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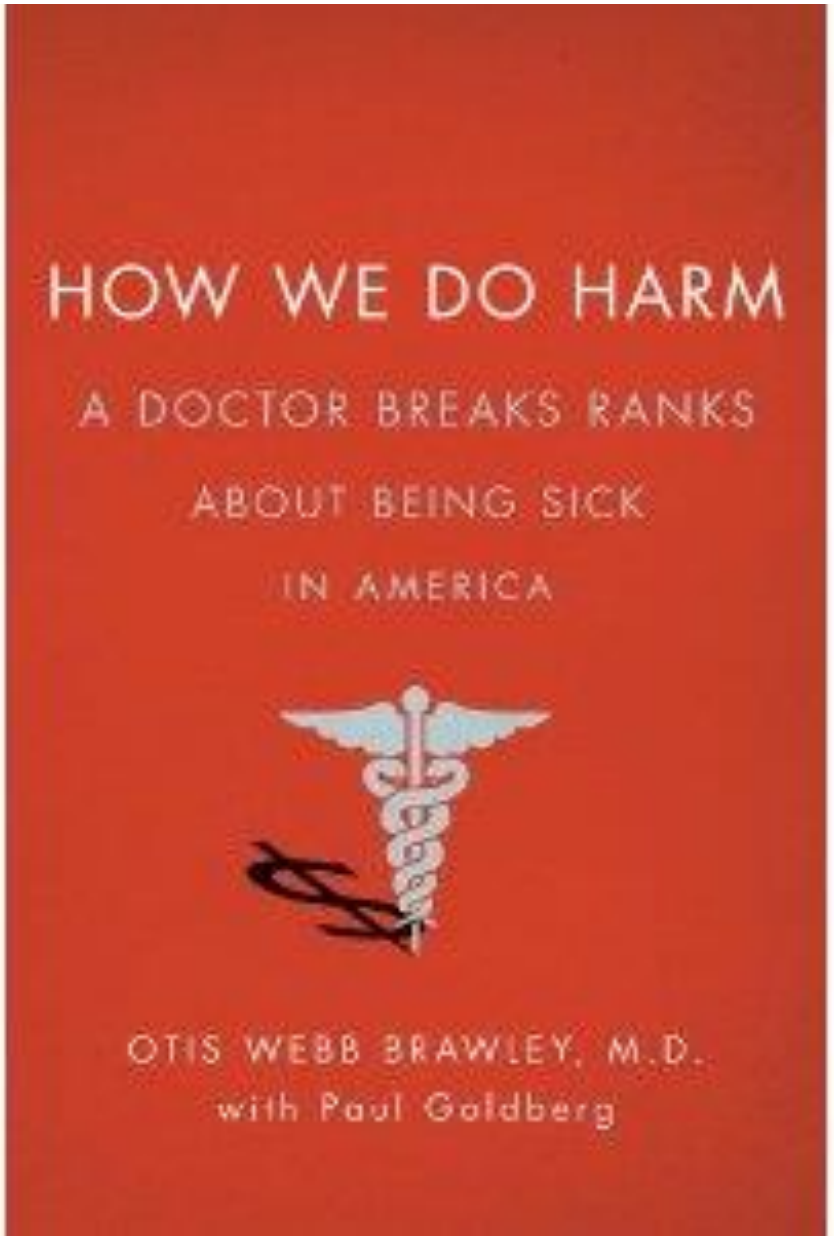
Disclosures

- Employment:
  - American Cancer Society
  - Emory University
  - Turner Broadcasting (CNN)
- Consulting
  - National Institutes of Health
  - Centers for Disease Control
  - Department of Defense


HOW WE DO HARM
A DOCTOR BREAKS RANKS
ABOUT BEING SICK
IN AMERICA
OTIS WEBB BRAWLEY, M.D.
with Paul Goldberg

Challenges to Ensuring that Patients Have Access to Diagnostic Expertise to Inform the Best Possible Cancer Care

The Most Important Question in Cancer Control

How can we provide adequate high quality care (to include preventive services) to populations that very often do not receive it?

