The New Face of Pathology in Precision Medicine

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Dean School of Medicine (NUSOM)

Nazarbayev University

Outline

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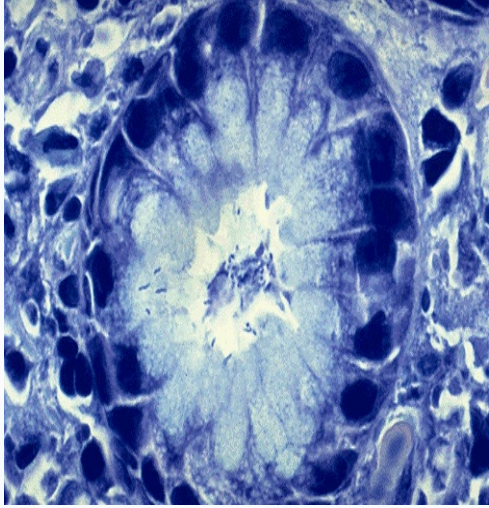
- Traditional ‘‘Old Face’’ Pathology
- 4P Medicine – Precision Medicine
- Translational ‘‘New Face’’ Pathology
- Stratified Medicine Programme
- NUSOM

Joseph Coats (1846-1899)
Chair in Pathology, Glasgow (1894)

“Old Face” of Pathology

- **Rudolf Virchow (1821-1902)**
- **Chair of Pathological Anatomy (1849)**
- ***Father of “Cellular Pathology”***
- ***Diseases originated within the cells rather than from imbalance of fluids***
- ***Understanding disease mechanisms at cellular level***

A history of modern medicine



***Robin Warren*, Nobel laureate in Medicine (2005) – Discovery of Helicobacter pylori and its role in peptic ulcer**

"There were numerous lymphocytes and plasma cells in the stroma. A thin blue line was visible on the surface, which on high power I thought consisted of numerous bacteria. My colleagues could not (or did not want to) see them, so I stained them….."

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The Impact of "Traditional" Pathology

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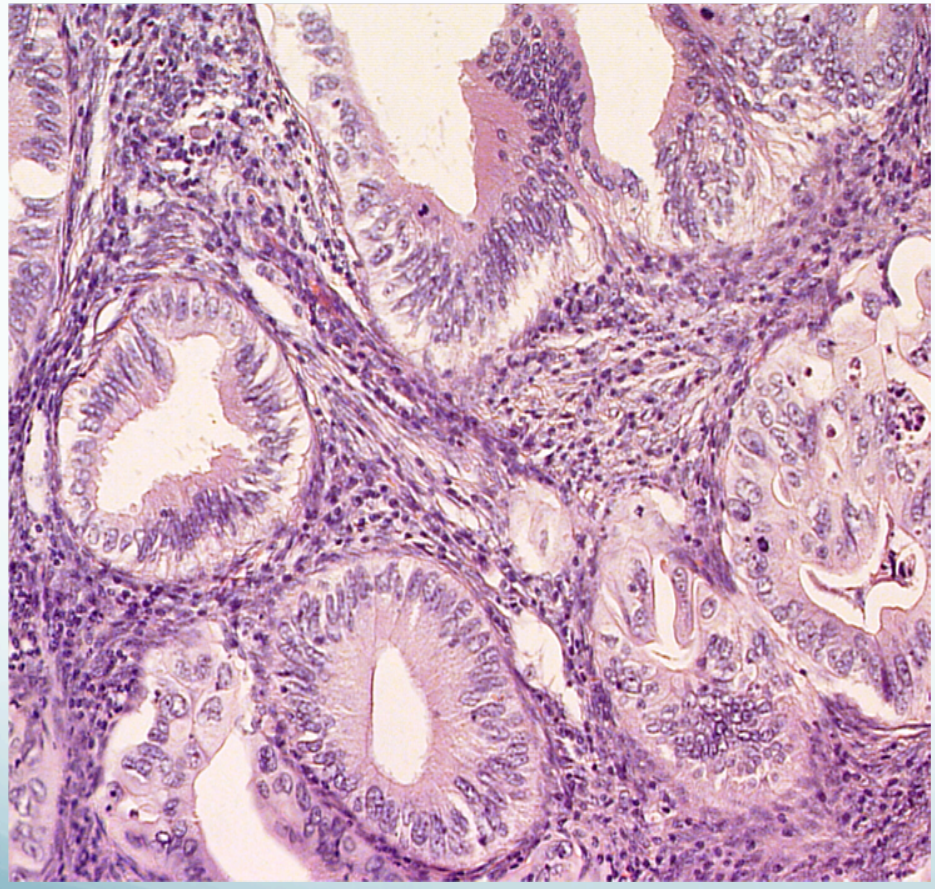
- *Morphological observation*
- *High quality tissue samples*
- *Intellectual curiosity*

