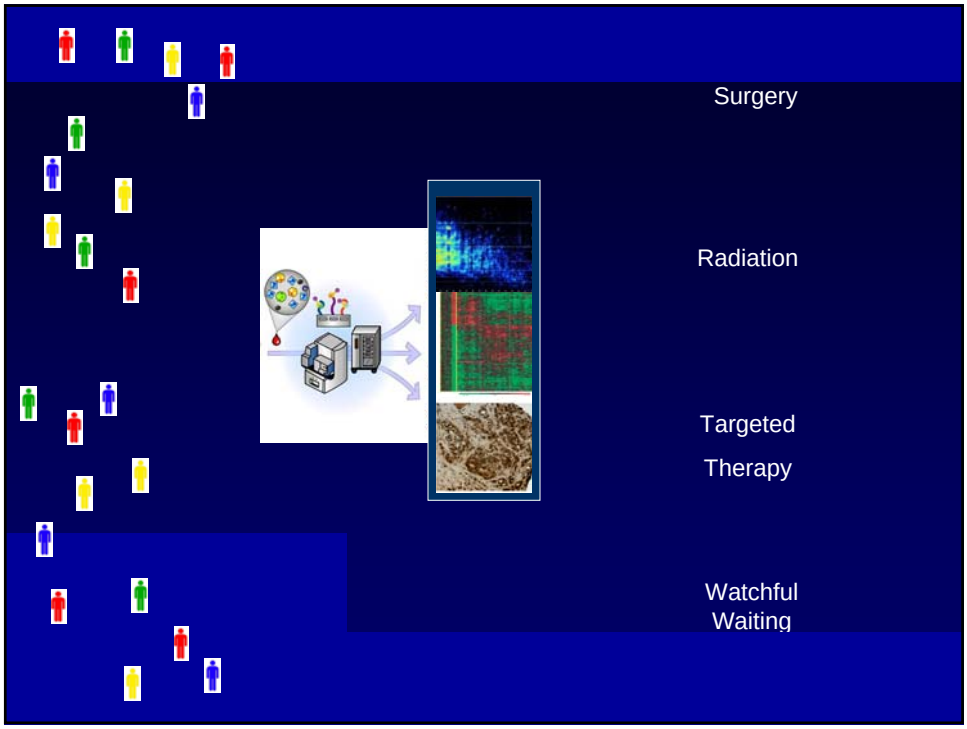
mTOR Is Activated in PCa



mTOR inhibitors in Clinical Trials for Solid Tumors

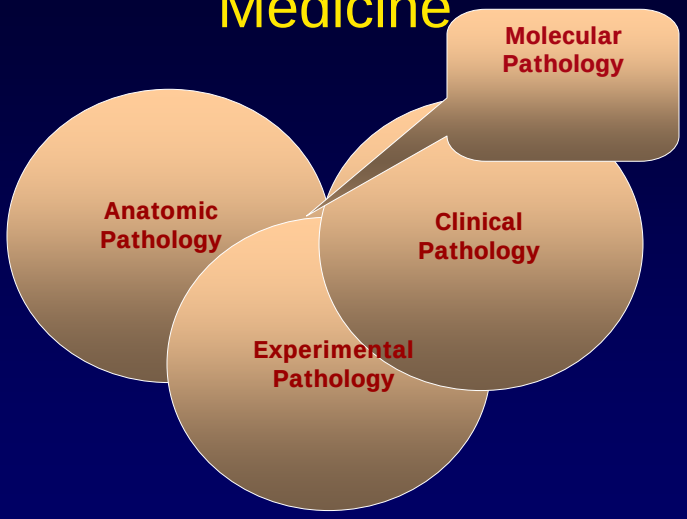
- **Rapamycin (Sirolimus)**
- **CCI-779 (Temsirolimus)**
- **RAD001 (Everolimus)**
- **AP23576**




Surgery
Radiation
Targeted
Therapy
Watchful
Waiting

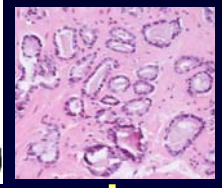

Dept of Pathology 2009-2019

Pathology and Laboratory Medicine



Diagnostic Pathologist

- reviews slides
- generates reports



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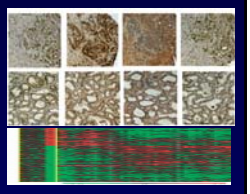
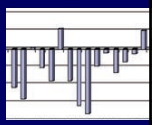


Diagnostic Oncologist

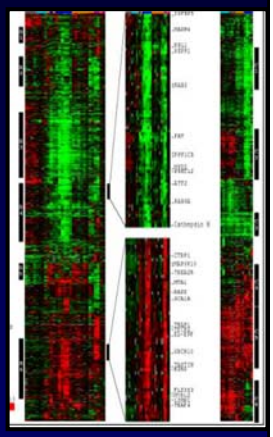
- participates in multidisciplinary care
- Integrates morphologic, molecular & outcome data
- Data generators & interpreters



