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

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Adèle Groyer (FIA)

07 May 2013

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

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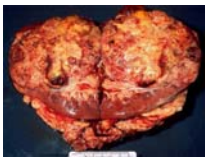
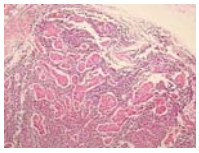
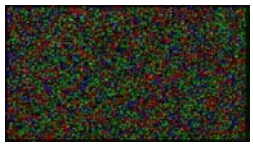
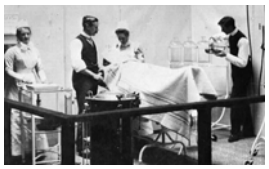
Changing paradigm of cancer diagnosis



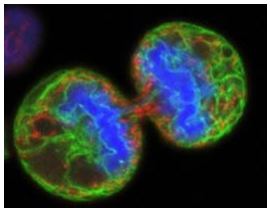




Macroscopic - Pathology	Microscopic - Histology	Laboratory_ Immunochemistry	Automated sequencing - Genomics, Proteomics

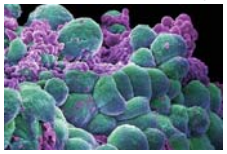


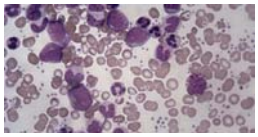
What is cancer?



http://www.wellcome.ac.uk/Funding/Biomedical-science/Funded-projects/Major-initiatives/Cancer-Genome-Project/index.htm

- 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





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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

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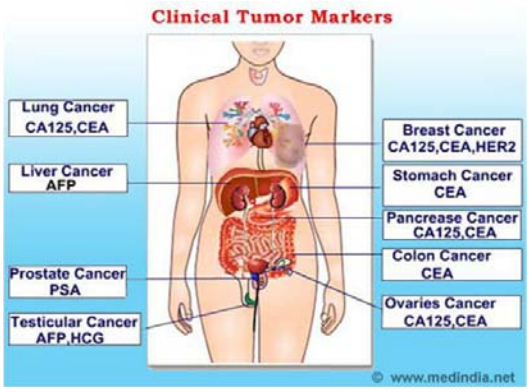
Tumour markers: Where are we now?



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

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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

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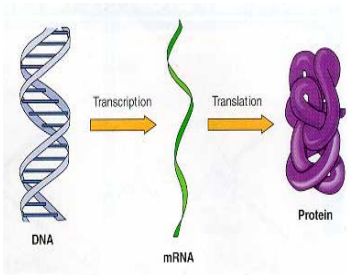
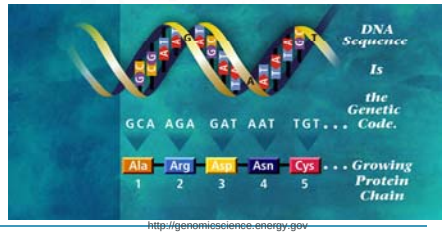
How do genes work?

- 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

Gene expression – when a protein is produced





http://genomicscience.energy.gov

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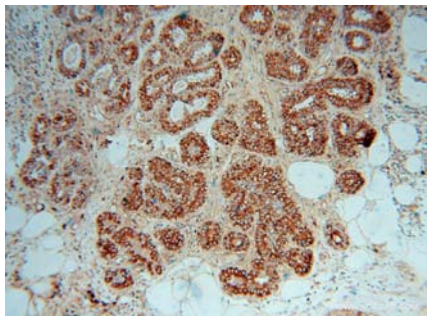
Cancer Immuno-histo-chemistry

- 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



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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'