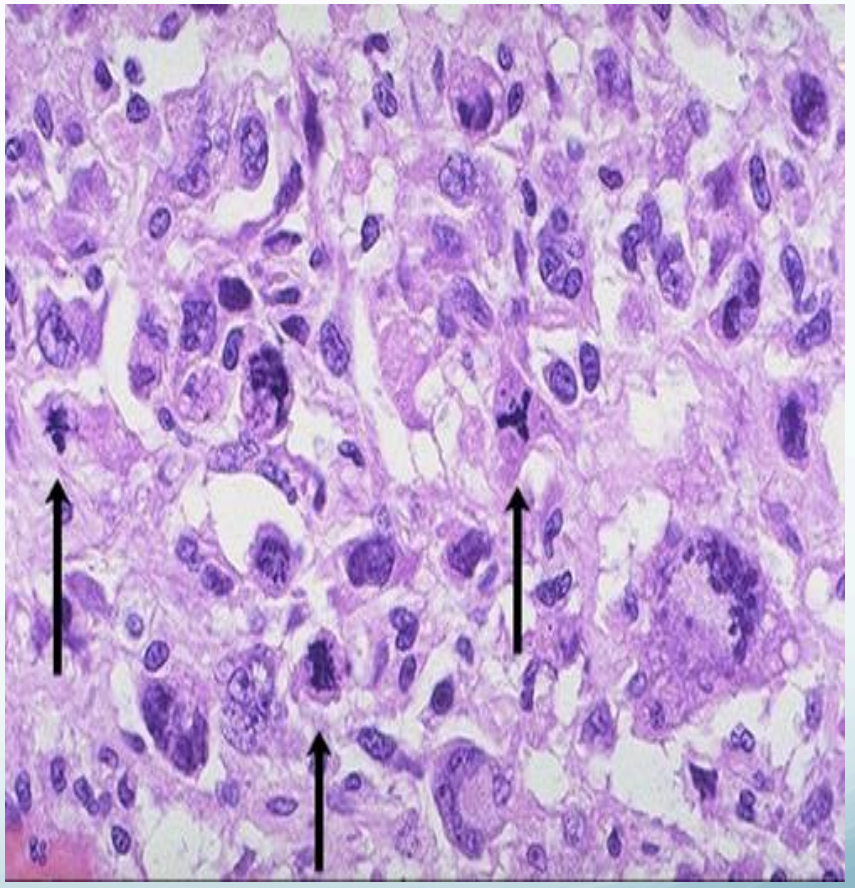
There is nothing more deceptive than an obvious fact!

Mechanistic/collaborative approach (with B Marshall, Junior Gastroenterologist, CS Godwin, Microbiologist, JA Armstrong ,Electromicroscopist)

