CLASSIFICATION OF UROLOGIC CANCERS: PAST, PRESENT AND FUTURE......

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TOWARDS PRECISION DIAGNOSTICS IN UROLOGIC PATHOLOGY:
AN INTEGRATED CLINICAL MORPHOLOGIC AND MOLECULAR APPROACH

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OPINION - I

• We (pathologists) live in the most exciting and promising times
• We (pathologists) live in the most concerning and challenging times
INFORMAL POLL

• HOW MANY IN THE AUDIENCE
  - agree with opinion I
  - agree with opinion II

TASK FOR THE SESSION

Attempt to convince you that both are true

Outline the important conceptual role and responsibilities of the contemporary pathologist
HISTORY OF OUR SPECIALTY

WE STAND AT AN UNPRECENDENTED IMPORTANT CROSS ROAD IN MEDICINE, PARTICULARLY IN OUR SPECIALTY

Marcus Cicero (106-43 B.C.)

*Not to know what happened before one was born is to always remain a child*

INACTION IS NOT AN OPTION
INNOVATE, CHANGE & ADOPT

Famous Roman Orator
WHY CLASSIFY

Uniform nomenclature used by all physicians, scientists, public health policy makers, tumor registrars & patients

• ESTABLISH PATIENT MANAGEMENT PARADIGMS
• IMPROVE PATIENT CARE
• FOSTER MEANINGFUL COMPARABLE RESEARCH
• FORMULATE HEALTH POLICY - CANCER REGISTRY & CLINICAL OUTCOME DATA
EVOLUTION OF OUR ROLE

FROM

Diagnostic Pathologist: reliable but reclusive, often in the basement

TO

THERANOSTIC ONCOLOGIST: Center of multidisciplinary clinical care
EVOLUTION OF OUR ROLE

- **Era of Autopsy Pathology** – Curious physicians (3000 B.C. – early 1900s) – Germanic Era
- **Era of Surgical Pathology** – Branched out from Surgery (early to mid-1900s) – American Era
- **Era of Precision (Personalized) Medicine** – Integrated Anatomic and Molecular Pathology (turn of the century) – Global Era
HOW DO WE CLASSIFY ("MANAGE") CANCER?

- Histopathological Classification: *Diagnosis*
- Grading
- Staging
- Risk Stratification
- Theranostic "Classification": *Diagnosis, Prognostication & Prediction*
ERA OF THE AUTOPSY: 3000 B.C – 1900’S A.D.

- **Autopsia:** *to see for oneself*
- Began in ancient Egypt & Greece
- Largely performed by curious treating physicians
- Foundation of anatomical basis of disease

Herophilus (335-280 BC)

Rembrandt depicting Dr. Tulp (1632)
THE LIGHT MICROSCOPE

Antonie van Leeuwenhoek (1632-1723)

Max Magnification: 2000X
Foundations of Pathology

- Rudolf Virchow (1821-1902)
- Made microscopy an integral part of the practice of pathology
- *Die Cellularpathologie* (1858)
  - Proposed the concept that changes at the cellular level lead to disease
THE ERA OF HEMATOXYLIN AND EOSIN

• Began with the exploration of the new world
• Hematoxylin derived from logwood tree dye used for fabrics (haematoxylum campechianum)
• First successfully used in 1865
THE BIRTH OF PHOTOMICROSCOPY

• Nitrocellulose film in the 1880’s
• Photomicroscope in 1895

• Early images

Frog kidney

American Medical Museum
The Near Death of Surgical Pathology

• In 1887, Frederick III, the German Emperor, developed a throat lesion

• Morel MacKenzie, a British ENT surgeon, brought to Berlin – biopsied the lesion (one of the first uses of biopsy)

• A semi-retired Rudolph Virchow brought in to review slides – interpreted as benign hyperplastic verrucous lesions

• Emperor’s lesions recurred, condition worsened

• Waldeyer diagnosed as a carcinoma

• Emperor died from complications of laryngeal ca - shock waves in the medical community in Germany & Britain
ELECTRON MICROSCOPE

• Co-invented by Max Knoll and Ernst Ruska (1931)
• Co-awarded the Nobel Prize for Physics (1986)
• Maximum magnification up to 2 million times

IMMUNOHISTOCHEMISTRY

• 1941: Coons identified pneumococci using a direct fluorescent method
• 1990s: Widespread use in histopathology
  - objective
PATHOLOGIC DIAGNOSIS

Surgical Pathology Approach (1950s -2000)

Gross

Microscopy

Clinical Information

Ancillary studies
STANDARDIZATION OF HISTOLOGIC CLASSIFICATIONS
Oncocytoma
Metanephric adenoma
Clear cell RCC
Papillary RCC

Cell type
Embryologic
Cytoplasm
Architecture

Collecting Duct Ca
Acquired Cystic Disease
Associated RCC

Anatomical
Background disease
Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome

AD, germline mutation of fumarate dehydrogenase gene
- Multiple cutaneous and uterine leiomyomas

Xp11.2 translocation associated Renal Cell Carcinoma

Younger patients
TFE3 gene fusion abnormalities
- Often metastatic at presentation – “favorable”

Succinic Dehydrogenase B Mutation Associate RCC

Pheochromocytoma/paraganglioma syndrome type 4;
Young pts. indolent

- G1 Stromal tumors
WHO CLASSIFICATION OF RENAL TUMORS 2015

- Clear cell RCC
- Multilocular cystic LMP
- Papillary adenoma and Papillary RCC
- Chromophobe RCC
  - Hybrid Oncocytic Chromophobe tumor
- Carcinoma of the collecting ducts
- Renal medullary carcinoma
- MITF family associated RCC
- Mucinous tubular and spindle cell carcinoma
- Acquired cystic disease – associated RCC
- Tubulocystic carcinoma
- Hereditary leiomyomatosis & RCC – associated RCC
- SDHB mutation – associated RCC
- RCC unclassified
WHO Classification of Renal Neoplasia