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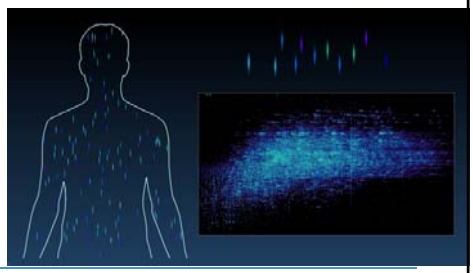
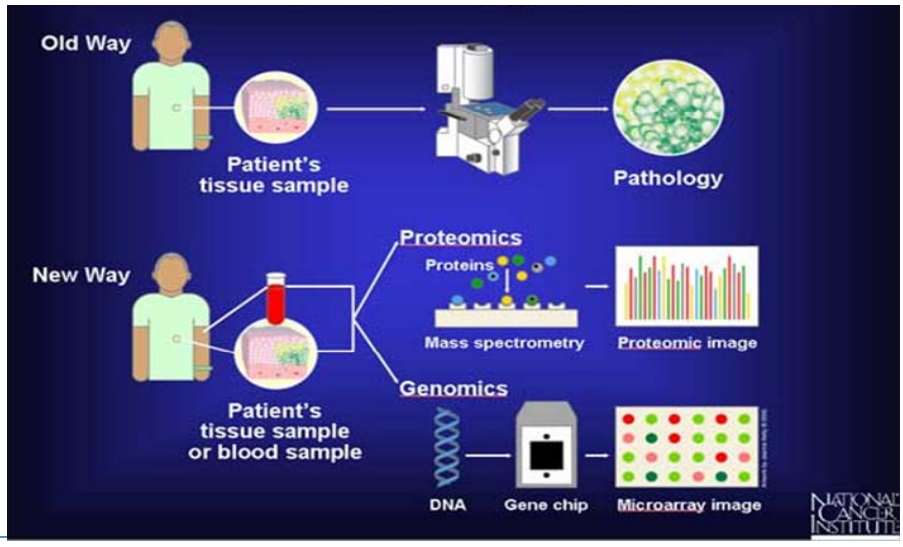
Cancer Proteomics

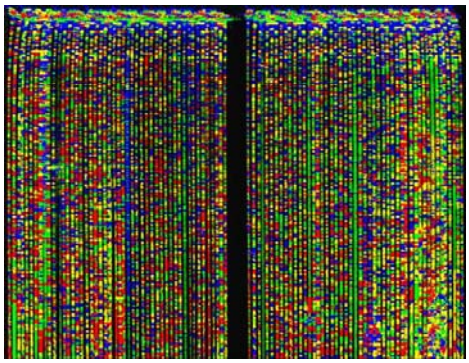
- Abnormal cells produce different proteins circulating in body
- Analysis possible with technological advances
  - Mass spectrometry allows minute difference to be detected
  - Protein Micro-arrays
  - High throughput analysis
- Menu list – what is going on now



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

SCIENCE VOL 286 15 OCTOBER 1999 REPORTS

Molecular Classification of Cancer: Class Discovery and Class Prediction by Gene Expression Monitoring

T. R. Golub,[1,2*†] D. K. Slonim,[1†] P. Tamayo,[1] C. Huard,[1] M. Gaasenbeek,[1] J. P. Mesirov,[1] H. Coller,[1] M. L. Loh,[2] J. R. Downing,[3] M. A. Caligiuri,[4] C. D. Bloomfield,[4] E. S. Lander[1,5*]

Although cancer classification has improved over the past 30 years, there has been no general approach for identifying new cancer classes (class discovery) or for assigning tumors to known classes (class prediction). Here, a generic approach to cancer classification based on gene expression monitoring by DNA microarrays is described and applied to human acute leukemias as a test case.

38 acute leukemias (27 ALL, 11 AML)

↓

Microarray Profiling

↓

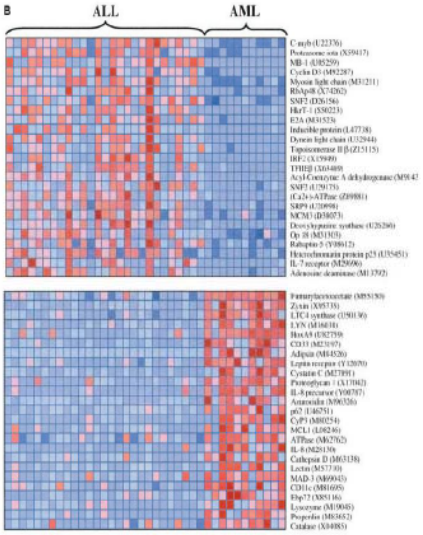
Develop class predictor (50 genes)

↓

Test on independent set (34 samples)

↓

Strong predictions on 29/34; accuracy 100%



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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*

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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