The American Healthcare System

Disparities related to:

- Access to care
- Receipt of care
- Quality of care

The American Healthcare System

Inefficient!!!

- Some over consume resources
  (This can be harmful to the over-consumer)
- Some under consume resources
  (This is the cause of disparities)
- Healthcare outcomes could be better
  (People die needlessly)

Diagnostic Testing

- Pathology and Radiology is often subjective (interpretation is skill dependent)

- Molecular testing is more objective but there is still some uncertainty

Clinical Trials Concepts

- Efficacy – Does the intervention work?
- Effectiveness – How well does it work in the real world

The National Lung Screening Trial

- **Nearly 54,000 at high risk enrolled in the trial**
  - age 55 and above
  - 30 pack year or greater history of smoking; if quit, did so less than 15 years prior to trial entry
  - Reasonable health
- **Subjects prospectively randomized to chest X-ray (sham) or low dose spiral CT (LDCT) yearly for three years**
  - Analysis 10 years from start of screening showed LDCT associated with a 20% reduction in relative risk of death
  - ***Done at 30 academic sites with lung cancer expertise***

CT: computed tomography

N Engl J Med. 2011 Aug 4;364(22):2148-54.

Lung Cancer Screening

Test is highly sensitive and not very specific among specialist radiologists

- 20% false positive in first screen
- 40% by third annual screen

The National Lung Screening Trial: A Closer Look

- **LDCT associated with a 20 % mortality reduction**

  Among 27,000 screened with LDCT

  - 87 less deaths in the screened group
  - About 350 in the screened group still died of lung cancer
  - 16 died due to interventions caused by screening
    - 6/16 did not have cancer

- **In this high risk group, the benefit/risk ratio of 5.4 lives saved for:**
  - Every 2 people with a complication due to an invasive procedure
  - Every 1 life lost prematurely due to diagnostic procedures

LDCT: low dose spiral CT

N Engl J Med. 2011 Aug 4;364(22):2148-54.

The National Lung Screening Trial

(one view of the 20 percent reduction in mortality)

Screening always has benefits and harms!

5.4 lives saved for:

- Every 2 people with a complication due to an invasive procedure
- Every 1 life lost prematurely

What will the ratio be for lung screening in community hospitals?

Quality of Radiology

- Availability of:
  - Well trained Radiologists
  - Up to date functioning equipment
  - Adequate time to do their work

Quality of Pathology

- Availability of:
  - Well trained pathologists
  - Up to date functioning equipment
  - Good reagents
  - Adequate time to do their work

Diagnostic Concordance in Breast Pathology

- Concordance was 75.3% (95%CI, 73.4%-77%) of 6900 biopsies studied

- Disagreement with reference pathologist was greatest in:
  - Lower weekly case volumes
  - Smaller practices
  - Non-academic settings

Elmore et al, JAMA 2015

Colon Cancer Quality of Surgery

A minimum 12 lymph node examination in an adequate colorectal cancer surgery

- About half have 12 or more LN examined.
- Hispanics, Blacks and the poor have higher odds of receiving an inadequate dissection.
- Inadequate examination associated with hospital where care was received.
- Inadequate staging leads to some of the talk that colorectal cancer is more aggressive among Blacks!!!