Pathological Grade and Prognosis

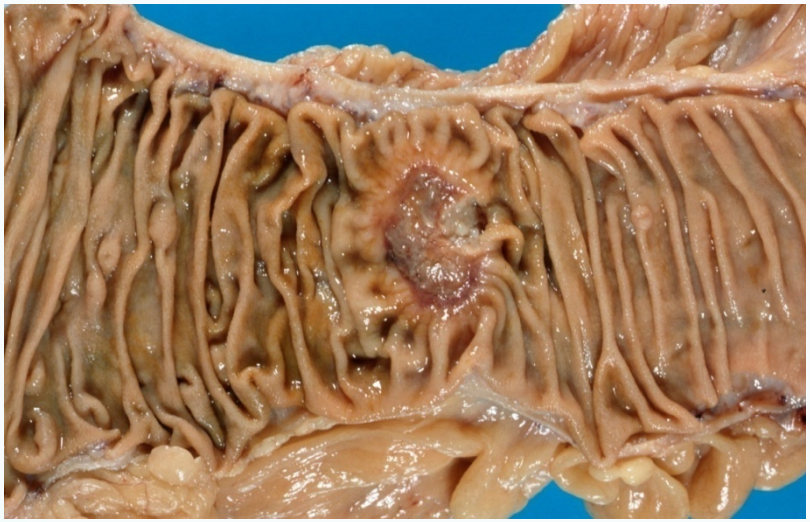


Good



Bad

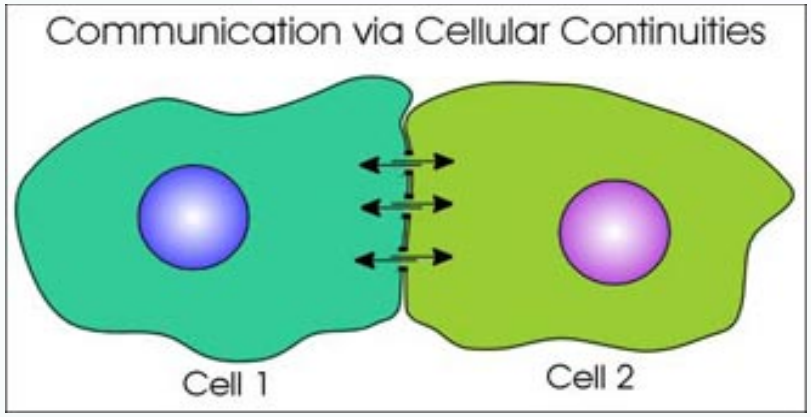
“Traditional” Role of the Pathologist

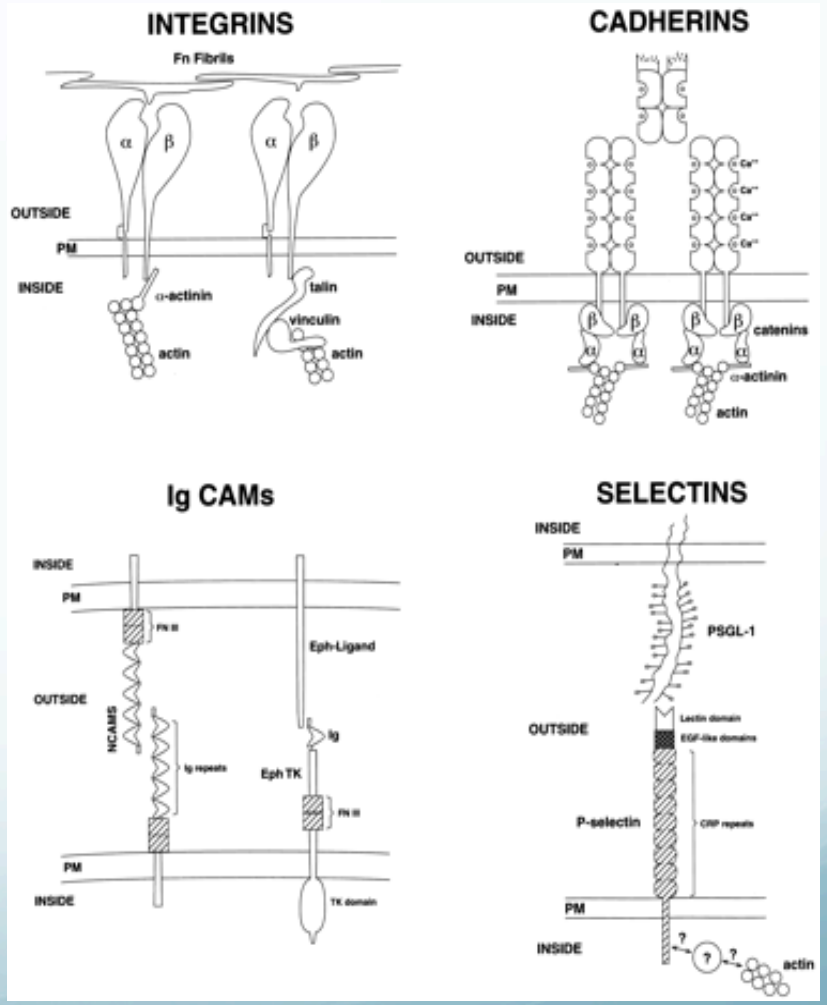


Pattern recognition!!!

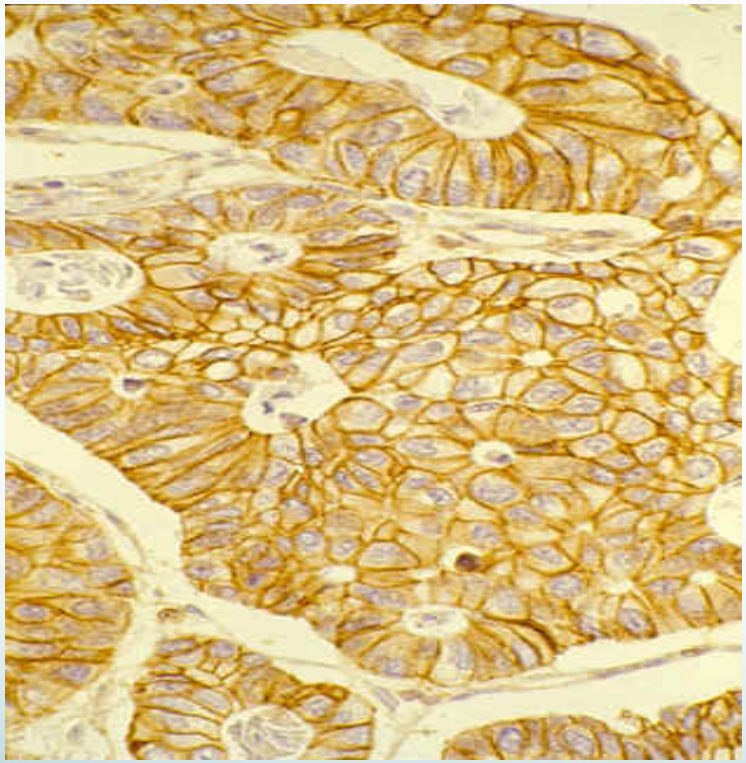
- Morphological evaluation of tissues and cells
  (can be subjective!)
- Unequivocal Diagnosis
  (not always possible!)
- Pathological stage and grade
  (needs to be standardised!)
  on which to base prognosis and therapy →
  Molecular biomarkers

