癌症治療的新趨勢
個人化的癌症治療

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台灣癌症全人關懷基金會

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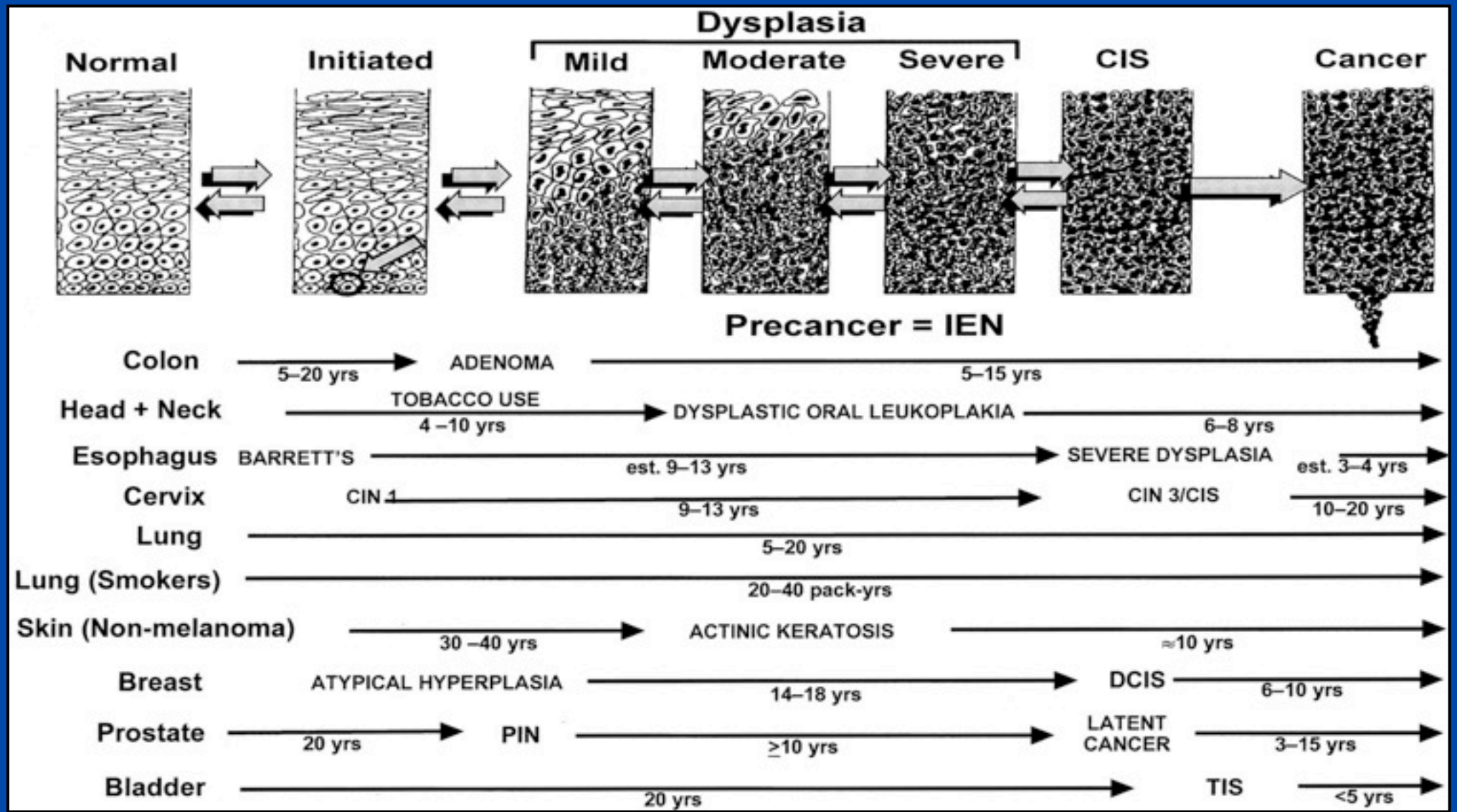
Cancer:
Disease of the Genes

- 癌症的演化是一個多步驟的過程,它包含了許多累積的對細胞遺傳物質的變化而中導致對遺傳物質的損傷所致.