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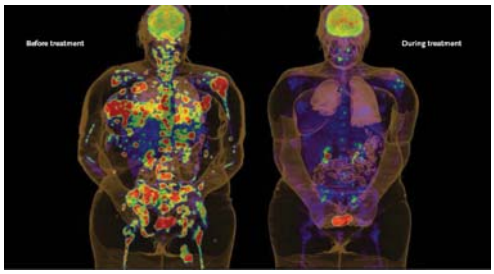
Cancer Medicine – personalised treatment

- Melanoma – BRAF Gene mutation – Vemurafenib



- Chronic Myeloid Leukaemia – Imatinib/Glevec
- Acute Lymphatic Leukaemia – DNA testing routine
- Gastro-Intestinal Stromal Tumours GISTs – Imatinib

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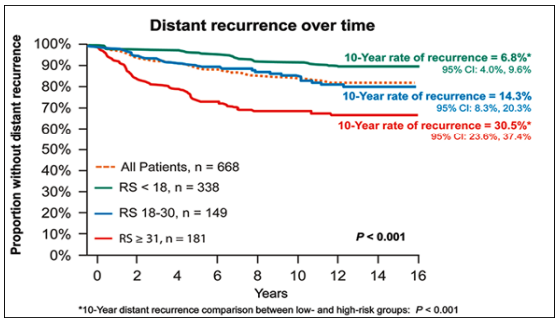
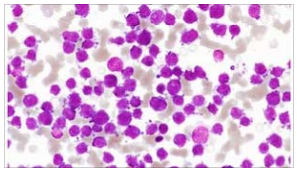
Genetic testing for breast cancer recurrence risk

21 different genes from a breast tumour

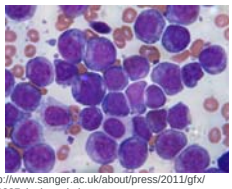


Immunochemistry from prognosis to diagnosis - *What is Leukaemia?*

- 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



http://news.bbcimg.co.uk/media/images/50288000/jpg/_50288098_m1321011-leukaemia_blood_cells,_light_micrograph-spl-1.jpg



http://www.sanger.ac.uk/about/press/2011/gfx/110327_leukaemia.jpg

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Immunochemistry from prognosis to diagnosis

blood

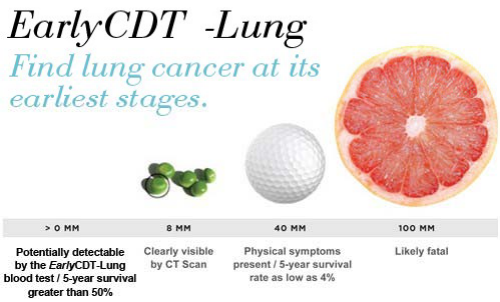
2002 100: 635-639
doi:10.1182/blood.V100.2.635

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 Hillmen

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



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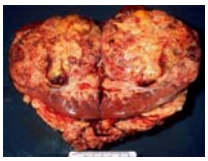
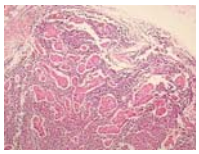
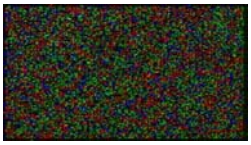
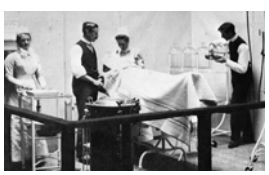
Changing paradigm of cancer diagnosis, Changing timing of cancer diagnosis



Macroscopic | Microscopic | Immunochemistry | Genomics, Proteomics

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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?

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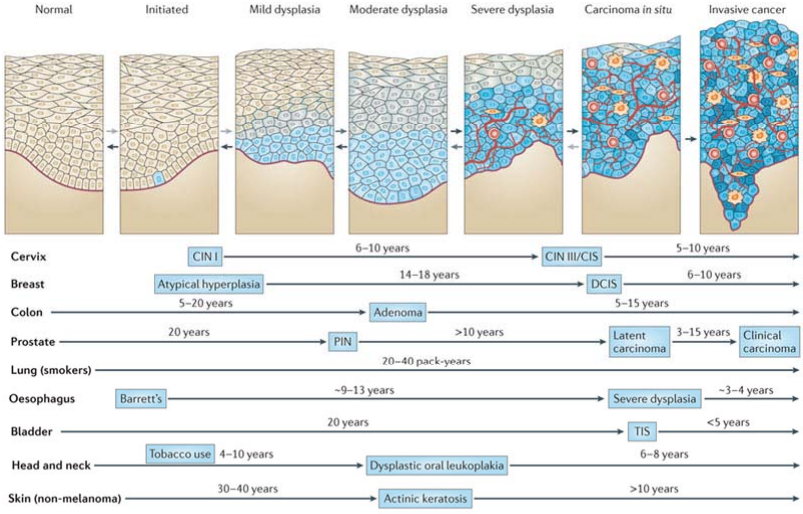
Development of cancer