- Emerging provisional entities
  - Thyroid-like follicular RCC
  - ALK-translocation RCC
- Entities moved in miscellaneous carcinoma group (less data than previously expected on clinicopathologic distinctiveness)
  - Post-neuroblastoma associated RCC
WHO CLASSIFICATION OF PROSTATIC CA

Malignant:

• Conventional (usual or small acinar) adenocarcinoma
• *Histologic variants*
  – Ductal carcinoma
  – Mucinous carcinoma
  – Signet ring cell
  – Small cell carcinoma
  – Adenosquamous carcinoma
  – Saromatoid carcinoma
• Urothelial (transitional cell) carcinoma
• Others: Squamous cell carcinoma, basal cell/adenoid cystic carcinoma
NEW IN PROSTATE: WHO 2016

I. Grade Grouping in addition to Gleason grading – enhance its prognostic strength

II. Classification of neuroendocrine differentiation – refined in view of potent anti-androgen therapies

III. Intraductal carcinoma – formally recognized – beyond HGPIN and not invasive ductal carcinoma
Intraductal carcinoma of prostate
CLASSIFICATION OF BLADDER EPITHELIAL TUMORS

- Flat Lesions
- Papillary Lesions
- Inverted Lesions
- Invasive Lesions
THE WHO (2105) / ISUP CLASSIFICATION OF UROTHELIAL (TRANSITIONAL CELL) NEOPLASMS OF THE URINARY BLADDER

- Normal
- Urothelial proliferation of uncertain malignant potential
- Flat lesions with atypia
  - Atypia (dysplasia)
  - CIS (high-grade intraurothelial neoplasia)
**Urothelial proliferation of uncertain malignant potential**

**Definition**
Urothelial proliferation of uncertain malignant potential is a marked thickening of the urothelium with no or minimal cytological atypia and no true papillary formation.

**Synonyms**
Papillary and flat urothelial hyperplasia (obsolete)
THE WHO (2015) / ISUP CLASSIFICATION OF UROTHELIAL NEOPLASMS

Papillary neoplasms

- Papilloma
- Papillary neoplasm of low malignant potential
- Papillary carcinoma, low grade
- Papillary carcinoma, high grade
CLASSIFICATION OF INVASIVE BLADDER CA

- **Urothelial carcinoma**
- **Squamous cell Ca**
  - conventional
  - verrucous
  - basaloid
- **Adenocarcinoma**
  - mucosal based
  - urachal
- **Variants of urothelial Ca**
  - nested (incl. large nested)
  - microcystic
  - micropapillary
  - lymphoepithelioma-like
  - sarcomatoid
  - diffuse/plasmacytoid
  - signet ring cell
- **Neuroendocrine carcinoma**
  - Small cell
  - Large cell
  - Well differentiated tumor
  - Paraganglioma
  - giant cell
  - lipid rich
  - clear cell
  - undifferentiated
WHO 2015 CLASSIFICATION OF GERM CELL TUMORS OF TESTIS

• ASSOCIATED WITH ITGCN / GCNI

- Classic seminoma

- Pure or Mixed (non-seminomatous) tumor
  - Embryonal carcinoma
  - Yolk sac tumor
  - Choriocarcinoma
  - Teratoma
  - Mixed – combinations of above incl. Seminoma

• NOT ASSOCIATED WITH ITGCN / GCNI

- Pediatric yolk sac tumor
- Pediatric teratoma
- Spermatocytic tumor
HISTOGENESIS

The most common GCT
HISTOGENESIS

Germ cell

GCNIS/ITGCN

SS

P-YST

P-TER.

SEM.

programmed

EC CELL

Non seminomatous GCTs

GCNIS/ITGCN
HISTOGENESIS

programmed EC CELL
CLASSIFICATION OF PENILE SCC

Non HPV-related

INTRAEPITHELIAL LESIONS

INVASIVE LESIONS

HPV-related

INTRAEPITHELIAL LESIONS

INVASIVE LESIONS
Penile intraepithelial neoplasia (PeIN)
Historical nomenclature

- Erythroplasia of Queyrat (glans)
- Bowen’s disease (shaft)
- Bowenoid papulosis
- Dysplasia (Mild, moderate, and severe)
- Carcinoma in situ
- Squamous intraepithelial lesion (SIL); low and high grade
- Penile intraepithelial neoplasia (PeIN 1, 2, 3)
Penile intraepithelial neoplasia (PeIN)

**HPV-UNRELATED**
- DIFFERENTIATED (Simplex) PeIN

**HPV-RELATED**
- UNDIFFERENTIATED PeIN
  - Basaloid
  - Warty
  - Warty/basaloid
<table>
<thead>
<tr>
<th></th>
<th>Differentiated PeIN</th>
<th>Undifferentiated PeIN</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>&gt;60</td>
<td>40-50</td>
</tr>
<tr>
<td>Location</td>
<td>Foreskin</td>
<td>Glans</td>
</tr>
<tr>
<td>Color</td>
<td>White/gray</td>
<td>Red</td>
</tr>
<tr>
<td>Multifocal</td>
<td>Sometimes</td>
<td>Often</td>
</tr>
<tr>
<td>HPV-related</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>p16</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>LS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Associated SCC</td>
<td>Usual Verrucous</td>
<td>Warty Basaloid Wartv-Basaloid</td>
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Warty PeIN
<table>
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<tr>
<th>Non HPV related:</th>
<th>HPV related</th>
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<tbody>
<tr>
<td>SCC:</td>
<td></td>
</tr>
<tr>
<td>- usual</td>
<td>Basaloid</td>
</tr>
<tr>
<td>- pseudoglandular</td>
<td>- classical</td>
</tr>
<tr>
<td>- Psudohyperplastic</td>
<td>- papillary variant</td>
</tr>
<tr>
<td>Verrucous:</td>
<td>Warty</td>
</tr>
<tr>
<td>- pure</td>
<td>- classical</td>
</tr>
<tr>
<td>- cuniculatum</td>
<td>- warty-basaloid</td>
</tr>
<tr>
<td>Papillary NOS</td>
<td>- clear cell</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>Lymphoepithelioma like</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
</tr>
<tr>
<td>Other rare</td>
<td></td>
</tr>
</tbody>
</table>
Distribution of penile SCC subtypes.

