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)

**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)

Approximately 2.5 million test results each year (30% outreach)

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
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)

• 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

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

BREAST CANCER: Report- 1985
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 can have adverse drug reactions (ADR)
- Reactive

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

One size fits all
Molecular Testing on Breast Cancer

Tumors genetic signature stratifies patients risk for metastasis (Oncodx™, Mamoprint™ etc)
Personalized Medicine

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

Genetic signature determines correct drug and dose - pharmacogenomics

Personalized Medicine

- Patient had family history of breast cancer
- Ashkenazi Jewish heritage
- Underwent sequencing for BRCA1 and BRCA2 mutations
- Patient detected to be BRCA2 mutation positive
- Patient had family history of breast cancer (50%-85%)
- Ovarian cancer (10%-20%)
- Increased risk of laryngeal, melanoma and pancreas cancers

Increased surveillance in opposite breast with choices for chemo-prevention and prophylactic surgery
Symptoms vs. Genetic-based Medicine

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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 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.”

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.

Obama to Broaden Role of Genetics in Medical Care

By Ricardo Alonso-Zaldivar

The Associated Press

Friday, November 20, 2008; 1:57 PM

"The president-elect has indicated his support for both advancing personalized medicine and increasing research funding," said Rep. James P. Langevin, D-R.I., a member of the House Committee on Energy and Commerce. "I'm pleased to see that this administration is committed to addressing the needs of the American people."
PERSONALIZED HEALTH CARE

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

Secretary Leavitt
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

Linus Pauling (1901-1994)
2 Nobel prizes for Peace and Chemistry

THE ERA OF SCREENING

- Serum PSA
- Transrectal ultrasound
- 18 gauge needle biopsy

Incidence of Prostate Cancer 1975-1997
Survival in Prostate Cancer

![Survival Chart](image)

<table>
<thead>
<tr>
<th>Year Range</th>
<th>Localized Survival</th>
<th>Metastatic Survival</th>
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<tbody>
<tr>
<td>1985-1989</td>
<td>60%</td>
<td>10%</td>
</tr>
<tr>
<td>1996-2003</td>
<td>90%</td>
<td>5%</td>
</tr>
<tr>
<td>2003-2007</td>
<td>90%</td>
<td>10%</td>
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Therapeutic Options

- **Surgery**
- **Radiation**
- **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."
Current Determination of Prognosis & Therapy

- Digital Rectal Exam
- Serum PSA
- Amount 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 die of prostate cancer (1 in 35 men)
- 9 out of 10 patient will have localized disease/regional spread
- 5 year relative survival rate is nearly 100%

Watchful Waiting Radiation Surgery
Challenges in Prostate Cancer 2008

• 1 out of 10 patients will develop metastatic disease.

Hope: targeted therapy

• 5 year relative survival rate is 32%

Currently there is no treatment - painful death.

Prognosis: Genomic Profiling
Towards a Molecular Gleason Grade

mTOR Is Activated in PCa

Growth Factors

PI3 Kinase

PTEN

AKT

mTOR

Inactivated in ~ 50% of prostate cancers

Activated in ~ 90% of Gleason 8-10 prostate cancers

New Blood Vessel Formation Inhibitor

Promote Survival/ Inhibit Apoptosis

Growth
mTOR inhibitors in Clinical Trials for Solid Tumors

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

Non Supportive of Metastatic Disease

- mTOR pathway
- Androgen related

- 25% probability of locally advanced cancer
- 5% probability of metastatic disease
- 8 protein classifier for locally aggressive phenotype
- PTEN IHC: mTORi susceptibility

88% probability of recurrence free survival after 3D RT.
5% probability of seminal vesicle invasion.
Watchful  Waiting  
Radiation  
Targeted  Therapy  
Watchful  Waiting  

Dept of Pathology 2009-2019
Pathology and Laboratory Medicine

Diagnostic Pathologist
- reviews slides
- generates reports

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
**Personalized Multidisciplinary Cancer Care**

- Surgery
- Medicine
- Radiation Oncology
- Genetics
- Pathology
- Radiation Oncology
- Medicine

**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.