Cancer Pathology: The Past, the Present, and the Future

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BC Cancer Agency
Microscopy in Pathology

The light microscope has been the major tool for pathologists.
The Compound Microscope was Invented in 1590

Zacharias Jansen, a Dutch spectacle-maker from Middelburg invented the compound microscope.

He was also fond of counterfeiting coins, for which he was arrested many times, but released because the bailiff's son was an accomplice.
Rudolf Virchow (1821-1902)

The father of histopathology and cellular pathology
The Discovery of DNA – 1898

DNA was first identified in 1868 by Friedrich Miescher, a Swiss biologist, in the nuclei of pus cells obtained from discarded surgical bandages. He called the substance nuclein.
First Generation Photomicrography

Pathologists had very large offices in those days
Electron Microscopy - 1931

Co-invented by Germans, Max Knott and Ernst Ruska in 1931, Ernst Ruska was awarded half of the Nobel Prize for Physics in 1986 for his invention. (The other half of the Nobel Prize was divided between Heinrich Rohrer and Gerd Binnig for the STM.)
Discovery of DNA Structure - 1953

The Nobel Prize in Physiology or Medicine 1962

"for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material"
Southern blot method -1975

Professor Edwin Southern
Oxford University
Kohler and Milstein Method for producing Monoclonal antibodies

1975

Nobel Prize
15 October 1984
The Revolution in Immunohistochemistry

CD20

CD5
Diagnostic and Therapeutic Monoclonal Antibodies

- **Murine**
  100% mouse protein

- **Chimeric**
  33% mouse protein

- **Humanized**
  approx. 10% mouse proteins

- **HuCAL antibody**
  100% human proteins
Human Combinatorial Antibody Library (HUCAL)

More than 12 billion distinct fully human antibodies.
Fluorescence in-situ hybridization

Locus-specific FISH validation of genetic copy number alterations for Trypsin gene. A. PRSS3 9p21.1-p12 amplification in KHM2 cell line. (B) PRSS1/PRSS2 7q32.2-q36.3 non-amplification in SR-786 cell line. Fadlelmola et al. Molecular Cancer 2008 7:2
Polymerase Chain Reaction

Invented in 1983 by Kary Mullis of Cetus Corporation (shared the Nobel prize in chemistry in 1993)
Pat Brown
Stanford University

Application of gene arrays for expression profiling of human cancers - 1995
Gene Arrays and Gene Chips

collagen, type IV, alpha 1
### Expression Profiling for Diagnosis and Prognosis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic (Dx) Value or Prognostic (Px) Value?</th>
<th>Accuracy</th>
<th>Predictor Gene Sets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Ductal Ca</td>
<td>Dx</td>
<td>82%</td>
<td>5</td>
</tr>
<tr>
<td>Malignant mesothelioma</td>
<td>Px</td>
<td>70-80%</td>
<td>8</td>
</tr>
<tr>
<td>Colorectal Ca Micro satellite status</td>
<td>Dx</td>
<td>96%</td>
<td>9</td>
</tr>
<tr>
<td>Papillary Thyroid Ca</td>
<td>Dx</td>
<td>95%</td>
<td>8</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>Px</td>
<td>?</td>
<td>3</td>
</tr>
<tr>
<td>Ca Unknown origin</td>
<td>Dx</td>
<td>88%</td>
<td>10</td>
</tr>
<tr>
<td>Ovarian Ca</td>
<td>Px</td>
<td>94%</td>
<td>3</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Dx</td>
<td>96%</td>
<td>100</td>
</tr>
<tr>
<td>Breast ca</td>
<td>Px</td>
<td>~90%</td>
<td>5-70</td>
</tr>
</tbody>
</table>
Diffuse Large B cell Lymphoma
Virtual Microscopy and Telepathology
Molecular Histology by MALDI (matrix-assisted laser desorption ionization) Imaging

Sören-Oliver Deininger[1], René Krieg[1], Sandra Rauser[2], Axel Walch[2]

[1] Bruker Daltonik GmbH, Bremen, Germany
[2] Institute of Pathology, GSF Neuherberg, Germany
Lean Production Systems in Clinical Laboratories

Labs deploying Lean Management Principles are achieving the following:

• Reduction of overtime by up to 60%
• Reduction in core lab staff by up to 20%
• Reduction in TAT by 50-60%
• Reduction in floor space by 20%
• Increased phlebotomist productivity by 300%
The Importance of Standardization in Lean Management

• Reduction of wasted time (non value added activity) and materials

• Reduction of errors through standardised work

• Staff training in Lean principles is essential for success

• Use a skill set required for the job - reduce intellectual waste
The John Cleese Lean Management Method
The Future of Performance Management**
**Warning - offensive language - cover your ears
Quality Assurance in Pathology

Dr. Gershon Ejeckam flagged serious problems regarding immunohistochemistry at a St. John's pathology lab in 2003.

