From small things big things one day come: the future of cancer diagnosis

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Cancer: diagnosis in the blood?

• Basic biology
  – how is it diagnosed?
• New methods of early diagnosis
• Screening
• Treatment related to markers
• The future diagnosis of cancer
Changing paradigm of cancer diagnosis

Macroscopic - Pathology
Microscopic - Histology
Laboratory - Immunochemistry
Automated sequencing - Genomics, Proteomics

What is cancer?

• A single cell goes ‘rogue’
  – Divides more frequently (increased mitosis)
  – Lives longer (reduced apoptosis)
  – Don’t stick with adjacent cells
  – Stay immature

• Clone ‘identical’ mutations
  – If ‘solid’ – ends up as a mass
  – If blood cell – circulating leukaemic cells

http://www.wellcome.ac.uk/Funding-Basics/understanding-funding-projects/Major-initiatives/Cancer-Genome-Project/index.htm
Early detection Cancer

**Why?**
- Surgery more likely to be possible
- Better cure rate
- Better survival
- Better survival rate anyway with lead time bias

**How?**
- Alert to symptoms – public education
- Early referral
- Asymptomatic – screening
  - Imaging
  - Tumour markers

Tumour markers: Where are we now?

- Mostly proteins (Single)
- Produced by the tumour itself OR
- by the body in response to cancer
- detected in the blood, body tissue or urine
Tumour Markers – the future?

- Multiple Proteins on cancer cells
- Multiple Proteins in blood
- Multiple Antibodies to cancer proteins
- Cancer DNA/RNA probes
- Abnormal genes of individual
- Circulating tumour cells

How do genes work?

- Each gene is responsible for a single protein
- Abnormal genes (mutations) produce abnormal proteins

- What kind of problems can mutations cause?
  - Altered protein function
  - Lack of protein
  - Change in how much protein is made

- Mutations occurring all the time
Cancer Immuno-histo-chemistry

• Antibodies to surface markers
• ‘Expression’ of gene
• Eg Herceptin in Breast cancer
  – Useful in treatment and prognosis
• Diagnosis and Prognosis of Leukaemias
  – Zap-70, IgVF

Cancer Genomics

• Abnormal genetic make-up of cancer cells
• SNPs – Single Nucleotide polymorphisms
  – One change in the genetic code
• Cancers will have multiple coding differences
• ‘Ingredients list’
Cancer Proteomics

- Abnormal cells produce different proteins circulating in body
- Analysis possible with technological advances
  - Mass spectrometry allows minute difference to be detected
  - Protein Micro-arrays
  - High throughput analysis
- Menu list – what is going on now

The future of prognosis and diagnosis
Looking for a pattern……

High throughput analysis

Each of the 96 columns represents one DNA sequence.

A different dye is attached to each nucleotide (A, C, G and T), allowing the sequencing machine to read their order.

- Look for common patterns in patients with one type of cancer
- Test again against new set of patients
Changing paradigm of treatment

• Germ theory of treatment
  – *Infection* – organ - type - treatment
  – *Cancer* — organ - type - treatment

• Genomic/Proteomic theory
  – *Cancer* - Abnormality – Gene or cell function – treatment

• *No longer* ‘Cancer of….organ’ *more what is the molecular abnormality*

New treatment strategies in Cancer

**Pre Genetic era**
- Biopsy tumour and Lymph nodes
- Define tumour grade and stage
- Predict risk recurrence
- Choose treatment – limited options

**Post Genetic era**
- Gene expression analysis on cancer tissue
- Predicts likelihood recurrence based on expression 21 genes
- Predicts benefits adjuvant therapy for hormonal and chemo-therapy
Cancer Medicine – personalised treatment

• Melanoma – BRAF Gene mutation – Vemurafenib

• Chronic Myeloid Leukaemia – Imatinib/Glevec

• Acute Lymphatic Leukaemia – DNA testing routine

• Gastro-Intestinal Stromal Tumours GISTs – Imatinib

Genetic testing for breast cancer recurrence risk

21 different genes from a breast tumour
Immunochemistry from prognosis to diagnosis - *What is Leukaemia?*

- No definition apart from a malignancy of blood forming cells.
- By implication bone marrow will always be involved
- Variable number of cells in peripheral blood
- Markers of clonal group(s) of abnormal cells
- Immunochemical and genetic markers used for diagnosis

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**Immunochemistry from prognosis to diagnosis**

![image](http://www.sanger.ac.uk/about/press/2011/gfx/110327_leukaemia.jpg)

![image](http://news.bbcimg.co.uk/media/images/50288000/jpg/_50288098_m1321011-leukaemia_blood_cells,_light_micrograph-spl-1.jpg)

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**blood**

2002;100:635-639

DOI: 10.1182/blood.V100.2.635

Monoclonal B lymphocytes with the characteristics of "indolent" chronic lymphocytic leukemia are present in 3.5% of adults with normal blood counts

Andy C. Rawstron, Michael J. Green, Anita Kuzmicki, Ben Kennedy, James A. L. Fenton, Paul A. S. Evans, Sheila J. M. O'Connor, Stephen J. Richards, Gareth J. Morgan, Andrew S. Jack, and Peter Hämmer