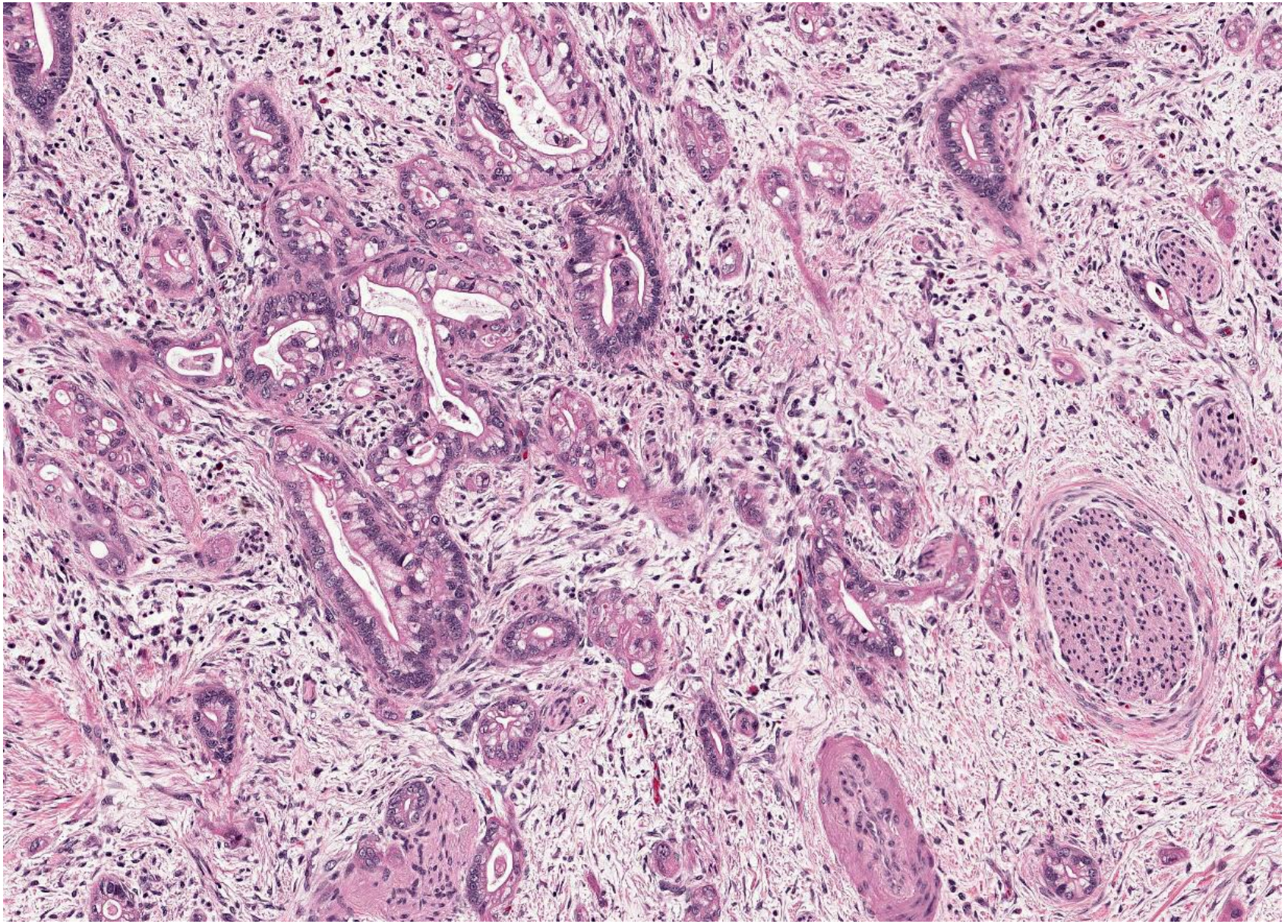
  – Rhoads et al, Cancer 2012 Jan 15;118(2):469-77

Redefining Cancer!