- **Usual**: 44%
- **Mixed**: 21%
- **Sarcomatoid**: 7%
- **Warty/Basaloid**: 4%
- **Warty**: 7%
- **Basaloid**: 7%
- **Pseudohyperplastic**: 3%
- **Papillary**: 2%
- **Verrucous**: 3%
- **Other**: 2%
II. GRADING OF CANCER

*Malignity only varies in degree...Rudolf Virchow*

- Von Hansemann *(1898)* -
  - *mitotic activity and anaplasia linked to biology & clinical outcome*

- Broders *(1920)* – Squamous cancer of lip and skin
  - *Well, moderately, poorly and undifferentiated cancer (G1-4)*

- Highly evolved over the years
  - grading based on cancer histologic-type or location
GRADING IN UROLOGIC CANCERS

- ISUP & WHO
  PROACTIVE STANCE
GRADING OF RCC (2016)

• WHO/ISUP SYSTEM – modified from Fuhrman system
• To factor in necrosis for clear cell RCC
• Recommended to be used in all types of RCC though not validated beyond clear cell RCC
GRADING BLADDER CANCER
WHO/ISUP (2016)

• Non invasive: Papilloma, PUNLMP, LG & HG
• Invasive: Low grade (rare) & high grade
The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma

Definition of Grading Patterns and Proposal for a New Grading System

Jonathan I. Epstein, MD,* Lars Egevad, MD, PhD, † Mahul B. Amin, MD, ‡ Brett Delahunt, MD, § John R. Srigley, MD, || Peter A. Humphrey, MD, PhD, ¶ and the Grading Committee
**WHO/ISUP Grading in penile SCC.**
- Gr I, well differentiated
- Gr II, moderately differentiated
- Gr III, poorly differentiated
Why the Need for Yet Another Consensus Conference in 2014

• Changes in prostate cancer practice has led some clinicians to challenge the existing grading system

• Important for the pathology community to respond

67 pathology experts & 18 clinicians, from 17 different countries participated
The Diagnosis of “Cancer” Drives Overtreatment

• Fear of death from cancer likely plays some role, and removing the label “cancer” could reduce unnecessary treatment of low grade disease.

• Proposed name: IDLE (indolent lesion of epithelial origin) (Esserman, Lancet Oncol et al., 2013)

“The problem for the public is you hear the word cancer, and you think you will die unless you get treated. We should reserve this term, ‘cancer,’ for those things that are highly likely to cause a problem.”
“We need a 21st-century definition of cancer instead of a 19th-century definition of cancer, which is what we’ve been using,” said Dr. Otis W. Brawley, CMO for Am Cancer Society

Gleason 6 is cancer based on

- Morphological features
- Molecular characteristics
- 20% undersampling of higher grade cancer with Gleason 6 on biopsy
- Patients will be lost to follow-up if called IDLE tumor – Call cancer & ask urologist to inform patients of prognosis
Reporting of Gleason score Prognostic Grade Groups

- Gleason score $\leq 6$:
  - Prognostic Grade Group I

- Gleason score $3 + 4 = 7$
  - Prognostic Grade Group II

- Gleason score $4 + 3 = 7$
  - Prognostic Grade Group III

- Gleason score 8
  - Prognostic Grade Group IV

- Gleason score 9-10
  - Prognostic Grade Group V

Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).

INCORPORATION OF PROGNOSTIC GROUPS ENDORSED BY THE ISUP (2105) & WHO (2016)
Probability of recurrence-free progression for different prognostic grade groups

Approx. 20,000 pts treated at 4 institutions
Why Address the Morphologic of Neuroendocrine Pca Classification Now?

- **Changing Natural History**
  - Awareness that new high potency anti-androgens may be shifting pattern of progression

- **New Molecular Insights**
  - Very recent findings of highly prevalent Aurora Kinase and N-Myc amplification and overexpression in NED

- **Clinical and Treatment Implications**
  - Rapid “explosive” progression in a subset
  - Prevalent high grade neuroendocrine phenotype
  - Potential for substantial response to cisplatin-based and or novel targeted therapies
Proposed Morphologic Classification of Prostate Cancer with Neuroendocrine Differentiation

Epstein*, Amin*, Beltran, Lotan Mosquera, Reuter, Robinson, Troncoso, Rubin

*co-first authors

III. PATHOLOGIC STAGING OF CANCERS

- VISIONARY STANCE BY OUR FOREFATHERS

- ACTIVE INVOLVEMENT IN ONGOING AND FUTURE REVISIONS
STAGING: Historical Perspective

- North American effort first organized as the American Joint Committee for Cancer Staging and End Results Reporting (AJC) (1959)
  - American College of Surgeons, American College of Radiology, College of American Pathologists, College of Physicians, American Cancer Society & the National Cancer Institute
- November (1969) – Joint meeting of UICC & AJC – consultation between the 2 groups – agreement of discussion before publication of a classification scheme by either group
- AJC (1970) – adopted “objectives, rules & regulations of the AJC” – resulted in formulation and publication of systems of classification of cancer
• Expansion of “relevant markers to make clear treatment decisions”
  • mitotic rate in GI stromal tumors
  • PSA & Gleason Score in Prostate Cancer
AJCC Vision