Cell Communication and Adhesion Molecular Morphology





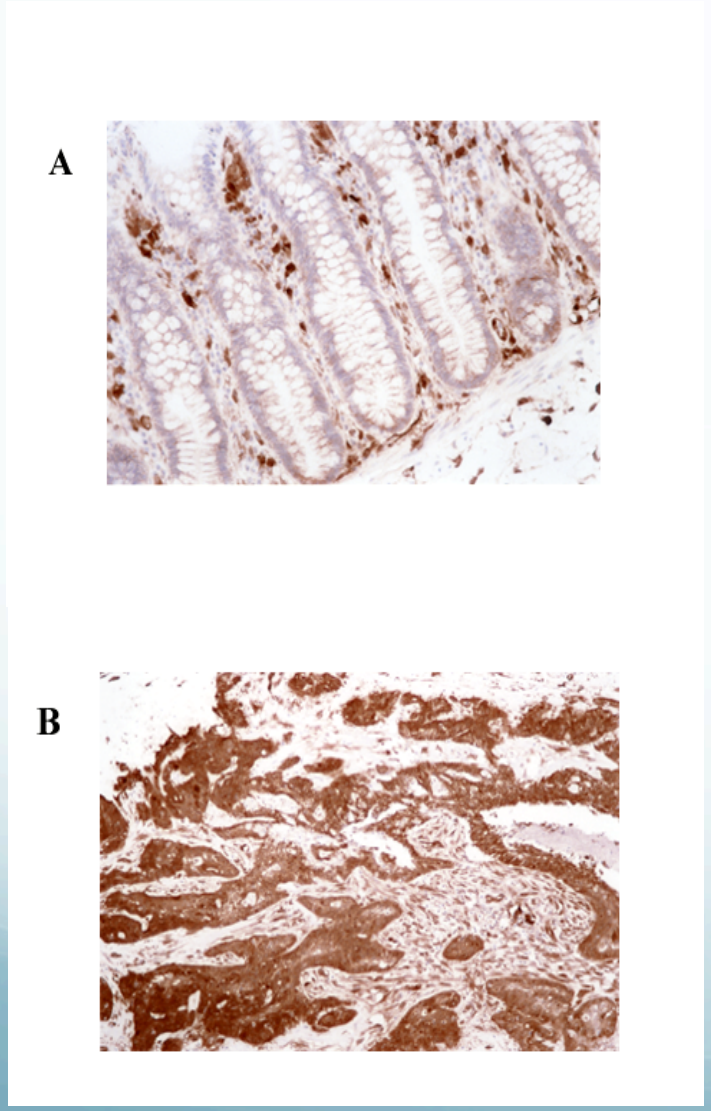
Abnormal β-catenin cellular localisation (nuclei) occurs in aggressive tumours



Beta-catenin is preserved at the cell-cell junctions

Beta-catenin nuclear localisation

Fascin expression in cancer

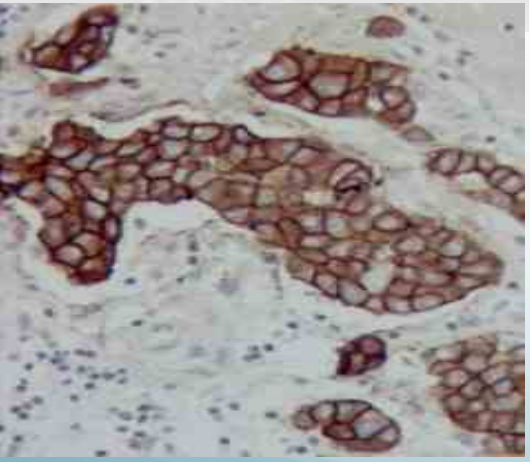


Poor prognostic marker:

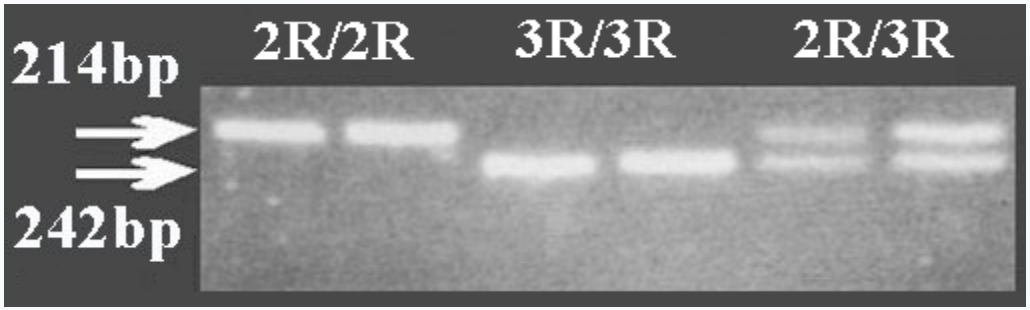
- **Colon cancer**
- **Prostate cancer**
- **Lung cancer**
- **Ovarian cancer**
- **Bladder cancer**

Translational Pathology

Accelerating discoveries at the bench to understand and eradicate disease at the bedside



Her-2 *neu*



Molecular biomarkers
to predict prognosis
and response to treatment:

Precision medicine

4P(5P) of Modern Medicine

- Preventive
- Predictive
- Partnership (Participatory, health literacy)
- Precision (Personalised healthcare)
- ***Pathology***

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Role of Pathology and Pathologists in Precision Medicine