American Cancer Society®

Rudolph Ludwig Karl Virchow

1821- 1902

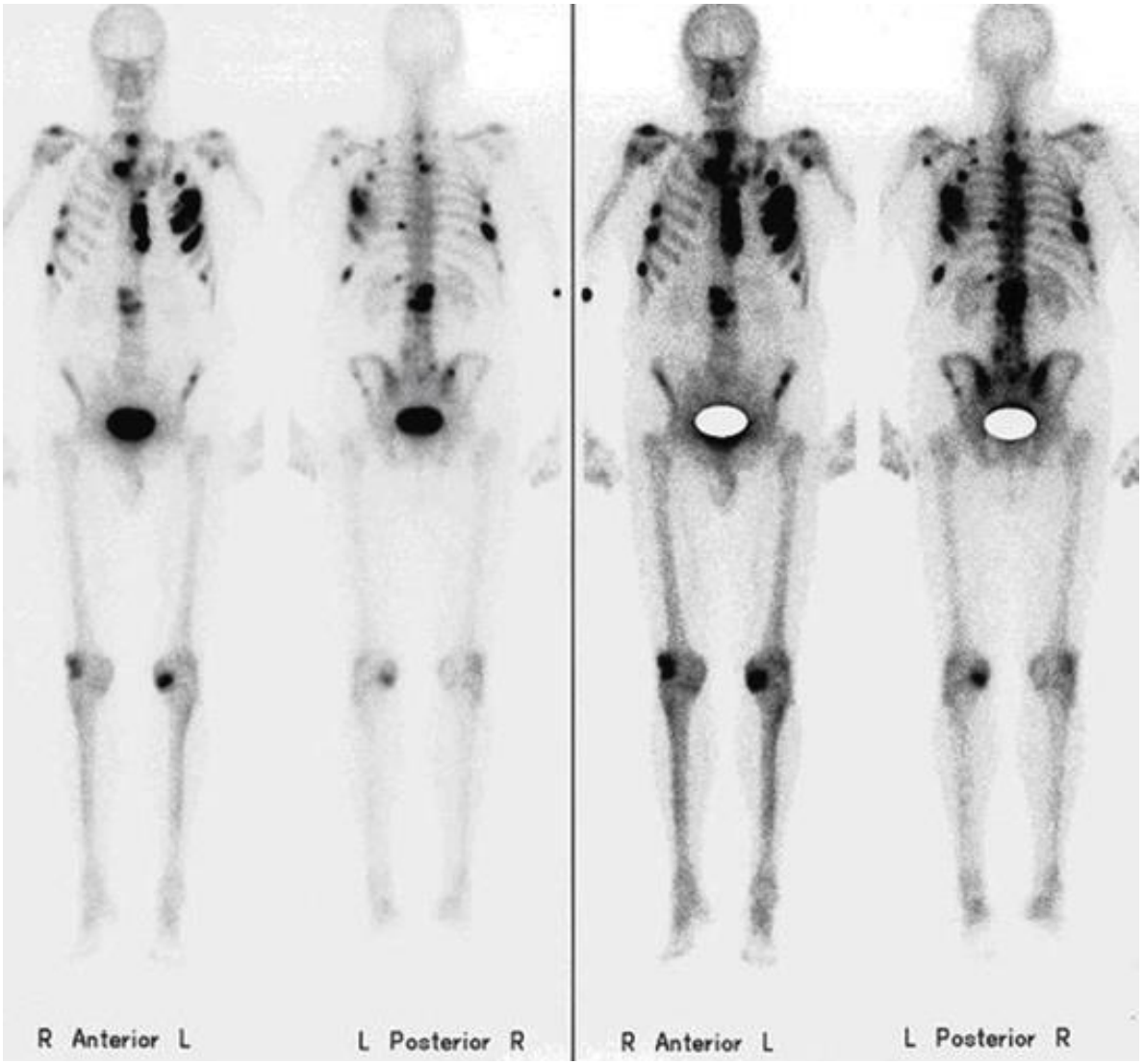


Adenocarcinoma

- Cancer is uncontrolled cell growth, uncontrolled mitoses

- Some cancerous cells can spread and interfere with bodily functions.

Bone Scan of Metastatic Adenocarcinoma



A 19th Century Definition of Cancer

American Cancer Society®

The Definition of Cancer

- **Currently based on morphology and histology defined in the mid 19th century by Rudolf Virchow using biopsies done at autopsy and a light microscope - these "cancers" obviously killed**

- **Advances in cancer diagnosis:**
  - X-ray – 1890's
  - Mammogram - 1950's
  - Ultrasound – 1960's
  - CT scanner - 1970's
  - MRI - 1980's
  - Stereotactic biopsy methods – 2000's to present

- **Small "localized cancers" found today microscopically look like the cancers that kill (these biopsies fit the profile of tumors that killed)**

CT: computed tomography
MRI: magnetic resonance imaging

Virchow. Vorlesungen über Cellularpathologie in ihrer Begründung auf physiologischer und pathologischer Gewebelehre, Berlin 1848
Welch HG, Black WC. J Natl Cancer Inst. 2010 Apr 22;102:605-13