...and Where It Fits in the 8th Edition:

Cancer Stage

Definitions of TNM

Prognostic Factors

Clinical Trial Stratification

Prognostic and Risk Assessment Models

Comprehensive Cancer Profile

Population

Personalized
“Prognostication is very difficult especially if it is about the future”

Niels Bohr, Danish Physicist
Nobel Prize 1922
PATHOLOGISTS ROLE
1980s-2000s

- Providing accurate diagnosis
- Providing prognostic information (stage, grade, other clinical and pathologic parameters)
- Providing standardized & synoptic reporting

DIAGNOSTICIANS & PROGNOSTICIANS

IV. PROGNOSTIC CLASSIFICATION
PREDICTION OF RADICAL PROSTATECTOMY FINDINGS

<table>
<thead>
<tr>
<th>PSA Range (ng/mL)</th>
<th>Pathologic Stage</th>
<th>Gleason Grade 3+3</th>
<th>Gleason Grade 3+4</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>2-4</td>
<td>5-6</td>
</tr>
<tr>
<td>0-2.5</td>
<td>Organ confined</td>
<td>86 (71-97)</td>
<td>73 (63-81)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>14 (3-29)</td>
<td>24 (17-33)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>2.6-4.0</td>
<td>Organ confined</td>
<td>78 (58-94)</td>
<td>61 (50-70)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>22 (6-42)</td>
<td>36 (27-45)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>1 (0-4)</td>
</tr>
<tr>
<td>4.1-6.0</td>
<td>Organ confined</td>
<td>73 (52-93)</td>
<td>55 (44-64)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>27 (7-48)</td>
<td>40 (32-50)</td>
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<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>2 (1-4)</td>
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<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>3 (1-7)</td>
</tr>
<tr>
<td>6.1-10.0</td>
<td>Organ confined</td>
<td>67 (45-91)</td>
<td>46 (36-56)</td>
</tr>
<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>33 (9-55)</td>
<td>46 (37-55)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>5 (2-9)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>—</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>Organ confined</td>
<td>54 (32-85)</td>
<td>30 (21-38)</td>
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<tr>
<td></td>
<td>Extraprostatic extension</td>
<td>6 (5-68)</td>
<td>51 (42-60)</td>
</tr>
<tr>
<td></td>
<td>Seminal vesicle (+)</td>
<td>—</td>
<td>6 (2-12)</td>
</tr>
<tr>
<td></td>
<td>Lymph node (+)</td>
<td>6 (5-22)</td>
<td>13 (6-24)</td>
</tr>
</tbody>
</table>

PSA, 10 ng/mL

**Table IV.** Clinical Stage T2c (palpable on both lobes)

**Gleason grade 3+3**

**Gleason grade 3+4**
2016 NCCN GUIDELINES: PROSTATE CA RISK STRATIFICATION

VERY LOW RISK
- T1c
- PSA less 10
- Gleason 6

LOW RISK
- T1-T2a
- PSA less 10
- Gleason 6

INTERMEDIATE RISK
- T2b-T2c
- PSA 10-20
- Gleason 7

HIGH RISK
- T3a
- PSA greater 20
- Gleason 8-10

VERY HIGH RISK
- T3b, T4
- Gleason 9-10 (any 5 pattern)
- 4 or more cores with Gleason 8-10
SELECT CONTRIBUTIONS OF THE LIGHT MICROSCOPE

- Classification of all neoplasms into carcinoma & sarcoma & their specialized types, blastomas, germ cell tumors, gliomas and lymphoma morphotypes
- Concept of grading and pathologic staging
- Identification of specific infectious diseases e.g. the AIDS complex, PML, CMV, etc.
- Recognition of distinct entities
  - Gonadoblastoma
  - PEComa
  - Desmoplastic round cell tumor
  - GI stromal tumors
  - SDH deficient tumors
Histopathology
Current Determination Of Prognosis & Therapy in PCa

- Digital Rectal Exam
- Serum PSA
- Amt. of tumor in biopsy
- Gleason score
V. THERANOSTIC (MOLECULAR) CLASSIFICATION
EVOLVING ROLE OF HISTOPATHOLOGY

• Conventional pathology (until 1990s) – focus on primary diagnosis - not adequate for pts. Management

• Molecular (Precision) pathology (2000.... and beyond.....)
<table>
<thead>
<tr>
<th>Year</th>
<th>Targeted Therapy</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>Androgen ablation</td>
<td>Huggins (Nobel prize)</td>
</tr>
<tr>
<td>1948</td>
<td>Folate Antagonists</td>
<td>Farber</td>
</tr>
<tr>
<td>1950</td>
<td>Anti-estrogens</td>
<td>Huggins</td>
</tr>
<tr>
<td>1962</td>
<td>Pyrimidine antimetabolities</td>
<td>Heidelberger</td>
</tr>
<tr>
<td>1981</td>
<td>Anti-lymphocyte mAb</td>
<td>Levy</td>
</tr>
<tr>
<td>1983</td>
<td>Anti-EGFR antibodies</td>
<td>Mendelsohn and Sato</td>
</tr>
<tr>
<td>1987-2001</td>
<td>HER2</td>
<td>Slamon</td>
</tr>
<tr>
<td>1996-2001</td>
<td>BCR-ABL</td>
<td>Drucker</td>
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Game Changer: The Convergence of Advanced Technologies: Molecular Biology & Bioinformatics