癌症不是一日形成的

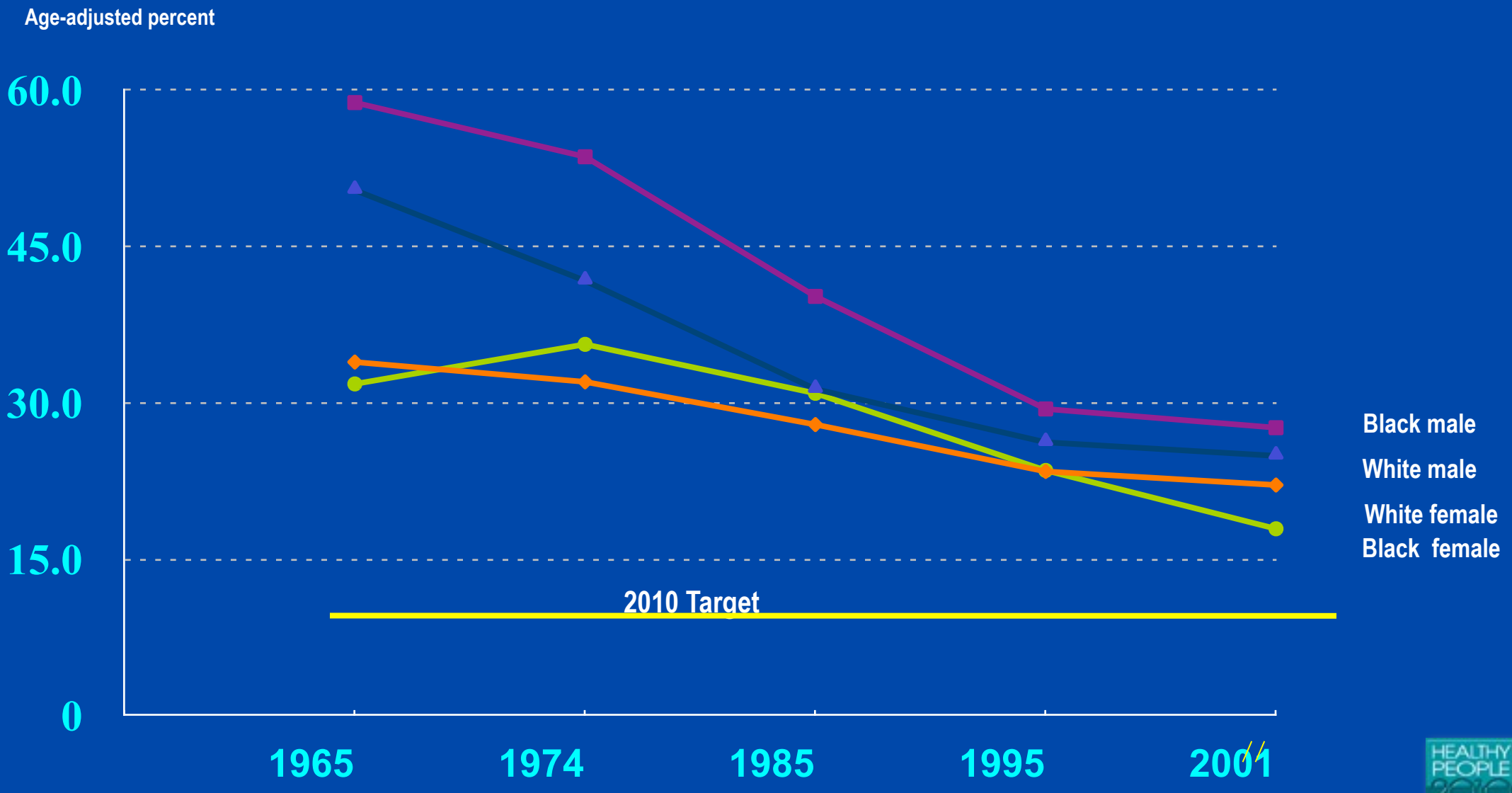


From Clin Cancer Res, 2002; 8:314

癌症的治療與預防

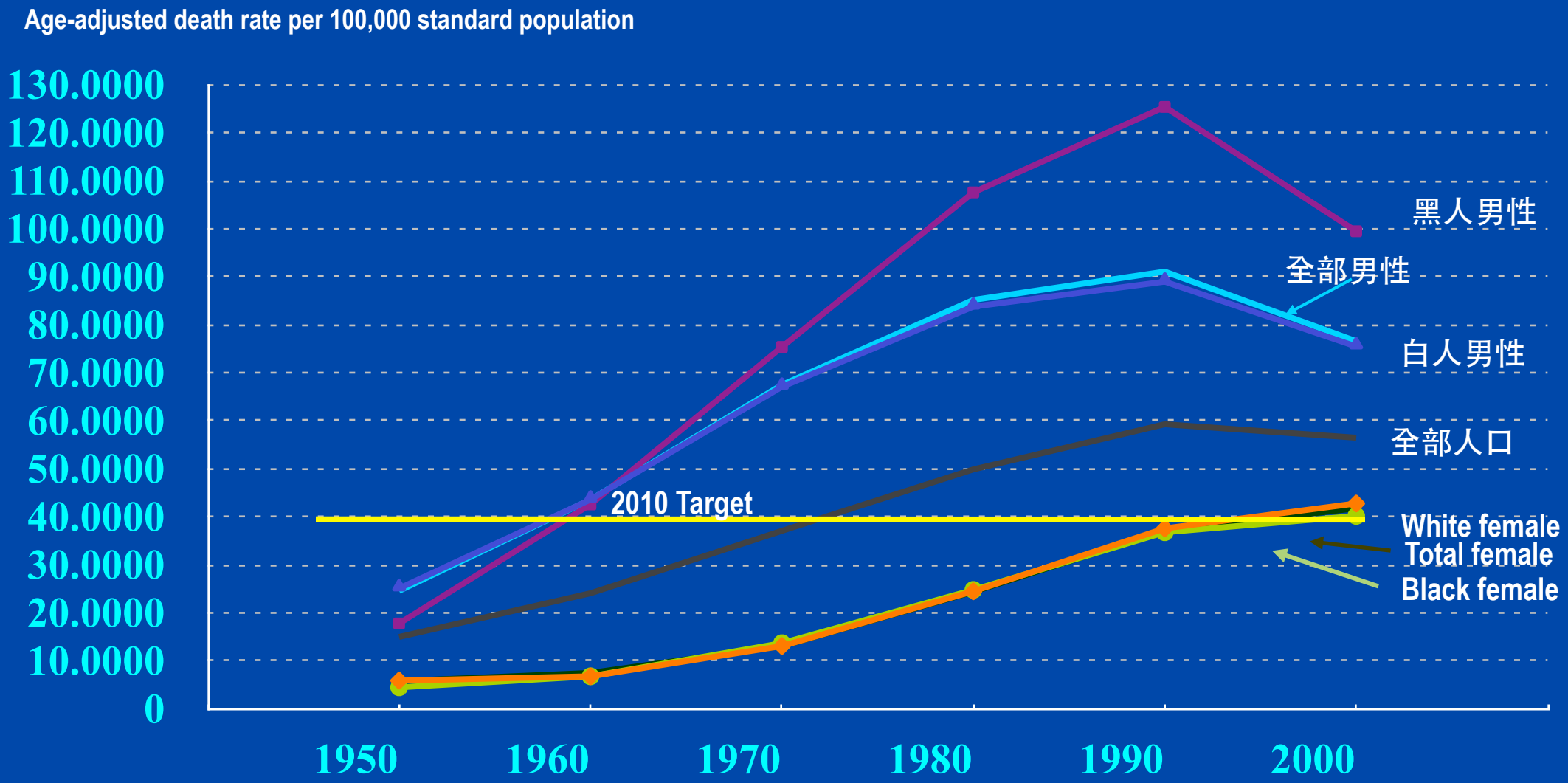
- 癌症也是一種疾病
- 預防重於治療