Cancer Overdiagnosis

- Cancers that would not go on to spread, cause symptoms, or death.
- Cancers that can be cured, but do not need to be cured!
- Estimates:
  - 15 to 20% of screen detected lung cancers
  - 15 to 25% of screen detected breast cancers
  - 40% of ultrasound detected thyroid cancers
  - 40 to 60% of PSA detected prostate cancers

Welch HG, Black WC. J Natl Cancer Inst. 2010 Apr 22;102:605-13

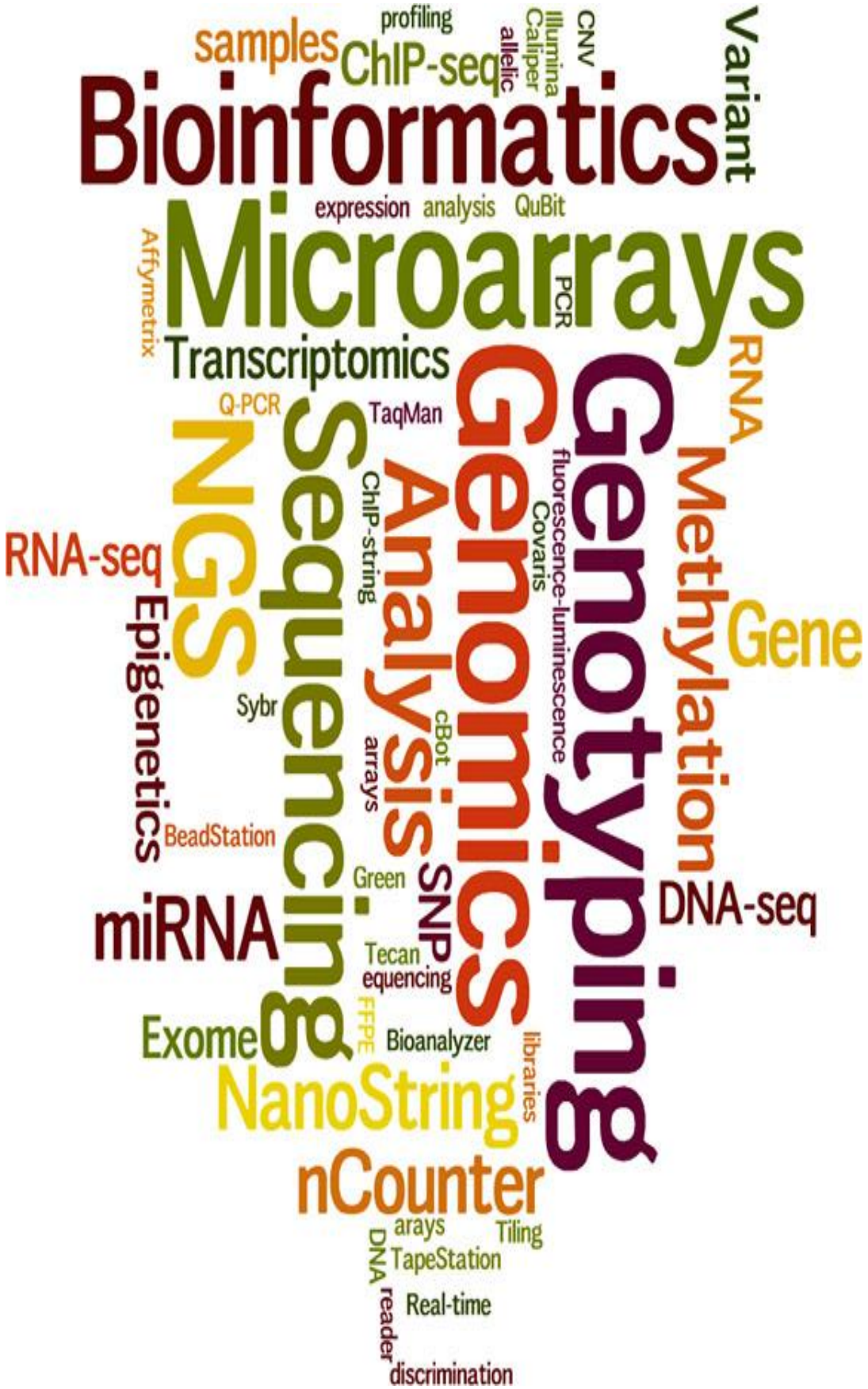
A 21st Century Definition of Cancer

A 21st Century Definition of Cancer

An understanding of the varying biologic behaviors of cancer based on histology and genomics.