Nature Reviews | Cancer

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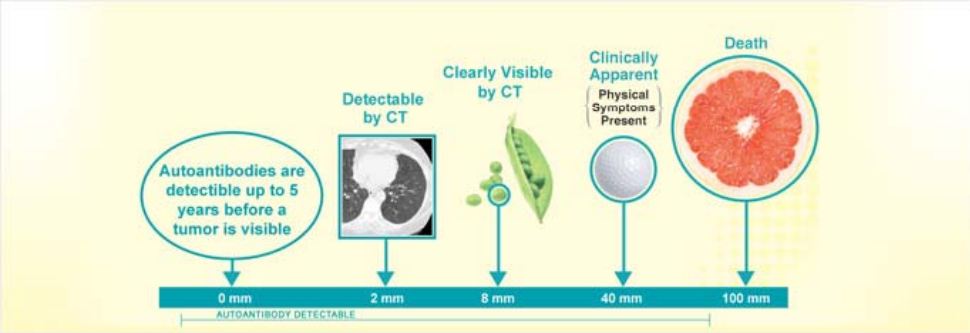
Accelerated diagnosis with EarlyCDT-Lung



Source: www.earlycdt-lung.co.uk

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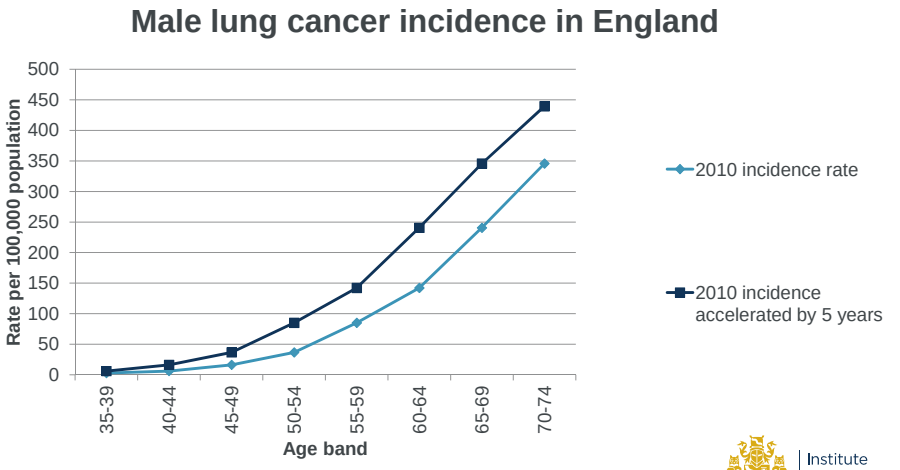
Acceleration of diagnosis



Source: ONS Cancer Registration Statistics, England 2010

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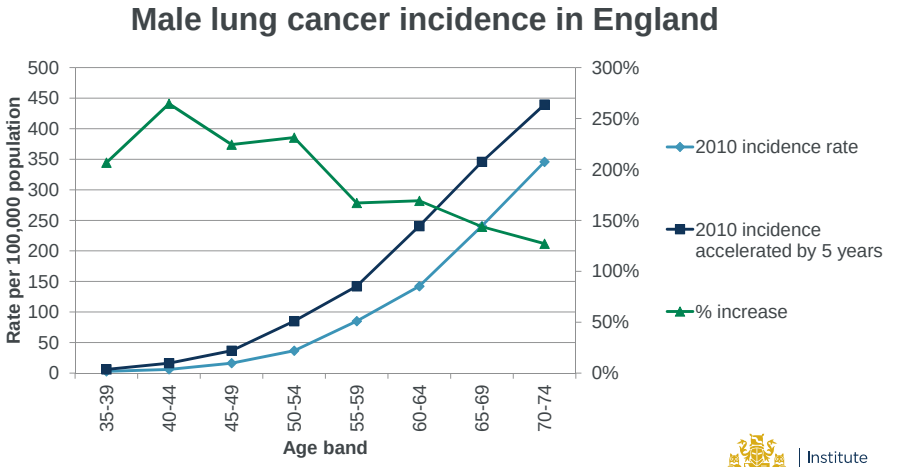
Acceleration of diagnosis