Role of the Pathologist

Traditional

"Guardian of the paraffin"



Contemporary

Guardian of the RNA, DNA and Protein
Consultant & Chief Informatician

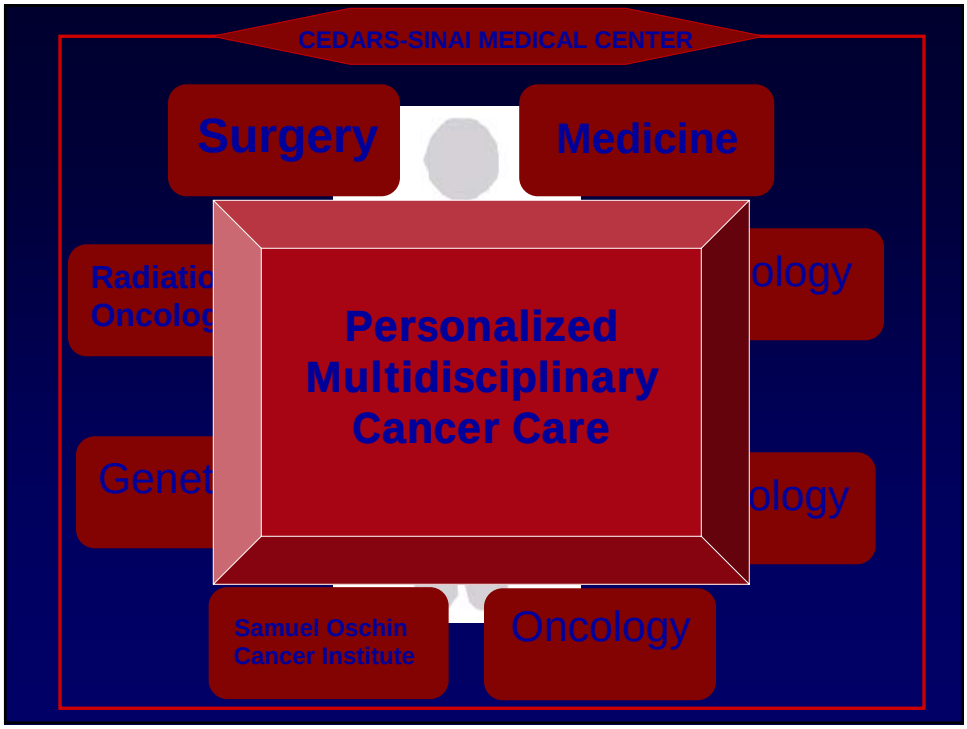
Tertiary Medical Center Laboratories

Traditional

Competition with local and regional centers

Contemporary

Consolidation
Partnerships – Pharma and Large referral labs



Molecular Medicine

Genomics, Proteomics and the omics era….

Physicians

-Value to pt. care
-Evidence based
- Reimbursement
- Risk deferment

Payors

- Increased Value
- Decreased Cost
- Patient Satisfaction
- Transformed Care

Pathologists

- Proactive role
in multidisciplinary care
- Informatician
- Education
- Iceberg is melting

The Cedars Sinai Experience…

- Define vision, mission & strategy for Pathology and Laboratory Medicine (PLM)
- Work with Medical Center that investment in PLM is the future of cost effective and value oriented Medicine
- Recognize that PLM is a Science, Art & Business which embodies the tripartite mission of academia: Education, Research and Clinical Service
- Need of the Hour: Sub-specialized Pathologists
- Recruitment: Create a triple threat Dept. not triple threat physicians
- Expansion: Primarily through Outreach
- Integrated Personalized Health Care into pragmatic business model
- Identified and allocated resources (IT, Molecular Pathology, Billing)
- Update and Sales and Marketing
- Implement and execute effectively with benchmarking

PERSONALIZED MEDICINE

- **Food for thought:**

  Everything that is needed to disrupt and transform and empower our specialty is available to us

- **Rate limiting steps:**

  - Strategic and visionary leaders (physicians and scientists and administrators)

  - Translational innovators (not scientists or clinicians)

  - Forward thinking smart & dynamic implementers – not the risk averse and reclusive pathologists

  - Agile and flexible hospital and laboratory information systems

Conclusions

Status: Pathology and Lab Medicine is at a critical crossroad of survival vs. extinction vs. transformation

Barriers: Challenging reimbursement environment, expanding expensive test menus, decreased capital, need for consolidation

Opportunities: Refine the role of the pathologist as an integral specialist in multidisciplinary care, not only as the diagnostician but also as the informatician and consultant

The paradigm of Personalized Medicine gives us a transformative opportunity – it is only ours to embrace.