2001 Human Genome Project Completed
## Evolution of Precision (Personalized) Medicine

<table>
<thead>
<tr>
<th>Year</th>
<th>Targeted Therapy</th>
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<tr>
<td>1983</td>
<td>Anti-EGFR antibodies</td>
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<td>1987-2001</td>
<td>HER2</td>
<td>Slamon</td>
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<td>1996-2001</td>
<td>BCR-ABL</td>
<td>Drucker</td>
</tr>
<tr>
<td>2001</td>
<td>Human Genome Project Completed</td>
<td></td>
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<tr>
<td>2005</td>
<td>The Cancer Genome Atlas Project</td>
<td>20-25 cancers comprehensively characterized</td>
</tr>
</tbody>
</table>
PROGNOSTIC/ PREDICTIVE FACTORS – Select listing

- HER2 amplification in breast cancer
- MET amplification in NSCLC
- PTEN deletion in Prostate cancer
- IDH1 & 1p/19q co-deletion in GBMs
- Gene signatures e.g. OncotypeDx, Mammaprint
- *List is rapidly growing************
The Cancer Genome Atlas (TCGA)

- Started in 2005
- **Mission:** Comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer
- New Bioinformatics development for platform integration

- *TCGA finalized tissue collection with matched tumor and normal tissues from 11,000 patients*
- *Comprehensive characterization of 33 cancer types and subtypes, including 10 rare cancers*
Genome Characterization

- TCGA finalized tissue collection with matched tumor and normal tissues from 11,000 patients
- Comprehensive characterization of 33 cancer types and subtypes, including 10 rare cancers
  - Copy Number Alteration (Single Nucleotide Polymorphism Characterization) – SNP/oligoarrays
  - Epigenomics (DNA methylation)
  - Gene (mRNA) Expression (expression arrays)
  - miRNA Analysis
  - Functional Proteomics (reverse phase protein arrays/Signal transduction pathways)
  - Genome sequencing- Whole genome/ Whole exome
EVOLVING ROLE OF HISTOPATHOLOGY

• Conventional pathology (until 1990s) – focus on primary diagnosis - not adequate for pts. Management

• Molecular (Precision) pathology (2000.... and beyond.....)
  - diagnosis of the tumors (diagnostic biomarkers – early detection and monitoring recurrence)
  - determine the outcome (prognostic biomarkers)
  - predict best treatment option (predictive biomarkers)
  - genetic predisposition (preventative biomarkers)
  - biomarkers for refractory (treatment resistance) cancer
Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haseleut, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.
Success Story Melanoma Zelboraf and BRAF V600E Mutation

Subcutaneous Milliary Nodules

Remission 15 weeks PLX4032

Relapse 23 weeks PLX4032

Wagle et al. 2011, JCO 29, 3085
Histologic and Molecular Correlations
Travis, Journal Thoracic Oncology, 2011

Small cell carcinoma

Non-small cell lung carcinoma (NSCLC)

LCNEC  SCC
AdenoSCC  AdenoCa  LC

No EGFR Molecular testing

EGFR Molecular testing

LCNEC: Large cell neuroendocrine, LC: Large cell carcinoma, SCC: Squamous cell carcinoma, AdenoSCC: Adenosquamous
Molecular Classification of Pulmonary Adenocarcinoma

Histology: Adenocarcinoma or Other Non-squamous

EGFR mutation analysis

+ TKI treatment

- EML4-ALK translocation

Young male
light or non-smoker
Acinar, papillary, mucinous

+ ALK inhibitor Crizotinib

- Chemotherapy

Travis, Journal Thoracic Oncology, 2011
Transitioning to Genomic Medicine at the Bedside

• Molecular pathways involved in tumor survival and progression are often enacted by genetic alterations
• Anticancer agents targeting oncogenic pathways have entered clinical trials
• Genomic technologies enable robust tumor genomic profiling in the clinical arena
Oncogenic Pathways in Human Cancers

Vogelstein et al. Science 2013;339:1546-1558

140 Driver genes that promote cancer: 12 signaling pathways 3 core cellular processes Cell fate, Cell Survival, Genome maintenance
The “Evolution” of Non–Small-Cell Lung Cancer

Histology-Based Subtyping

- NSCLC as one disease
- Others 11%
- Squamous 34%
- Adenoca 55%

Adenocarcinoma
- ALK
- HER2
- BRAF
- PIK3CA
- AKT1
- MAP2K1
- NRAS
- ROS1
- RET
- EGFR
- KRAS
- Unknown

Squamous Cell Cancer
- EGFRvIII
- PIK3CA
- EGFR
- DDR2
- FGFR1 Amp
- Unknown

JCO 2013;31:1039-1049
<table>
<thead>
<tr>
<th>Morphological diagnosis</th>
<th>Molecular diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Similar looking</td>
<td>Molecular stratification</td>
</tr>
<tr>
<td>Lung adenocarcinoma</td>
<td>EGFR activation mutation (treat with EGFRi)</td>
</tr>
<tr>
<td></td>
<td>ALK rearrangement (treat with ALK inhibitors)</td>
</tr>
<tr>
<td>Different looking</td>
<td>Molecular similarity</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>BCR/ABL tyrosine kinase activation (treat with TKi)</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>KIT tyrosine kinase activation (treat with TKi)</td>
</tr>
</tbody>
</table>
Moving Away From the One Gene One Test World…

Next Generation Sequencing - How does it work?
## Evolution of Personalized Medicine

<table>
<thead>
<tr>
<th>Year</th>
<th>Targeted Therapy</th>
<th>Investigator / Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Anti-EGFR antibodies</td>
<td>Mendelsohn and Sato</td>
</tr>
<tr>
<td>1987-2001</td>
<td>HER2</td>
<td>Slamon</td>
</tr>
<tr>
<td>1996-2001</td>
<td>BCR-ABL</td>
<td>Drucker</td>
</tr>
<tr>
<td>2001</td>
<td>Human Genome Project Completed</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Targeted therapies</td>
<td>$2 Billion worldwide</td>
</tr>
<tr>
<td>2005</td>
<td>The Cancer Genome Atlas Project</td>
<td>20-25 cancers comprehensively characterized</td>
</tr>
<tr>
<td>2011</td>
<td>Targeted Therapies</td>
<td>$21 Billion worldwide</td>
</tr>
<tr>
<td></td>
<td>NGS testing, clinical samples</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>&gt;1100 unique clinical trials with 800 targeted therapy</td>
<td></td>
</tr>
<tr>
<td>2016...</td>
<td>Chromosomal microarrays &amp; targeted panels</td>
<td></td>
</tr>
</tbody>
</table>
Molecular Stratification of PCa Pts.