Source: ONS Cancer Registration Statistics, England 2010

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Cancer prevalence

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

  J. Maddams et al. Cancer prevalence in the United Kingdom: estimates for 2008

  Br J Cancer. 2009 August 4; 101(3): 541–547.

- But how many people actually have cancer?

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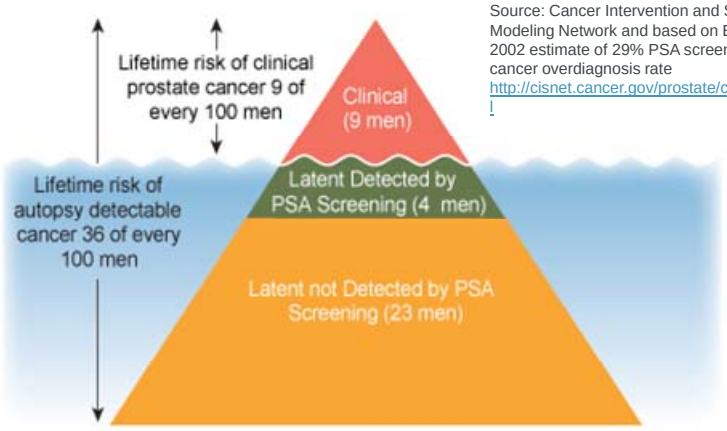
Latent cancer

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 http://cisnet.cancer.gov/prostate/comparative.html

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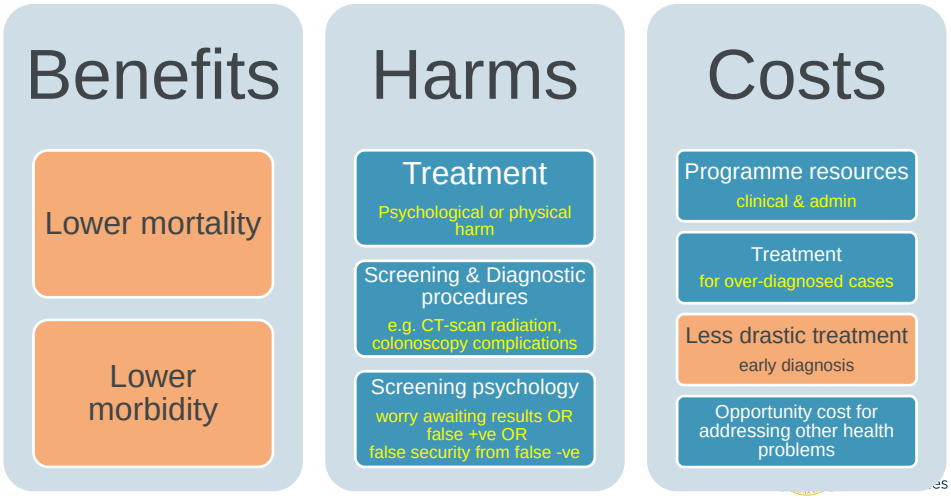
Reservoir of undetected cancer

Cancer site	Age range	Autopsy surprise prevalence	Source
Prostate cancer	All ages 50 - 59 60 – 69	12% ar…	…M et al, J Urol. 2008 …79(3):892-5 …om 1994 – 2007 (PSA era)
Thyroid cancer	All		…et al, Cancer. 1985 Aug …(3):531-8.
Invasive breast cancer		…%	Welch H and Black W *Ann Intern Med.* 1 December 1997;127(11):1023-1028
DCIS		0% to 14.7% 0% to 39%	""
Lung ca…	…All <70	0.7% (15% increase) 0.8%	Chan CK et al, Chest 1989; 96:291-96 1973 – 1982 data used
Uterine cancer	All	4 – 6x population incidence	Horwitz RI et al, Lancet. 1981 Jul 11; 2(8237):66-8.