Updated information and services can be found at:

[http://bloodjournal.hematologylibrary.org/cgi/content/full/100/2/635](http://bloodjournal.hematologylibrary.org/cgi/content/full/100/2/635)

Articles on similar topics may be found in the following Blood collections:

*Neoplasia* (2264 articles)
Immunochemistry from prognosis to diagnosis

- Screen testing for circulating antibodies to tumour proteins
  - CAGE, GBU4-5, HuD, MAGE, A4, NY-ESO-1, p53, SOX-2

- If positive go onto next phase of screening – CT scan

Changing paradigm of cancer diagnosis, Changing **timing** of cancer diagnosis
What does this mean for Critical Illness pricing?

Considerations

• How much sooner can the test detect cancer?
• How many additional cases can be diagnosed?
• How many people will be screened?
  – As part of a formal screening programme
  – Informally
• Is there a preventative component?
Development of cancer

Accelerated diagnosis with EarlyCDT-Lung

Source: www.earlycdt-lung.co.uk
Acceleration of diagnosis

Male lung cancer incidence in England

Source: ONS Cancer Registration Statistics, England 2010
Cancer prevalence

- Roughly 3% of the UK population has had a cancer diagnosis
  
  

- But how many people actually have cancer?

Latent cancer

most studies focus on prostate cancer

Source: Cancer Intervention and Surveillance Modeling Network and based on Etzioni, Penson 2002 estimate of 29% PSA screen-detected cancer overdiagnosis rate

Only a few cancer sites have been researched in this way. What else can be found?
Performance of a blood test to screen for ovarian cancer

<table>
<thead>
<tr>
<th></th>
<th>Ultrasound only</th>
<th>Blood test then u/sound</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of women screened</td>
<td>48,230</td>
<td>50,078</td>
</tr>
<tr>
<td>Women recalled for biopsy</td>
<td>845</td>
<td>97</td>
</tr>
<tr>
<td>Cancers detected</td>
<td>45</td>
<td>42</td>
</tr>
<tr>
<td>Symptomatically diagnosed</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>within 1 year of screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>5.3%</td>
<td>43.3%</td>
</tr>
<tr>
<td>i.e. % of first round positive test results actually positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blood tests currently under evaluation for national screening

• Serum CA125 for Ovarian Cancer
  – *UK Collaborative Trial of Ovarian Cancer Screening*
  – Randomised study of 200,000 women
  – Currently in follow-up phase with results expected in 2015

• Early Lung CDT for Lung Cancer
  – Randomised study of 10,000 heavy (ex) smokers started in Scotland in 2012

Take-up of formal screening in the UK

<table>
<thead>
<tr>
<th>Screening programme</th>
<th>Take-up/coverage rate*</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>69.7%</td>
<td>Programme Annual report 2012</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>78.6%</td>
<td>Programme Annual report 2012</td>
</tr>
<tr>
<td>Bowel cancer</td>
<td>50% men, 54% women</td>
<td>Logan R et al, Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests, Gut doi:10.1136/gutjnl-2011-300843</td>
</tr>
</tbody>
</table>

* Higher take-up in more affluent socio-economic groups
Informal screening:
PSA testing rate in Ireland

16% of Irish men had a PSA test in 2004.

In the UK the figure was 8.6%.

Source: “Recent trends in Prostate Cancer”
National Cancer Registry Ireland publication Cancer trends No. 3

Comparison of prostate cancer incidence

<table>
<thead>
<tr>
<th>Country</th>
<th>World age-standardised rate per 100,000 population</th>
<th>Worldwide rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ireland</td>
<td>126.3*</td>
<td>3</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>83.8</td>
<td>18</td>
</tr>
<tr>
<td>U.K.</td>
<td>64.0</td>
<td>33</td>
</tr>
</tbody>
</table>

* Now equal to rate in USA 1995 - 2005

Thyroid cancer incidence in South Korea

<table>
<thead>
<tr>
<th>Site</th>
<th>1999</th>
<th>2008</th>
<th>Percent Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>11.9</td>
<td>20.4</td>
<td>20.1</td>
</tr>
<tr>
<td>Breast</td>
<td>24.5</td>
<td>42.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Stomach</td>
<td>28.3</td>
<td>26.6</td>
<td>-0.5</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>17.1</td>
<td>20.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Lung</td>
<td>12.9</td>
<td>14.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>8.6</td>
<td>7.9</td>
<td>-4.4</td>
</tr>
<tr>
<td>Liver</td>
<td>12.6</td>
<td>10.8</td>
<td>-1.5</td>
</tr>
</tbody>
</table>

Age-standardized incidence rate (ASR) uses “mid-year population in 2000” as standard population.

Thyroid cancer screening in South Korea

- South Korea has the highest incidence of thyroid cancer worldwide.
- A 2009 study found that 13.2% of adults had undergone screening by thyroid ultrasonography at some stage.
- Only 21.6% of those who underwent screening did so because they had experienced abnormal symptoms.