- 早期診斷早期治療

吸菸人口
Adults 18 Years and Older

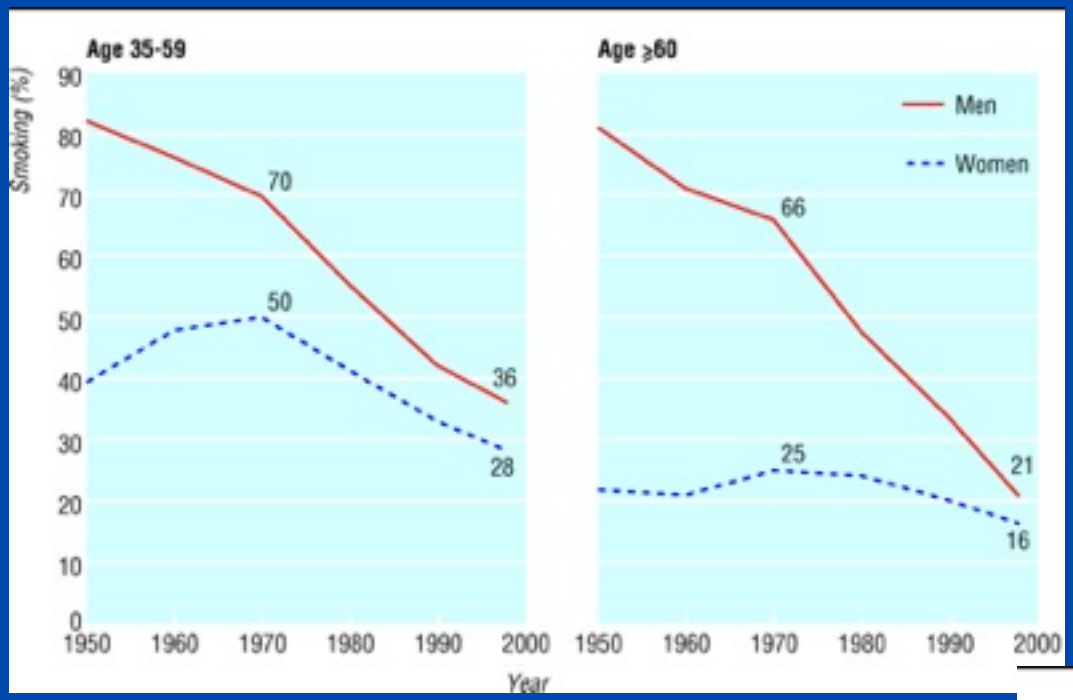


Notes: Data are age adjusted to the 2000 standard population. Survey redesigned in 1997 and data for 1998 and subsequent years may not be directly comparable to earlier years. Source: National Health Interview Survey (NHIS), NCHS, CDC.