Numerous molecular targets have and are being defined. Some are drugable targets.

An understanding of the varying vulnerabilities of cancers to medical interventions.


profiling
samples
ChIP-seq
allelic
Illumina
Caliper
CNV
Variant
Bioinformatics
expression
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QuBit
Microarrays
Affymetrix
PCR
Transcriptomics
RNA
Genotyping
Q-PCR
TaqMan
NGS
Sequencing
Analysis
Genomics
fluorescence-luminescence
Covaris
ChIP-string
Methylation
RNA-seq
Epigenetics
Gene
Sybr
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arrays
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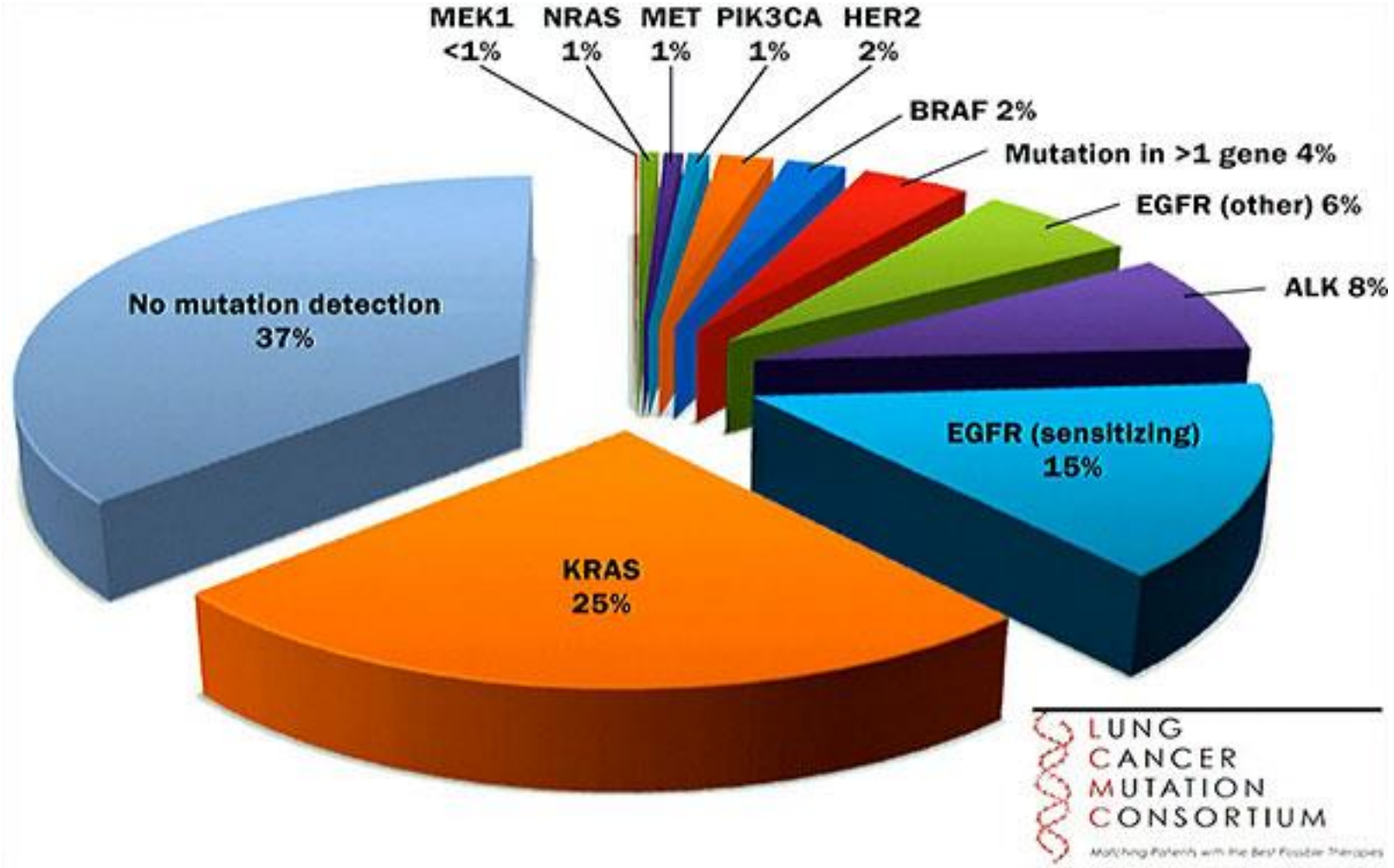
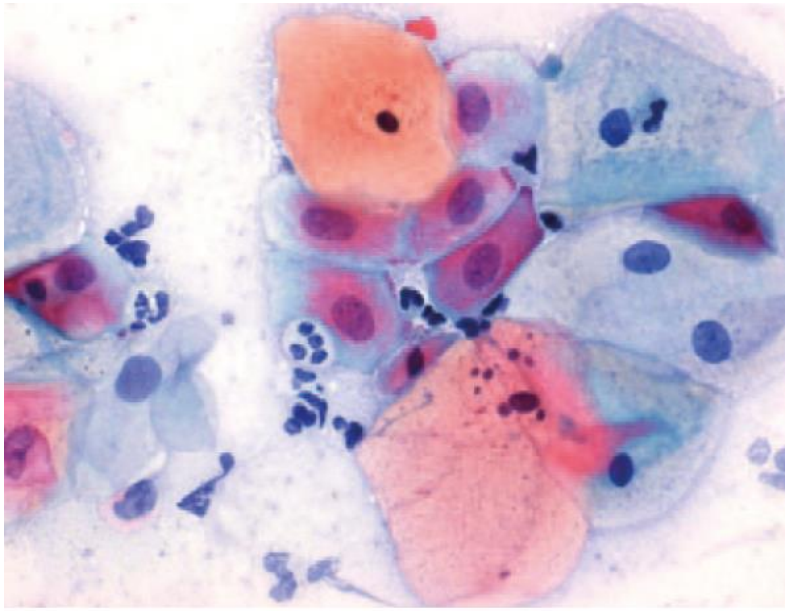