Surgery

- Urinary PCA3 & TMPRSS2/ERG Gain
- PTEN deletion
- MYCC gain/amplification
- Loss of 8p21
- AR gene amplification
- MET overexpression
- VEGFR2 overexpression

(+) More studies needed

Non-surgical therapy

(−)
<table>
<thead>
<tr>
<th>Gene/protein/phenotype</th>
<th>Molecular aberration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTEN loss</td>
<td>Deletion, methylation</td>
<td>AKT pathway/mTOR inhibitors</td>
</tr>
<tr>
<td>RAF</td>
<td>Gene fusion</td>
<td>RAF kinase inhibitor</td>
</tr>
<tr>
<td>SPINK1</td>
<td>Gene fusion</td>
<td>EGFR inhibitor</td>
</tr>
<tr>
<td>Her2</td>
<td>Overexpression</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Hyperproliferation</td>
<td>Aurora kinase inhibitor</td>
</tr>
<tr>
<td>BRCA2/ ATM</td>
<td>Mutation</td>
<td>PARP inhibitor</td>
</tr>
<tr>
<td>C-MET/VEGFR2</td>
<td>Overexpression</td>
<td>Crizotinib, Cabozantinib</td>
</tr>
</tbody>
</table>

**BIOMARKERS IN PROSTATE CANCER**

**THERAPEUTIC TARGETS**
<table>
<thead>
<tr>
<th>Gene/protein/phenotype</th>
<th>Molecular aberration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMPRSS2-ERG/ETS</td>
<td>Gene fusion</td>
<td>PARP inhibitors</td>
</tr>
<tr>
<td>TP53</td>
<td>Mutation</td>
<td>Wee-1 inhibitors</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutations/loss</td>
<td>mTORi</td>
</tr>
<tr>
<td>AR</td>
<td>Mutations/amplifications</td>
<td>AR directed therapies</td>
</tr>
<tr>
<td>RB</td>
<td>Deleted/methylated</td>
<td>Hypomethylating agents</td>
</tr>
<tr>
<td>APC</td>
<td>Promoter methylation</td>
<td>Wnt inhibitors</td>
</tr>
<tr>
<td>MYC/AURK</td>
<td>Amplification</td>
<td>AURKA inhibitors</td>
</tr>
</tbody>
</table>
### BIOMARKERS IN BLADDER CANCER

<table>
<thead>
<tr>
<th>Gene/protein/phenotype</th>
<th>Molecular aberration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGFR3</td>
<td>Mutation</td>
<td>FGFR inhibitors</td>
</tr>
<tr>
<td>EGFR/ Her 2</td>
<td>Overexpression</td>
<td>EGFR inhibitors</td>
</tr>
<tr>
<td>PIK3CA/AKT/TSC/PTEN</td>
<td>Activation</td>
<td>PIK3 kinase/ mTORi</td>
</tr>
<tr>
<td>Tyrosine kinase (multiple)</td>
<td>Mutation, amplification</td>
<td>Cabozantinib/ Bevacizumab</td>
</tr>
<tr>
<td>RAS</td>
<td>Activation</td>
<td>Farnesyl transferase inhibitors</td>
</tr>
<tr>
<td>PD-1</td>
<td>Upregulation</td>
<td>Anti-PD-1 Ab</td>
</tr>
</tbody>
</table>

**THERAPEUTIC TARGETS**
<table>
<thead>
<tr>
<th>Gene/protein/phenotype</th>
<th>Molecular aberration</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polo-like kinase 1 (Plk1)</td>
<td>Overexpression</td>
<td>Plk-1 inhibitors</td>
</tr>
<tr>
<td>Aurora kinase A</td>
<td>Amplification</td>
<td>AURKA inhibitors</td>
</tr>
<tr>
<td>Cyclin dependant kinase (CDK)</td>
<td>Deletion/amplification</td>
<td>CDKI</td>
</tr>
<tr>
<td>Histone deacyetylase</td>
<td>Mutation</td>
<td>HDAC inhibitors</td>
</tr>
</tbody>
</table>