Only a few cancer sites have been researched in this way. What else can be found?

Criteria for approval for formal screening



Performance of a blood test to screen for ovarian cancer

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

Source: Menon U et al, !Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), Lancet Oncol. 2009 Apr;10(4):327-40

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Fewer recalls with blood test as first line screening without increasing risk of false negatives

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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

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Take-up of formal screening in the UK

Screening programme	Take-up/coverage rate*	Source
Breast cancer	69.7%	Programme Annual report 2012
Cervical cancer	78.6%	Programme Annual report 2012
Bowel cancer	50% men 54% women	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

* Higher take-up in more affluent socio-economic groups

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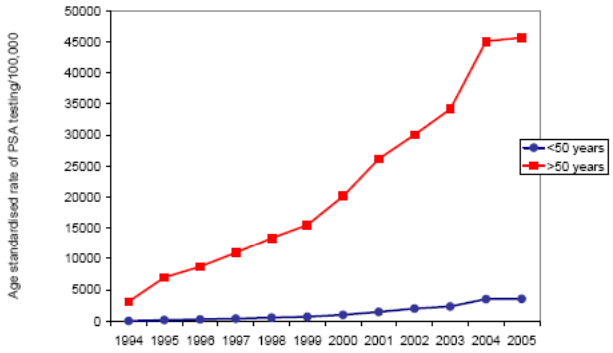
Informal screening: PSA testing rate in Ireland

Figure 5. Annual number of PSA tests 1994-2005



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

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

In the UK the figure was 8.6%.

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Comparison of prostate cancer incidence

Country	World age-standardised rate per 100,000 population	Worldwide rank
Ireland	126.3*	3
U.S.A.	83.8	18
U.K.	64.0	33

* Now equal to rate in USA 1995 - 2005

Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 07/03/2013.

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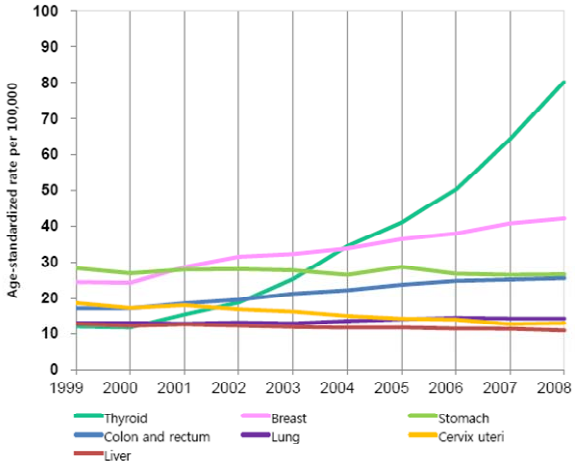
Thyroid cancer incidence in South Korea



Site	Year		Annual Percent Change (%)
	1999	2008	
Thyroid	11.9	80.2	25.7*
Breast	24.5	42.1	6.5*
Stomach	28.3	26.6	-0.5
Colon and rectum	17.1	25.6	5.2*
Lung	12.9	14.2	1.5*
Cervix uteri	18.6	12.9	-4.4*
Liver	12.6	10.8	-1.5*

* P < .05

Age-standardized incidence Rate(ASR) uses "mid-year population in 2000" as standard population.

Source: National Cancer Registration & Statistics 2008, the Korea Central Cancer Registry

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 ultrasonagraphy 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

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Comparison of thyroid cancer incidence rates by country

Country	World age-standardised incidence rate per 100,000	Age standardised mortality rate per 100,000	Annual change since 1998
Republic of Korea	35.44	0.53	+25.7%
U.S.A.	9.90	0.28	+6.5% SEER 13 age-adjusted incidence trends 1998-2009
U.K.	2.78	0.26	+5% Cancer Research UK EASR trend

Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 07/03/2013.

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Cost of private screening tests

Look out for the Finger Prick icon.

These tests can also be done on a simple finger prick blood sample. The blood sample can be taken quickly and conveniently in the privacy of your home.

See just how easy it is, view our 'How to take a finger prick blood sample' video.

For our full list of finger prick blood tests click here.

To view our finger prick blood test FAQs click here.