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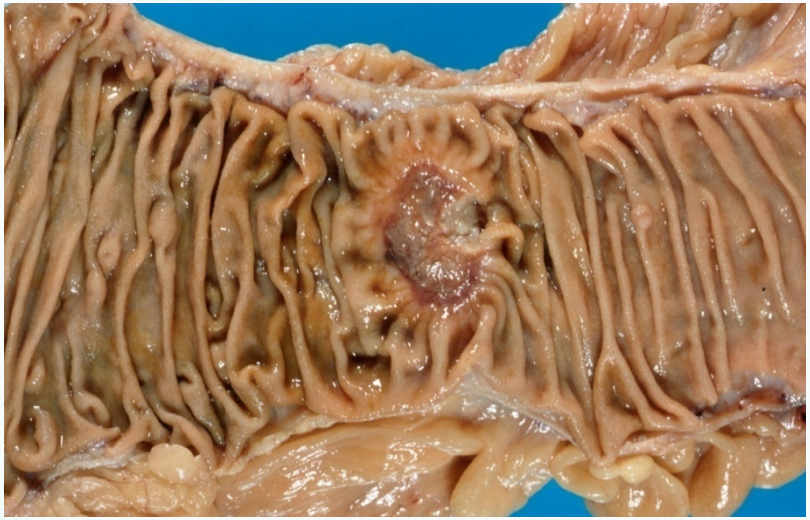
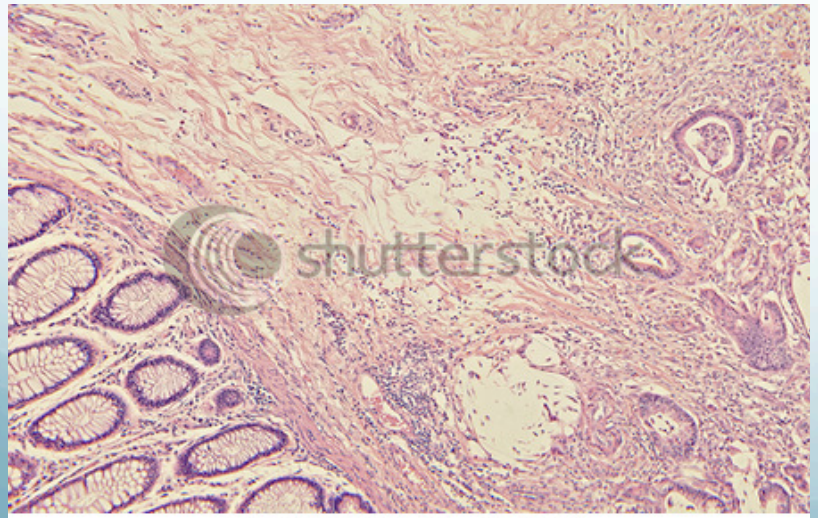
- Customisation of Healthcare
- Targeting drugs for each unique genetic profile
- Key requirements:
  - ✓ Molecular diagnostics
  - ✓ Drug development programme
  - ✓ High quality Pathology including good tissue sample history (rubbish in….rubbish out: *TISSUE IS THE ISSUE!*)

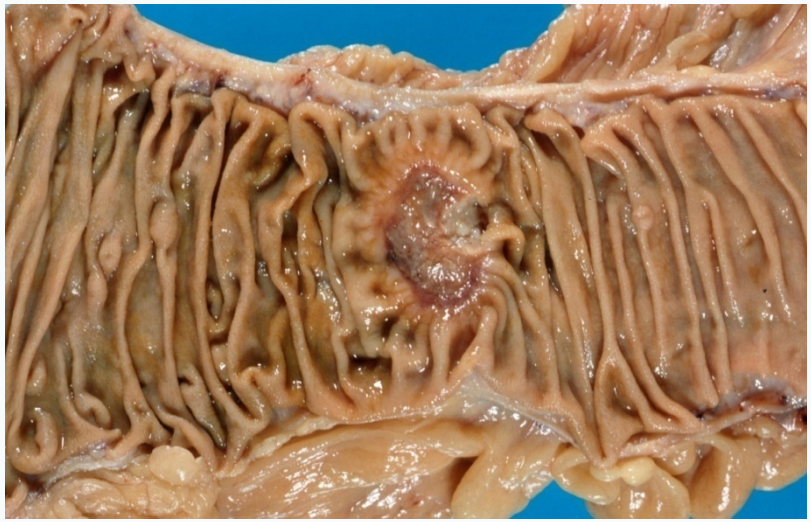
Role of the Pathologist/1





- Provision of high quality tissue samples
- Evaluation and integration of morphology and molecular analysis
- Clinical context and interpretation of results

Role of the Pathologist/2



- ***Pattern recognition still very important***
- Morphological evaluation of tissues and cells *(less subjective!)*
- Unequivocal Diagnosis *(is possible!)*
- Prognosis and Therapy is based on molecular signatures as well as pathological staging
- ***Molecular biomarkers***

The NEW ENGLAND JOURNAL of MEDICINE

The Path to Personalized Medicine

Margaret A. Hamburg, M.D., and Francis S. Collins, M.D., Ph.D.

16th June, 2010

Another important step will be expanding efforts to develop tissue banks containing specimens along with information linking them to clinical outcomes. Such a resource will allow for a much broader assessment of the clinical importance of genetic variation across a range of conditions. For exam-

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- ***Basic Science***
- ***Translational Science***
- ***Regulatory Science***

For example:

- *Gleevec (TK inhibitor) in GIST*
- *Herceptin (HER2) in breast cancer*

(approved companion tissue-based diagnostic tests)

SYLLABUS FOR RESEARCH MODULE (Royal College of Pathologists 2010)

- Fundamentals of the scientific process and evidence-based medicine.
- The role of research in the modern NHS
- ***The ethical background of research on people and human tissue***
- The ethical background to research on animals
- ***Tissue banking***
- Study design
- Statistics
- ***Working in a research laboratory***
- *The scope of pathology techniques*
- ***The pathologists role in the research team***
- The pathologist as educator, advisor, facilitator and supervisor of research
- Managing research grants and people employed on research grants
- The importance of probity in research
- Evaluation of the impact and cost of introducing research based discoveries into clinical practice
- Critical assessment of own and other people's data
- Applying for grant funding
- Writing a paper, preparing a paper, and/or writing a chapter or book
- Reviewing publications, theses and grants

Biorepository

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- Infrastructure to streamline to process of tissue acquisition and distribution
- Tissues, blood, urines, cytological preparations (normal and diseases)
- Ensuring researchers are compliant with both legal and ethical principles of storing and using human tissues in research