*Asian Pacific J Cancer Prev, 12, 1657-1663*
### Comparison of thyroid cancer incidence rates by country

<table>
<thead>
<tr>
<th>Country</th>
<th>World age-standardised incidence rate per 100,000</th>
<th>Age standardised mortality rate per 100,000</th>
<th>Annual change since 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Republic of Korea</td>
<td>35.44</td>
<td>0.53</td>
<td>+25.7%</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>9.90</td>
<td>0.28</td>
<td>+6.5% (SEER 13 age-adjusted incidence trends 1998-2009)</td>
</tr>
<tr>
<td>U.K.</td>
<td>2.78</td>
<td>0.26</td>
<td>+5% (Cancer Research UK EISBR trend)</td>
</tr>
</tbody>
</table>


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### Cost of private screening tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EarlyCDT – Lung</td>
<td>£210 to £240</td>
</tr>
<tr>
<td>Basic Cancer Test</td>
<td>£96.00</td>
</tr>
<tr>
<td>Blood Test</td>
<td>£156.00</td>
</tr>
<tr>
<td>Blood Test for MBC</td>
<td>£200.00</td>
</tr>
<tr>
<td>Breast Cancer Screen</td>
<td>£206.00</td>
</tr>
<tr>
<td>Breast Cancer Check</td>
<td>£203.00</td>
</tr>
<tr>
<td>Breast Cancer Screen</td>
<td>£185.00</td>
</tr>
<tr>
<td>Breast Cancer Genetic Test</td>
<td>£1,099.00</td>
</tr>
<tr>
<td>Breast Cancer Screen</td>
<td>£1,699.00</td>
</tr>
<tr>
<td>Cancer Check for MBC</td>
<td>£209.00</td>
</tr>
<tr>
<td>Cancer Check for MBC (Male)</td>
<td>£219.00</td>
</tr>
<tr>
<td>Cancer Check for MBC (Female)</td>
<td>£229.00</td>
</tr>
<tr>
<td>Carcinoid Cancer Screen</td>
<td>£109.00</td>
</tr>
<tr>
<td>Carcinoid Cancer Screen</td>
<td>£169.00</td>
</tr>
<tr>
<td>Carcinoid Cancer Screen</td>
<td>£359.00</td>
</tr>
<tr>
<td>Carcinoid Cancer Screen</td>
<td>£399.00</td>
</tr>
</tbody>
</table>

07 May 2013
### Informal screen-detected cancer in Ireland

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Cancer site</th>
<th>No of cases in 2008</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
<td>762</td>
<td>13.5%</td>
</tr>
<tr>
<td>C18</td>
<td>Malignant neoplasm of colon</td>
<td>12</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>D07</td>
<td>Carcinoma in situ of other and unspecified genital organs</td>
<td>96</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>C34</td>
<td>Malignant neoplasm of rectum</td>
<td>7</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>C20</td>
<td>Malignant neoplasm of bronchus and lung</td>
<td>7</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>D47</td>
<td>Other neoplasms uncertain/unknown behaviour</td>
<td>5</td>
<td>1.3%</td>
</tr>
<tr>
<td>D47p</td>
<td>Other neoplasms uncertain/unknown behaviour of lymphoid/haematopoietic related tissue</td>
<td>5</td>
<td>1.3%</td>
</tr>
<tr>
<td>C91</td>
<td>Lymphoid Leukaemia</td>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td>C15, C90, C64</td>
<td>Malignant neoplasm of oesophagus, Multiple myeloma, Malignant neoplasm of kidney</td>
<td>3, 3</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Source: National Cancer Registry Ireland Incidence Data

### Preventative component

- More likely to be approved for population screening
- Can reduce cost of CI cover
- Examples
  - Cervical cancer
  - Bowel cancer
- Or more reasons for partial payments

Apart from prostate cancer, take-up of informal screening is low.
Summary

• Accelerated diagnosis increases age-specific cancer incidence rates.
• Overdiagnosis further increases cancer incidence rates.
• A good first line blood test makes population screening more viable.
• Informal screening take-up rates are generally low
  – but prostate and thyroid cancer examples demonstrate the risks of relying on apathy.
• Cancer screening advances have the potential to increase the cost of CI cancer cover significantly
  – and some of the pricing puzzle pieces are missing.

Latest:
Genomics: SNiPs – from cancer prognosis to cancer risk

• SNPs – Single Nucleotide polymorphisms
  – One change in the genetic code
• Each SNP may increase risk by small amounts
• Multiple SNPs may multiply the risk
British scientists, who led the research, believe it could lead to a DNA screening test within five years.

Future cancer diagnosis

- No histology
  - Possible ‘hot spot’ on scan
    - Unable to biopsy
  - OR clone blood cells
- Serial abnormal blood markers
  - Proven linkage to diagnosis
- Treatment with chemotherapy
Small things now – watch out……………

Expressions of individual views by members of the Institute and Faculty of Actuaries and its staff are encouraged.

The views expressed in this presentation are those of the presenter.