肺癌的死亡率

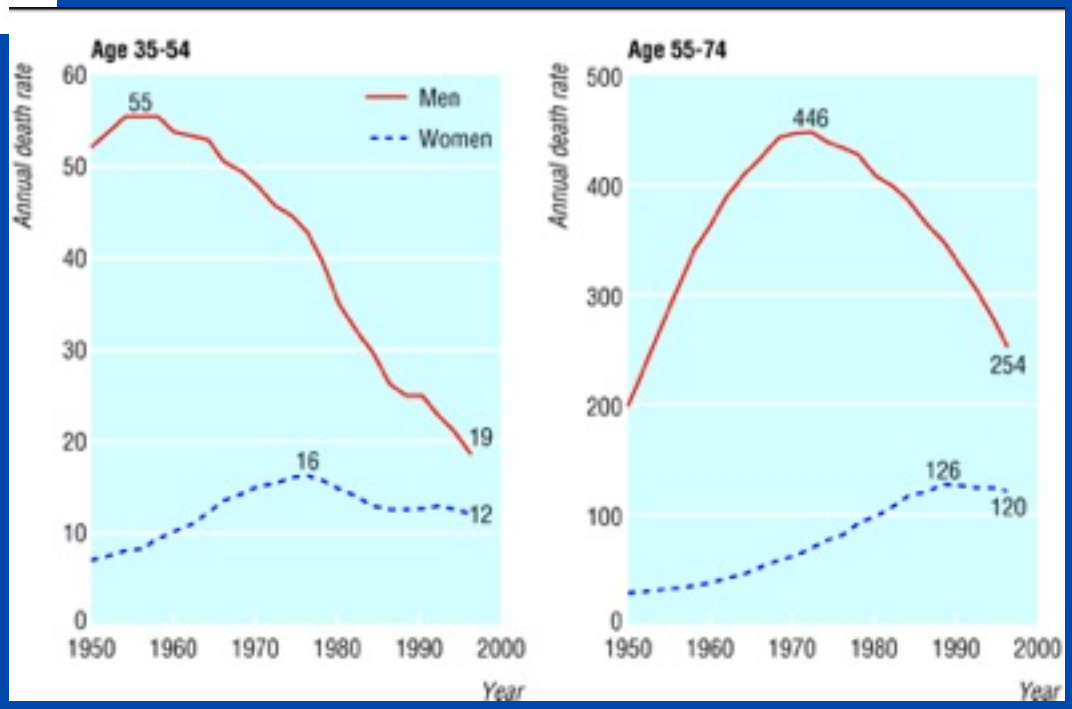


Notes: Data are age adjusted to the 2000 standard population.
Source: National Vital Statistics System-Mortality (NVSS-M), NCHS, CDC.



英國成人抽菸比例
逐年減少

肺癌死亡率有
明顯減少



自1990年以來美國癌症死亡率首次出現減低

- 美國國家癌病署(NCI)在1996年底宣布在1991-1995年間全美癌症死亡率減少了百分之三.
- 1930年代開始有癌症登記以來首次出現癌病死亡率未增反減的現象.
- 在抗癌戰爭上經由不斷的研究發展,人類也能有嚇阻癌病繼續擴大的能力.

美國癌症死亡率的增減

1971-1995

- 1971-1975 → +0.33%
- 1976-1980 → +2.09%
- 1981-1985 → +2.41%
- 1986-1990 → +1.14%
- 1991-1995 → - 2.59%

美國癌症死亡率的減低(91-95)

- 所有部位 → -2.6%
- 肺癌 → -1.5%
- 乳癌 → -6.3%
- 攝護腺癌 → -6.2%
- 大腸直腸癌 → -5.4%
- 卵巢癌 → -4.8%
- 子宮頸癌 → -9.7%

現代醫學控制癌症的方法

手術切除 →	Remove known tumor masses
放射線治療 →	Kill rapidly dividing tumor cells, including tumor cells in adjacent tissues
化學治療 →	Kill rapidly dividing tumor cells
賀爾蒙治療 →	Inhibit the growth and survival of hormone-dependent tumor cells

現代醫學控制癌症的方法

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荷爾蒙治療 →	Inhibit the growth and survival of hormone-dependent tumor cells
分子標靶治療 →	特異性地抑制腫瘤細胞生長所必需的分子路徑

實證醫學

(EBM, Evidence-based Medicine)

以流行病學和統計學的方法，從龐大的醫學資料中嚴格評讀、綜合分析並找出值得信賴的部分，並將所能獲得的最佳文獻證據，應用於臨床工作中，使病人獲得最佳的照顧。

傳統醫療 vs 實證醫學

傳統醫療:

- Identify the Problem
- Use your Experience
- Ask a Colleague
- Consult a Textbook
- Read a Review

實證醫學

- Formulate a Question
- Conduct Search of Literature
- Select Key Articles
- Critically Judge the Articles
- Apply result to Patient

癌症臨床試驗的重要性

- 目前我們在治療癌症的各種進步都是經由臨床試驗而來的
- 癌症患者可以活的更久都是因為臨床試驗帶來的治療演進的結果

Cancer:
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癌症與基因

- The changes that cause a cancer in an individual patient is called the molecular signature or **genetic fingerprint**
- The signature dictates how aggressive it will be and what treatment will work best
- We can now measure the genes in a tumor and classify the patient on the basis of its gene signature into groups

The Cancer Genome Atlas

http://cancergenome.nih.gov

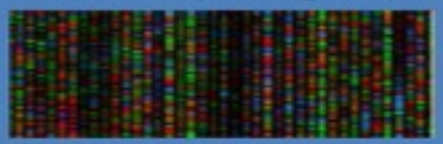
Data Management, Bioinformatics, and Analysis

An integrated database providing access to all of the information generated by the TCGA pilot project

Technology Development

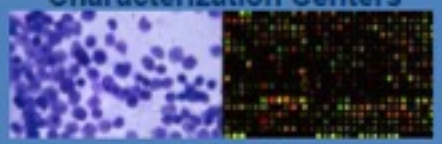
Throughout the pilot project, technology development will enable improvements to genomic analysis