Pre-analytical phase in Pathology

- Tissue handling, preservation, storage and transport
- Fixation (time, type) and paraffin embedding
- Storage of frozen specimens (when possible)
- Dissection and block selection for microscopic and molecular analysis

Analytical phase in Pathology

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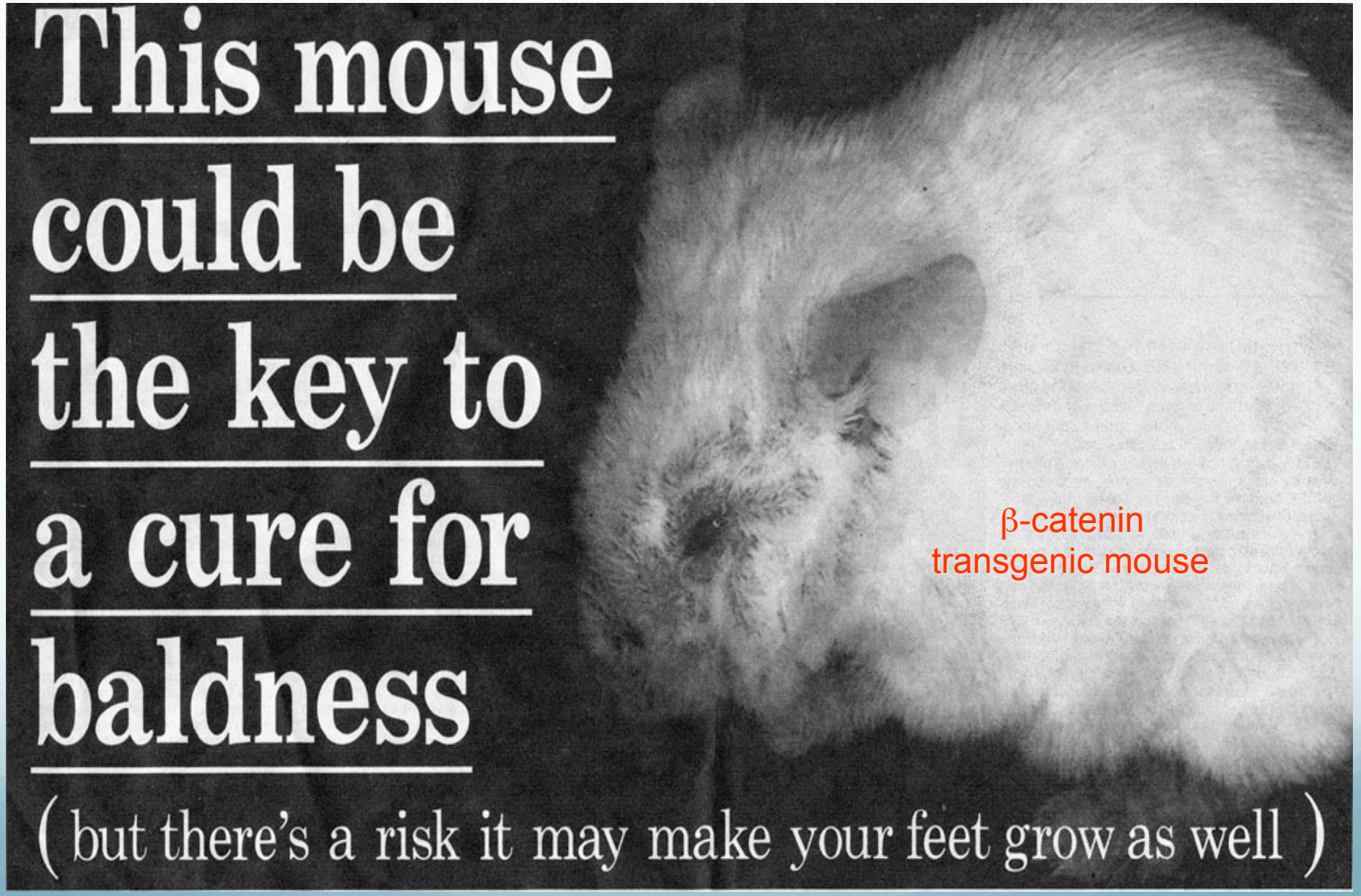
- Image-based procedure (cutting, microdissection, TMA, conventional staining techniques, immunohistochemistry)
- Molecular analysis (nucleic acid extraction, PCR based technologies, next generation sequencing)
- Evaluation and integration of results


This mouse could be the key to a cure for baldness
(but there's a risk it may make your feet grow as well)
β-catenin
transgenic mouse

Over-expression of oncogenic beta-catenin is associated with increased cell proliferation

- De novo hair follicle morphogenesis and hair tumour formation (pilomatricoma)
- Intestinal dysplasia and adenoma
- Liver cell hyperplasia and hepatomegaly
- Polycystic kidney disease