**BIOMARKERS IN BLADDER CANCER**

**THERAPEUTIC TARGETS**
Luminal Vs Basal Bladder Ca
*Cancer Cell.* 2014; 25(2): 152–165

• 3 molecular subtypes of MIBC that resembled established molecular subtypes of breast cancer
  – Basal MIBCs shared biomarkers with basal breast cancers and were characterized by p63 activation, squamous differentiation, and more aggressive disease at presentation
  – Luminal MIBCs contained features of active PPARγ and estrogen receptor (ER) transcription and were enriched with activating *FGFR3* mutations and potentially FGFR inhibitor sensitivity
  – p53-like MIBCs were consistently resistant to neoadjuvant MVAC chemotherapy, and all chemoresistant tumors adopted a p53-like phenotype after therapy.
Molecular Subtypes of UBCA
# Targeted therapy in Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Known somatic alterations</th>
<th>Involved pathway</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td><em>VHL, PBRM1, SETD2, BAP1, mTOR, PI3K</em></td>
<td>VEGF pathway mTOR pathway</td>
<td>Tyrosine kinase inhibitor; TKI (sorafenib, sunitinib) Newer TKI (pazopanib, axitinib) mTOR inhibitors (everolimus &amp; temsirolimus)</td>
</tr>
<tr>
<td>Papillary RCC</td>
<td><em>MET</em></td>
<td>MET/HGF pathway</td>
<td>TKI, mTOR inhibitors, dual MET/ VEGFR inhibitor (foretinib)</td>
</tr>
<tr>
<td>Chromophobe RCC</td>
<td><em>TP53</em></td>
<td>Upregulation of the mTOR pathway</td>
<td>mTOR inhibitors (everolimus &amp; temsirolimus)</td>
</tr>
<tr>
<td>Tumor type</td>
<td>Known somatic alterations</td>
<td>Involved pathway</td>
<td>Targeted therapy</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------</td>
<td>-------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Collecting duct Ca</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown (cytotoxic chemotherapy is common)</td>
</tr>
<tr>
<td>MiT family RCC</td>
<td>Xp11.2 and t(6;11) translocations</td>
<td>MET signals as a downstream consequence of aberrant TFE3 activity</td>
<td>MET inhibitor (tivantinib) (in small cohort)</td>
</tr>
</tbody>
</table>
Comprehensive molecular characterization of clear cell renal cell carcinoma

The Cancer Genome Atlas Research Network*
TIMELINE: PROGRESS AGAINST KIDNEY CANCER

1960

1970

1980

1990

2000

2010

2015

1985
Immunotherapy benefits with advanced renal cell carcinoma

1992
First Immunotherapy approved

2000
Combination of Surgical Removal & Immunotherapy

2005
First FDA Approval of A Targeted Drug for kidney cancer “Sorafenib”
2006–2007
Sunitinib, Temsirolimus

2009
Everolimus, Bevacizumab, Pazopanib

2011
Axitinib

ASCO cancer.net
The Emerging Paradigm
Era of Precision Medicine

FDA Approved drugs

Drugs in Clinical Trials

Studies to understand pathway alterations and tumor biology

Other actionable alterations

EGFR, ALK, KRAS, BRAF

STAT, PIK3, MTOR, MET...

Targeted Exome

Whole Exome

Whole Genome
Molecular Diagnostic Consultation
50 Gene Cancer Panel, 2800 Mutations, by Next-Generation Sequencing

Specimen: Right lung FNA
Indication: Adenocarcinoma

RESULTS: Reportable Hotspot Mutations Detected

<table>
<thead>
<tr>
<th>Gene</th>
<th>Nucleotide Change</th>
<th>Amino Acid Change</th>
<th>Chromosome</th>
<th>Exon</th>
<th>COSMIC ID</th>
<th>% Mutant Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>c.2239-2250del</td>
<td>L747_A750del</td>
<td>7</td>
<td>19</td>
<td>COSM218(del)</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>c.2252_2264delHinsT770C0770CA</td>
<td>T771_A755delinsWPH</td>
<td>7</td>
<td>19</td>
<td></td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>c.2369C&gt;C1</td>
<td>790T&gt;TMI</td>
<td>7</td>
<td>20</td>
<td>COSM 6240</td>
<td>35%</td>
</tr>
<tr>
<td>TP53</td>
<td>C.343G&gt;GA</td>
<td>243R&gt;Q</td>
<td>17</td>
<td>5</td>
<td>COSM10661</td>
<td>29%</td>
</tr>
<tr>
<td>CTNNB1</td>
<td>c.121A&gt;AG</td>
<td>41T&gt;YA</td>
<td>3</td>
<td>2</td>
<td>COSM45654</td>
<td>12%</td>
</tr>
</tbody>
</table>

INTERPRETATION

Mutations Related to FDA-approved therapy in NSCLC
- The EGFR T790M resistance mutation confers resistance to first generation EGFR TKIs
- TP53 inactivation may confer resistance to etoposide, cisplatin, and radiation

Mutations Related to Off-Label Therapy*
- None detected by this assay.

Mutations Related to non-FDA-approved Therapy
- T790M specific EGFR TKIs such as CO-1686 showed benefit in tumors resistant to first generation TKIs in phase 1 studies.
- Wee-1 inhibitor MK-1775 has shown some benefit in TP53 mutated tumors in phase 1 trials.
- Hsp90 inhibitors may be effective in T790M mutated NSCLC in preclinical studies.
- Kenacepin may be effective in drug resistant TP53 mutated cancers in preclinical studies.

Mutations Associated with Eligible Clinical trials in NSCLC
- Phase 1/2 trials, namely NCT01646125 and NCT01526928, are available for NSCLC with EGFR T790M resistance mutation.
- Phase 1 trials, namely NCT01664000, are available targeting TP53 mutations.
- Phase 1 trials, namely NCT01302405 and NCT01808867, are available targeting solid tumors with CTNNB1 activating mutations.

Mutations with Prognostic Significance
- Aberrant beta-catenin expression has been associated with larger tumor size, pleural and lymphatic/vascular invasion, and advanced tumor stage in lung adenocarcinomas.
INTERPRETATION

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Mutations with Prognostic Significance

- Aberrant beta-catenin expression has been associated with larger tumor size, pleural and lymphatic/vascular invasion, and advanced tumor stage in lung adenocarcinoma.
The Evolving Landscape (2001-2016....)