MEK1 <1%
NRAS 1%
MET 1%
PIK3CA 1%
HER2 2%
BRAF 2%
Mutation in >1 gene 4%
EGFR (other) 6%
ALK 8%
EGFR (sensitizing) 15%
KRAS 25%
No mutation detection 37%
LUNG CANCER MUTATION CONSORTIUM

Beware: Premature Dissemination of New Technologies!!!

George Papinicolau
1883-1962



Cervical Cytology

A Brief History of Cervical Screening

From 1930 to the early 1960's the Pap test was used as a diagnostic test but:

- Cervical pathology was not standardized and cervical dysplasia was not distinct from cervical cancer.
- Many gynecologists treated dysplastic lesions with radical hysterectomy or radiation therapy.

A Brief History of Cervical Screening

Many (thousands) of these had:

– Dysplastic lesions that would now be called CIN 1 or CIN 2.

– These lesions are now watched as most regress over time.

Lesson: Carefully study the science before dissemination

The Breast Cancer Detection Demonstration Project

The American Cancer Society and National Cancer Institute launched it in 1972.

By 1977, 506 “minimal” breast lesions” of less than one centimeter in diameter had been found in BCDDP participants.

The Breast Cancer Detection Demonstration Project

In one audit, 66 of the 506 lesions were not invasive cancer nor carcinoma in situ.

Most of the 66 women had already received definitive therapy which was radical mastectomy.

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