Basic Cancer Test	£99.00
Bile Duct Cancer Screen	£388.40
Bladder Cancer Screen	£299.00
Bladder Cancer Test	£99.00
Bowel Cancer Check	£69.00
Bowel Cancer Screen	£249.00
Breast Cancer Genetic Test	£1,999.00
Breast Cancer Screen	£199.00
Cancer Check (Female)	£599.00
Cancer Check (Male)	£599.00
Carcinoid Cancer Screen	£199.00
Cervix Cancer Screen	£299.00
Gastrointestine Cancer Screen	£249.00
HE4 (Ovarian Cancer Test)	£236.25
Liver Cancer Screen	£199.00
Lung Cancer Screen	£599.00
Ovarian Cancer Test	£99.00
Pancreas Cancer Screen	£199.00
PCA3 Prostate Cancer Test	£449.00
Prostate Check	£79.00
Prostate Check Plus	£129.00
PSA Test	£79.00
Testes Cancer Screen	£189.00
Thyroid Cancer Screen	£395.00

EarlyCDT – Lung: £210 to £240

Informal screen-detected cancer in Ireland

ICD-10 Code	Cancer site	No of cases in 20	% of cases
C61	Malignant neoplasm of prostate		13.5%
C18	Malignant neoplasm of col		1%
D07	Carcinoma in situ of oth		%
C34			<1%
C20			<1%
	viour ed tissue	5	1.3%
C9	oid Leukaemia	4	1%
C15	Malignant neoplasm of oesophagus	3	
C90	Multiple myeloma	3	<1%
C64	Malignant neoplasm of kidney	3	

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

Source: National Cancer Registry Ireland Incidence Data

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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

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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.

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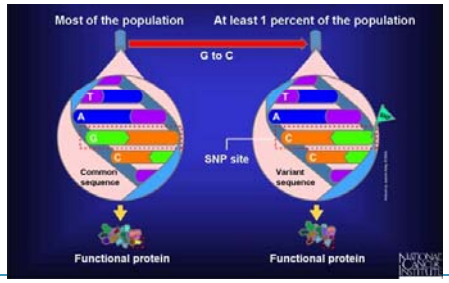
Latest:
Genomics: SNiPs – from cancer prognosis to cancer risk

- SNPs – Single Nucleotide polymorphisms
  - One change in the genetic code
- Each SNP may increase risk by small amounts
- Multiple SNPs may multiply the risk

http://www.mdsupport.org/images/geneticsexplained2.jpg



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The Telegraph

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Could new cancer tests make you uninsurable?

A £5 test could soon allow doctors to see how likely you are to develop cancer, this could make a huge difference to the cost of life insurance or critical illness cover.

A £5 test could soon allow doctors to see how likely you are to develop cancer Photo: Alamy

By Rosie Murray-West
7:00AM BST 08 Apr 2013

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'ch, believe it
ithin five years.'

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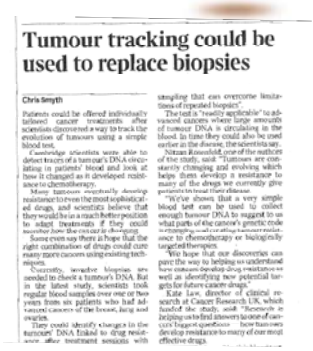
Future cancer diagnosis

- 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



Tumour tracking could be used to replace biopsies

Chris Smyth

Patients could be offered individually tailored cancer treatments after scientists discovered a way to track the evolution of tumours using a simple blood test.

Cambridge scientists were able to detect traces of a tumour's DNA circulating in patients' blood and look at how it changed as it developed resistance to chemotherapy.

Many tumours eventually develop resistance to even the most sophisticated drugs, and scientists believe that they would be in a much better position to adapt treatments if they could monitor how the cancer is developing.

Some even say there is hope that the right combination of drugs could cure many more cancers using existing techniques.

Currently, invasive biopsies are needed to check a tumour's DNA. But in the latest study, scientists took regular blood samples over one or two years from six patients who had advanced cancers of the breast, lung and ovaries.

They could identify changes in the tumours' DNA linked to drug resistance after treatment sessions with

The Times April 8th 2013

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Small things now – watch out……

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Questions

Comments

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.

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