Nobody listened.
Five years later: “Death count mounts in breast cancer test fiasco” – CBC headline Feb 2008

Health Minister
Ross Wiseman
The Futility of Providing Early Warning to Administrators
Laying Blame When Things Go Predictably Wrong
Automation in Histology

Tissue-Tek Xpress®
Continuous-specimen-flow, high throughput, 1-hour tissue processor

Tissue-Tek Auto-TEC®
Fully automated, the AutoTEC will handle and embed 120 specimens per hour - faster than manual methods by approximately 50%.
Rapid Fixation by Ultrasound

Wei-Sing Chu et al.  
Modern Pathology  
(2005) 18, 850–863
Possible Future Histopathology TAT

- Fix tissues within 10 minutes of biopsy
- Process within 60 minutes
- Embed in 2 minutes
- Section in 5 minutes
- Stain and coverslip in 1 minute
- Whole slide scan in 2 minutes - no slides to be delivered to pathologist
- Pathologist can view digital image on his desktop computer remotely from anywhere with intranet/internet connection - no microscope needed.
- Report dictated into LIS by voice recognition, edited and signed out - no waiting for transcription.
- Total elapsed time 2-4 hours (depending on slide number) from receipt of biopsy.
Human Genome Project Draft completed in 2001

Craig Venter & Francis Collins
Human Genome Project completed in April 2003
Emerging Paradigms

- Novel therapies will likely be gene-based
- 20% of current pharmaceutical R&D is gene-based – over 1600 gene-based therapies are in development (66% in preclinical stage)*
- Patient selection is required for targeted therapy (e.g. trastuzumab) thus a predictive test for every new targeted therapy will be mandatory
- Genetic analysis may predict for drug toxicity or efficacy (pharmacogenomics)

*Source: R&Dfocus 2000
Gene-based drug R&D programmes by therapy area
Source: R&Dfocus
Quality Assurance Issues

- Technologists and pathologists must be highly skilled
- Need to test >100 cases a month to be proficient (JNCI 2002 94:788-789; 855-857)
- 33% of patients are misclassified as Her2neu+ by small labs, with the following drawbacks:
  - Patients may inappropriately receive an expensive ($46,788) potentially cardiotoxic drug
  - No therapeutic benefit (the drug only works on a subset of true+ cases).
  - Decentralised testing results in unnecessary drug expenditures of $12 million in an adjuvant setting
- Other biomarkers e.g. PTEN can further improve patient selection for Her2neu response, but would add $209,303 to annual cost based on current technology.
Tissue Microarrays

Kallioniemi et al, 2001
Cost Comparisons  
Testing all 3000 New Patients in BC (ER, PR, Her2neu IHC + FISH on equivocal cases)

<table>
<thead>
<tr>
<th>Method</th>
<th>Cost (IHC)</th>
<th>Cost (FISH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Section Method</td>
<td>$655,437</td>
<td>$144,130</td>
</tr>
<tr>
<td>TMA Method</td>
<td>$219,644</td>
<td>$80,000</td>
</tr>
</tbody>
</table>

$799,567 (Total)  
$209,303 for each new biomarker per year by IHC

$299,644 (Total)  
$19,970 for each new biomarker per year by IHC
### The Limitations of Today’s Drug Therapies – selected examples

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Efficacy Rate</th>
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</thead>
<tbody>
<tr>
<td>Hypercholesterolemia</td>
<td>70%</td>
</tr>
<tr>
<td>Depression</td>
<td>62%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>60%</td>
</tr>
<tr>
<td>Asthma</td>
<td>60%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57%</td>
</tr>
<tr>
<td>Migraine (Acute)</td>
<td>50%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>50%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>48%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>47%</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>30%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30%</td>
</tr>
<tr>
<td>Cancer (all)</td>
<td>25%</td>
</tr>
</tbody>
</table>

*Average of all drugs = 60%*

*From: Spear B et al. Trends in Molecular medicine Vol 7 201-204, 2001*
Drug Costs (Retail) in Canada (CIHI)

- Estimated costs in 2006 = $25 billion
- If, on average, 40% of drugs are ineffective, Canada is wasting $10 billion on useless therapy.
The Cost of Cancer Treatment Failure in Canada per annum