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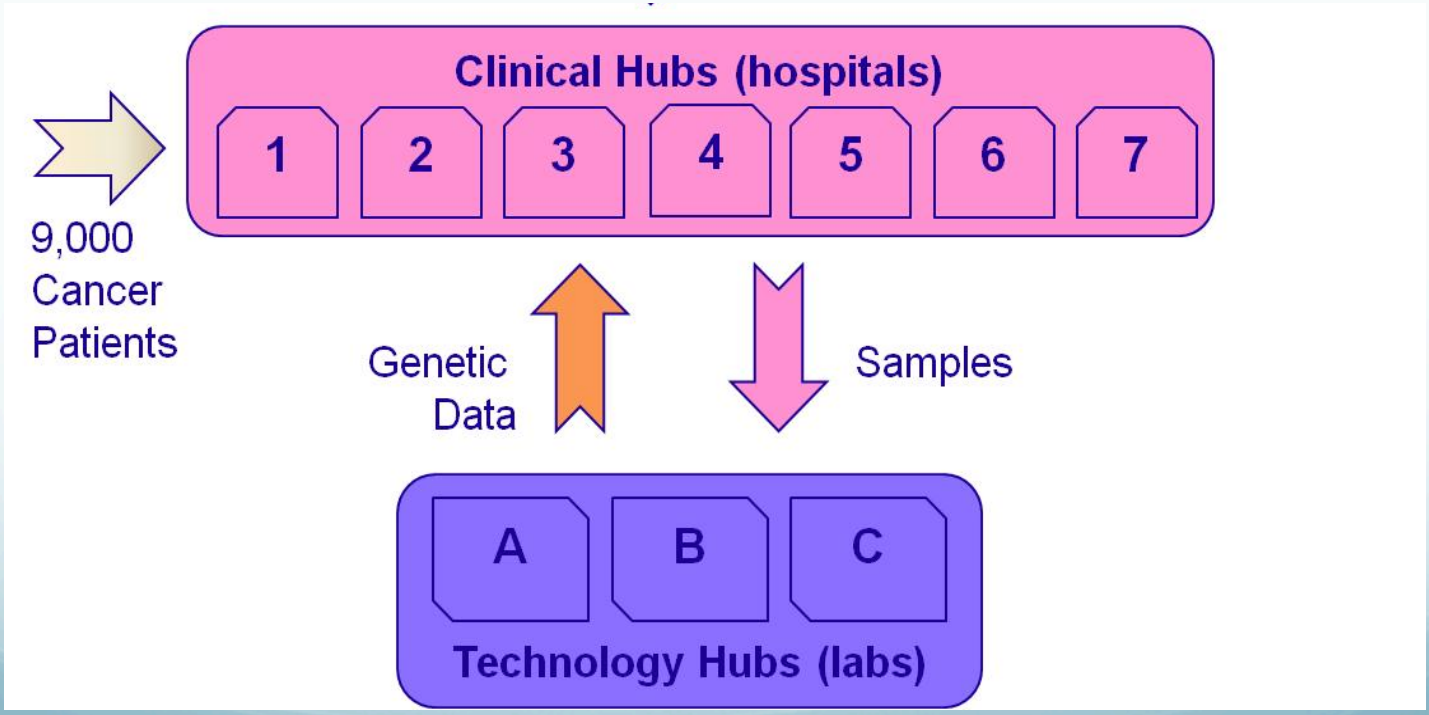
Personalised Cancer Care

"The new face of oncology stresses the importance of a multidisciplinary approach to cancer care and requires a close collaboration with Pathology"

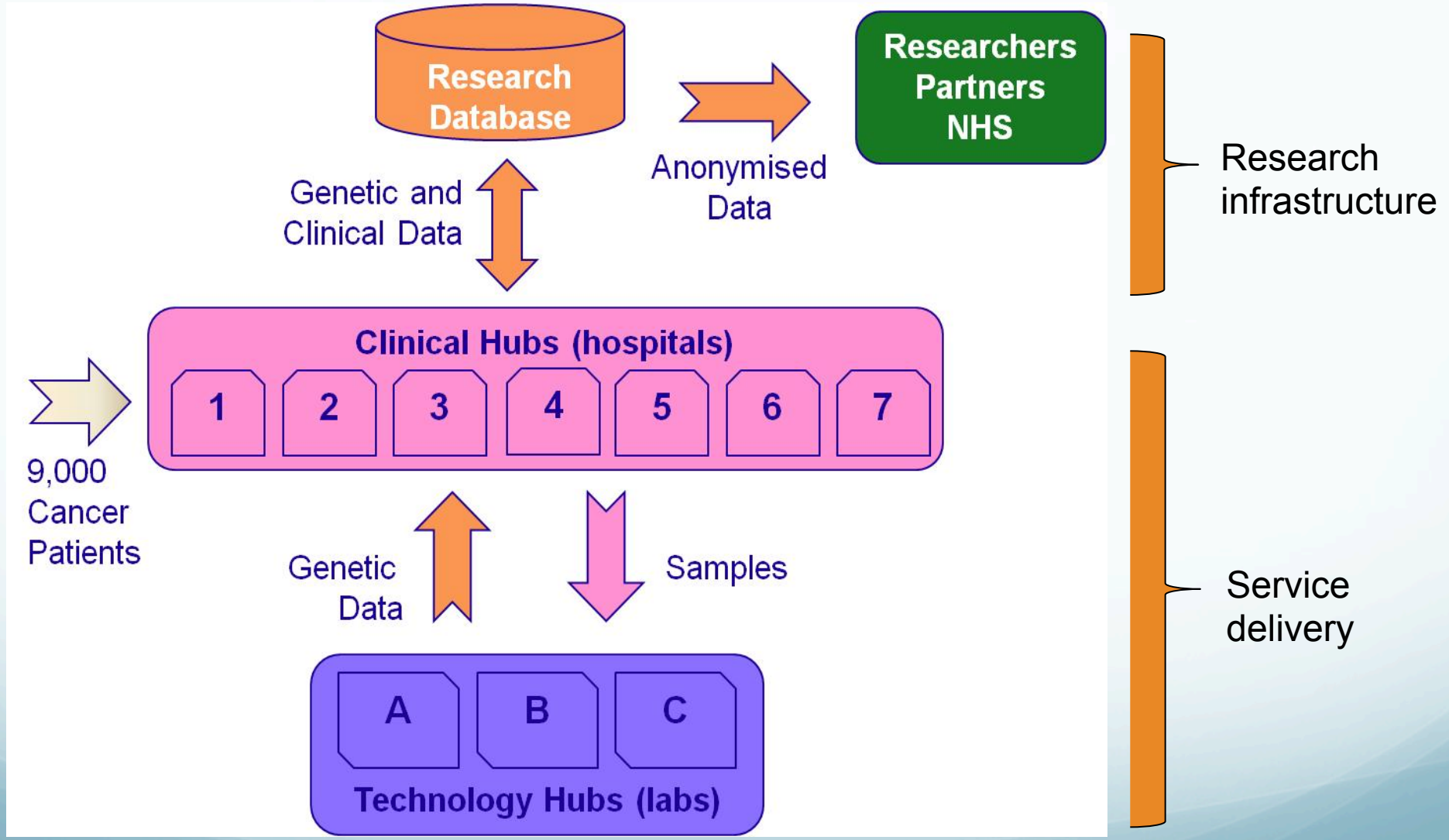
The vision of the Stratified Medicine Programme