Genome Sequencing Centers



High-throughput sequencing of genes identified through cancer genome characterization centers

Cancer Genome Characterization Centers



Technologies to investigate and characterize genes that may be associated with cancer

Human Cancer Biospecimen Core Resource

Centralized facility to catalog and store tumor samples, and distribute genetic material to TCGA research centers

個人化醫療 Personalized Medicine

- Personalized Medicine —what is it?
- Then and now —what we can do today that we couldn't do before
- Biomarkers and (genetic) testing
- Dose and drug selection —some key points to consider
- Drug—test co--development —a paradigm change?
- Theme:Evidence and Benefit- Risk considerations

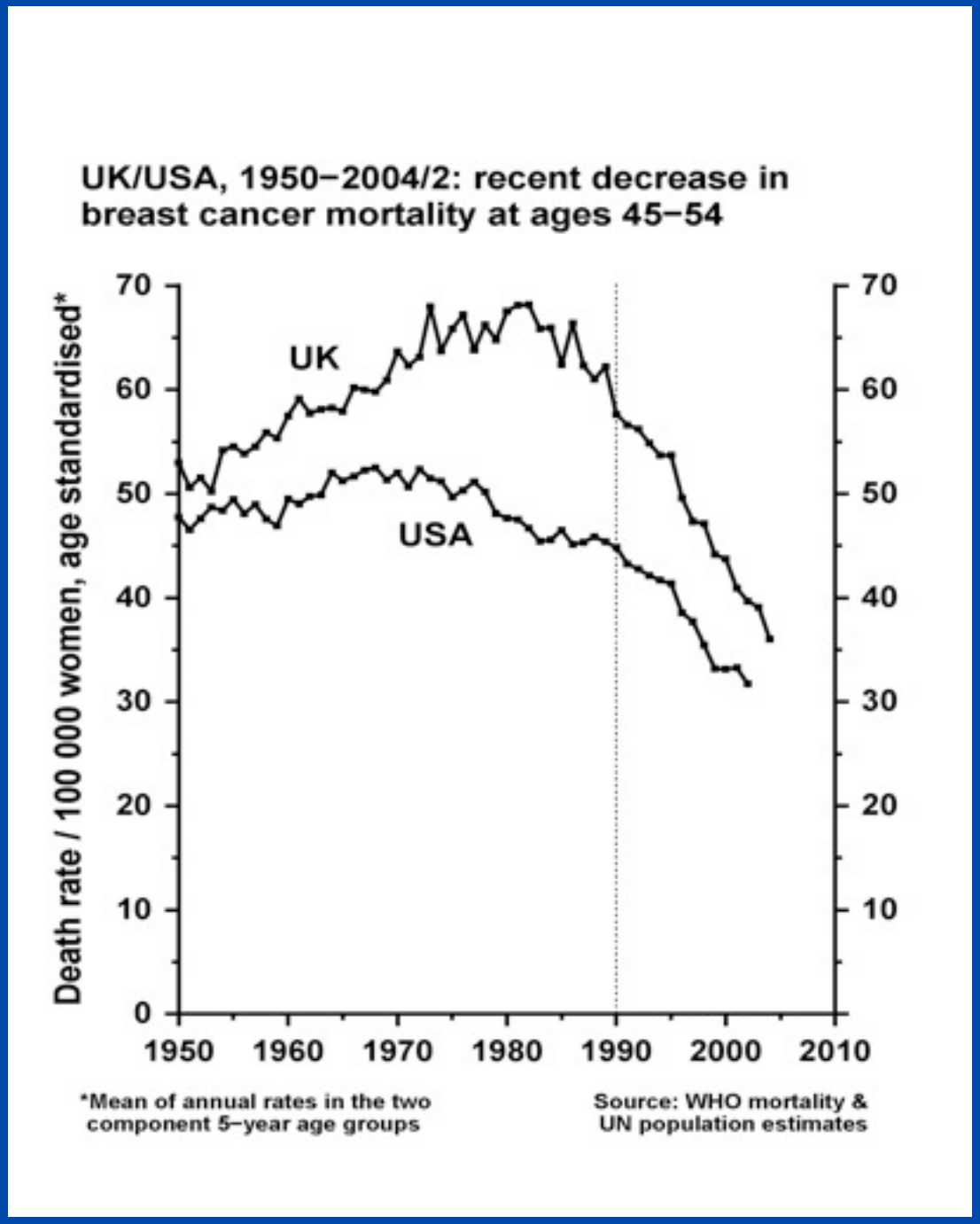
個人化醫療 Personalized Medicine

'The management of a patient's disease or disposition by using molecular knowledge to achieve the best possible medicinal outcome for that individual'