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost of treatment failures</td>
<td>$1.2 billion</td>
</tr>
<tr>
<td>Top 5 most costly cancers</td>
<td>$1 billion</td>
</tr>
<tr>
<td>Top 10 most costly cancers</td>
<td>$1.18 billion</td>
</tr>
</tbody>
</table>
Theranostics

Theranostics is the term coined to describe the use of diagnostic testing to diagnose a given disease, choose the correct treatment regimen and dose, and monitor the patient response to therapy on an individualized basis.
Utility of Theranostics

• Disease risk prediction
• Disease diagnosis
• Disease prognosis
• Patient stratification
• Therapeutic stratification
• Monitoring therapeutic response
## Return on Investment of Theranostics

<table>
<thead>
<tr>
<th>Optimised assay cost per test (labour and materials)</th>
<th>$3,800</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients per year to be tested</td>
<td>Test cost per year</td>
</tr>
<tr>
<td>Top 5 cancers</td>
<td>59,590</td>
</tr>
<tr>
<td>Top 10 cancers</td>
<td>106,690</td>
</tr>
</tbody>
</table>
Ethical Issues of Personalized Therapy

• A technology that identifies patients who will benefit from a given therapy automatically identifies those who won’t benefit – denial of therapy

• “Never underestimate the desperation of a patient to obtain a drug” – Jan Platner (National Breast Coalition)

• How accurate is the predictive test? – “Shopping” for a positive test

• Offering toxic therapy to unselected patients (current practice)
When her hairdresser asked her last fall whether she would continue wearing her hair long, Elizabeth Sloan broke down crying.

Unbeknown to the hairstylist, Ms. Sloan had recently had a breast tumor removed and was expecting to begin chemotherapy, which would probably mean losing her hair.

But later that day, Ms. Sloan received the results of a new $3,500 genetic test, which indicated that her cancer probably would not come back even if she skipped chemotherapy.

"It was a huge relief," said Ms. Sloan, 40, a mother of two young boys who lives in Manhattan. "I did not want to napalm-bomb my body with chemicals."

The test taken by Ms. Sloan, Oncotype DX, is part of a new wave of sophisticated genetic or protein tests that are starting to remake the diagnostics business, both for the technology they use and the way they are developed and sold.
Predictive and Personalized Oncology Concept

- Unselected group
  - All treated with chemotherapy
  - 80% No therapy required
  - 20% Therapy required

- Poor prognostic gene signature group
  - 80% No therapy required
  - 20% Therapy required
Oncotype DX

- 21 gene set (16 genes + 5 reference genes) – stratifies into low (score <18), intermediate (>18 < 30)), and high (≥30) risk of recurrence at 10yrs
- Works on formalin-fixed tissue
- Recurrence score has predictive power better than that of the St. Gallen or National Comprehensive Cancer Network risk stratification guidelines
- About half of the 92% of patients who were in the high-risk National Comprehensive Cancer Network category were reclassified as low-risk by the recurrence score, with a 10-year relapse risk of 7% (CI, 4% to 11%)

From: Paik S. The Oncologist 2007; 12:631-635
MammaPrint

- 70-gene signature
- Requires frozen tissue
- 40% of patients would fall into a good prognosis group with 15% 10 yr recurrence rate (vs. 15% of patients being classified as within the good prognostic group by St. Gallen index)
- 33% of St. Gallen high risk group reclassified as low risk

Barriers to Theranostics

- The Pharmaceutical Industry’s blockbuster-drug business model
- The lack of interest in predictive tests from the drug industry – fear of loss of profits
- Subset analysis of clinical trials results is discouraged
- Funding mechanisms for drugs, physicians, and laboratories
- Entrenched physician behaviour and unfamiliarity with concepts of genetic factors that influence response to drugs
- Glacial pace of translating research discoveries to the clinical arena
- Lack of funding from granting agencies for true translational research
The DNA sequence of Craig Venter was sequenced to 7.5-fold redundancy using random shotgun sequencing. PLoS Biol. 5, e254–e286 (2007).

The DNA sequence of James D. Watson was sequenced to 7.4-fold redundancy in picolitre-size reaction vessels. Nature 452, 872-876 (17 April 2008).

The Watson sequencing was completed in two months.

The cost was one-hundredth of the cost of traditional capillary electrophoresis methods.

Watson and Venter are different from each other by 7,648 protein coding changes.
Sequencing speed and Costs

• It currently costs roughly $60,000 to sequence a human genome.
• Research groups are hoping to achieve a $1,000 genome within the next three years.
• 2 biotech companies are collaborating to sequence your genome for less than the price of a nice pair of jeans—and the technology could read the complete genome in a single workday.
A Glimpse at the Future of Genomics
Genomic Passkeys
Genomic Identity Validation
Predictive Genomics