Our vision is to establish a national molecular diagnostics service delivering high quality, cost effective tests for patients, with routine consent for the collection, storage and research use of genetic, treatment and outcomes data.

Phase One of the CR-UK Stratified Medicine Programme (2011-13) is a mixture of service delivery…



…and research infrastructure



Total Cases over 2yrs	1340

Tissue Type	Number
Breast	300
Colon	300
Lung	250
Prostate	220
Ovarian	100
Melanoma	170

Tumour Type	Gene		Tumour Type	Gene
Colon	KRAS		Lung	EGFR
Colon	BRAF		Lung	KRAS
Colon	NRAS		Lung	EML4-ALK
Colon	P13KCA		Lung	BRAF
Colon	TP53			
Breast	P13KCA		Ovary	P13KCA
Breast	TP53		Ovary	TP53
Breast	PTEN		Ovary	PTEN
Prostate	PTEN		Melanoma	BRAF
Prostate	TMPR882-ERG		Melanoma	cKIT
			Melanoma	NRAS
			Melanoma	P13KCA

Phase One of the programme will deliver on five core aims that enable stratified medicine delivery and research

1. **Significant scale across many sites**
   - 9,000 samples collected from 6 hospitals and analysed for c.20 markers in 3 labs with associated data available for research.

2. **Proven service model**
   - Detailed costs, protocols and service models for adoption across the NHS of a genetic testing service, delivered within clinical turnaround times.

3. **Routine consent for research**
   - All patients consented for DNA, diagnostic, treatment and outcome data to be linked and stored in a secure research database

4. **Bioinformatics database**
   - Detailed specifications for an information system that can link and extract anonymised diagnostic, treatment and outcome data

5. **New cancer assays**
   - Development of a standardised and validated £300 panel of genetic tests for the important clinical and research markers in the major solid tumours

Lessons to learn from Phase One: to improve molecular diagnostic testing service in order for it to be successfully rolled out nationally

- Integrate lessons learnt from Phase One into broader practise in clinics
- Adoption of new technologies such as next generation sequencing.
- Focus on specific cancer types.
- Application in other disease areas.
- Broaden the scope and utility of datasets captured

- National consolidated molecular diagnostics service delivering quality assured, continuously improving and cost effective tests for patients.
- Network will ensure that consent remains routine practice for molecular diagnostics.

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SCHOOL OF MEDICINE

Professor Massimo Pignatelli
MD, PhD, FRCPath
Dean, NUSOM in partnership with

University of Pittsburgh
School of Medicine

NU Medicine

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- **Integrated Academic Health System**

- **National Medical Holding was established in 2008**
  Six specialist hospitals in Astana (four are already JCI accredited) 3000 beds

- **New National Oncology Research Center**

(To open in 2016-17) in partnership with UPMC

- **Center of Life Sciences – precision medicine, regenerative medicine, global health, genomic medicine**

- **School of Medicine (NUSOM) opened in 2014**

Vision - NUSOM

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World class center of excellence in

- **Health Care Education**
- **Biomedical research**
- **Patient care**

To improve health and well-being of Republic of Kazakhstan, Central Asia and beyond

Mission - NUSOM

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- To educate science-based, compassionate and skilled clinicians to practice medicine in the 21st Century
- To do cutting edge research to advance the understanding of medical science and improve human health

What makes a great doctor?

"The good physician treats the disease; the great physician treats the patient who has the disease."

~William Osler

A great doctor should be:

Intelligent, Science-based, Skilled, Compassionate, Caring, Listener, Confident, Approachable, Decisive

NUSOM Organisational Structure

- Biomedical Sciences (already established) 23 faculty members
- Medicine (to be established in 2015-2016)
- Surgery (to be established in 2015-2016)
- Research Priorities – cancer, cardiovascular, neuroscience, population health, infection and immunity

Medical School Building (2016)

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