• Advances in molecular underpinnings of cancer - TCGA etc - oncogenesis, progression, resistance – molecular classification of cancer

• Increasing availability of high throughput testing, mutational analysis (sequencing), microarrays (RNA, mi RNAs, SNPs, etc)

• Advances in informatics & computational biology; increased adoption of EHRs, data interoperability, real time risk calculating strategy apps (nomograms, tables, etc)

• Cancer care is increasingly coordinated through well defined clinical multidisciplinary teams

• Surgical, medical (targeted) and radiation oncology therapies that continue to become more sophisticated; as are diagnostic modalities (imaging and pathology)

• Globalization of cancer – universal applicability of treatment & molecular advances
Surgical Pathology Approach (1950s-2000)

Gross

Microscopy

Clinical Information

Ancillary studies

PATHOLOGIC DIAGNOSIS
FUTURE CLASSIFICATION SCHEMA

FURTHER ENABLE
CLINICAL MANAGEMENT
FOR ERA OF PRECISION MEDICINE

- diagnosis of the tumors (diagnostic biomarkers – early detection and monitoring recurrence)
- determine the outcome (prognostic biomarkers)
- predict best treatment option (predictive biomarkers)
- genetic predisposition (preventative biomarkers)
- biomarkers for refractory (treatment resistance) cancer
CLASSIFICATION (2016 & Beyond……)

EXTENT OF DISEASE

HISTOLOGIC

THERANOSTIC

CANCER IS A COMPLEX ECOSYSTEM: INTEGRATED APPROACH

ERA

MOLECULAR SIGNATURE

GRADING
PATHOLOGY REPORT
(CLASSIFICATION)

ACCURATE    TIMELY    RELAVANT

COMPLIANT    PORTABLE    COMPREHENSIVE

DRIVING CLINICAL CARE
Thank you!!!
THE COMPLETE SURGICAL PATHOLOGY REPORT IN 2015:
Over 100 M reports generated world wide

• “PATIENT - CENTRIC”

Accurate  Relevant  Timely  Integrated

Compliant  Standardized - Synoptic  Portable

DIAGNOSIS

PROGNOSIS

PREDICTION

PREVENTION
MOLECULAR SIGNATURE AS A CLASSIFIER

• Hype or Hope?

• Fact: Lethal cancer is going to increasingly become a “chronic” disease

• Answer to Hype or Hope? – partially both – depends on how we continue the journey......
CHALLENGES

• Tumor related
• Technique selection - related
• Pathologist related
• Extrinsic factors
New “clone”

TUMOR HETEROGENITY
Intra & Inter tumoral
Intra & Inter metastasis

TUMOR SAMPLING
FOR MOLECULAR (?)

PROSTATE CANCER
IS
MULTIFOCAL

NEW MOLECULAR
CLASSIFICATION IN
METASTASES

MET. TUMORS DEVELOP
RESISTANCE –
II. EMBRACING THE "OMICS" ERA

The "Next Generation Histopathologist"

- Genomics
- Epigenomics
- Proteomics
- Transcriptomics
- Metabolomics
- Pharmacogenomics
- Otheromics
III. TECHNIQUES & TECHNOLOGY

- IHC
- FISH
- RT-PCR
- Next generation sequencing
- RNA-seq
- Chip seq
- Mass Spec
- Protein Microarrays
- Other
IV. EXTRINSIC FACTORS

- Regulation of the health care profession and industry
- Constricting Reimbursement
- Clinician & Patient acceptance
- Clinician & Patient expectation
PRECISION MEDICINE

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

THERANOSTICS

The right test, for the right person at the right time with the right technique, for right diagnosis and for improved patient care
CONTINUING EVOLUTION OF OUR SPECIALITY

• Ongoing journey
  - 350 years since Leeuwenhoek and the microscope
  - 84 years since the League of Nations and staging
  - 95 years since Broders grading
  - 72 years since the Huggins & his Nobel prize (precision medicine)

In terms of molecular classification we are at stage of discovery of the microscope – the level we were 300-350 years ago

Fasten your seat belts – become a life long learner
  - Human knowledge is set to double every 10-15 years
  - The next 25 – 30 years will be the opportunity of our specialty
CONCLUSIONS

• We (pathologists) live in the most exciting and promising times and the most concerning and challenging times

• The opportunity is ours to seize!!!!!
Anatomic Profiling of Cancer

Genomic Profiling of Cancer
EMBRACING THE “OMICS” ERA

• Genomics
  – Study of the entire diploid genome in health and disease
  – Protein-coding sequences comprise approximately 2% of genome (Exome) - *which are probably the most relevant for cancer*
  – The Encyclopedia of DNA Elements (ENCODE) project discovered that 80% of the genome has biochemical functions which needs further study
  – Typically studied by next generation sequencing methods

• Pharmacogenomics
  – Deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug’s efficacy or toxicity
  – Pharmacogenomics aims to rationalize drug therapy
EMBRACING THE “OMICS” ERA

- **Epigenomics**
  - Reversible chemical modifications to the DNA, or histones that produce changes in the expression of genes without altering their base sequence
  - Cytosine methylation and histone modifications – best characterized
  - Histone modifications include acetylation, methylation, phosphorylation, ubiquitination ... etc
  - Studied by Chromatin Immunoprecipitation Sequencing (Chip-Seq)

- **Transcriptomics**
  - Transcriptome is the complete set of all RNA molecules in a given tissue
  - Transcriptomics refers to analysis of protein coding RNA (mRNA) as well as non-coding RNA such as microRNA (miRNA) that regulate gene function
  - Only about 2 percent of the genome is represented in the transcriptome as protein-coding genes
  - RNA sequencing (RNAseq) is the preferred technology
EMBRACING THE “OMICS” ERA

Proteomics
- Complete set of proteins expressed by a cell, tissue, or organism.
- Inherently complex and varies with time, tissue, physiologic and pathologic conditions
- Post-translational modifications (glycosylation, phosphorylation, acetylation, ubiquitylation) change protein structure and function
- Studied by mass spectrometry and protein microarrays

Metabolomics
- Complete set of small molecule metabolites found within a biological sample: carbohydrate, lipid, amino acid, nucleic acid, hormones, other signaling molecules, as well as exogenous substances such as drugs and their metabolites
- Alterations in energy balance may be relevant for targeted therapies because of the enhanced susceptibility of cancer cells to changes in sources of energy
- Mass spectrometry and nuclear magnetic resonance spectroscopy