個人化醫療 Personalized Medicine

Personalized medicine is the use of information from a patient's genotype to:

- Initiate a preventative measure against the development of a disease or condition , or
- Select the most appropriate therapy for a disease or condition that is particularly suited to that patient.

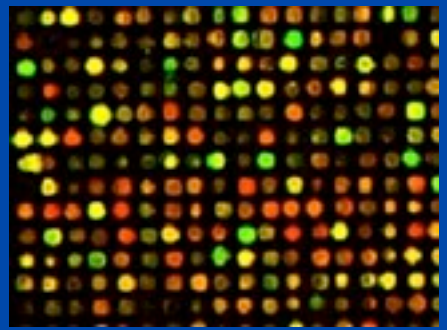

UK/USA, 1950–2004/2: recent decrease in breast cancer mortality at ages 45–54
Death rate / 100 000 women, age standardised*
70
60
50
40
30
20
10
0
UK
USA
1950
1960
1970
1980
1990
2000
2010
*Mean of annual rates in the two component 5-year age groups
Source: WHO mortality & UN population estimates

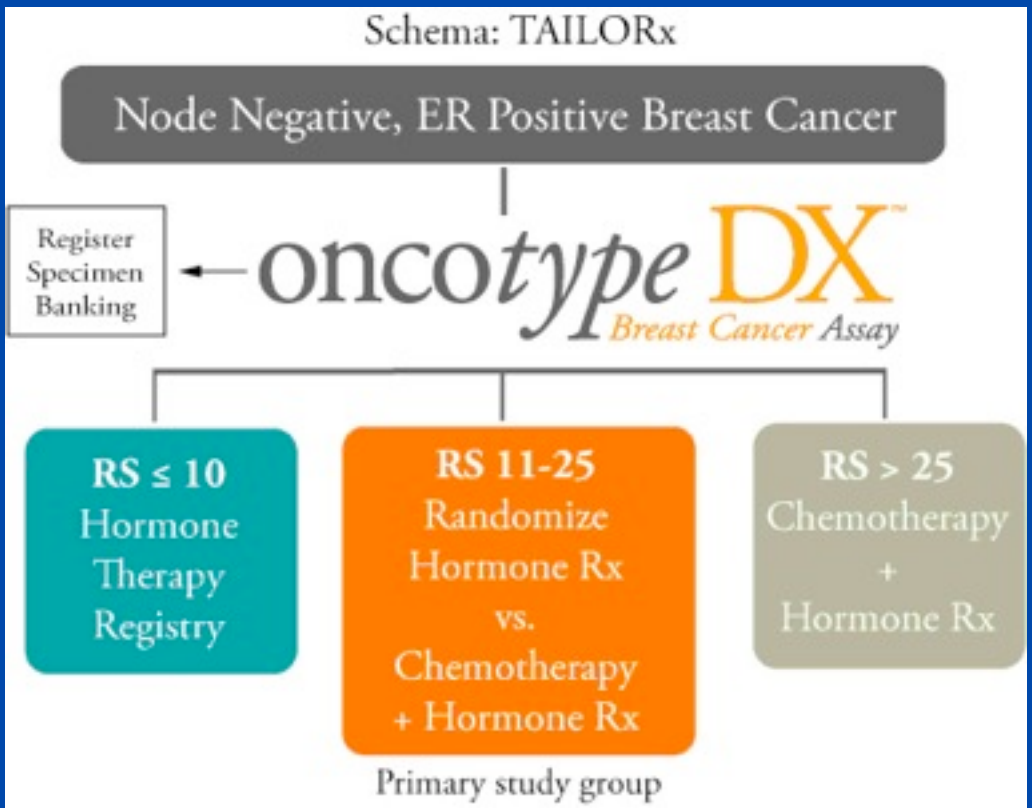
乳癌死亡率降低

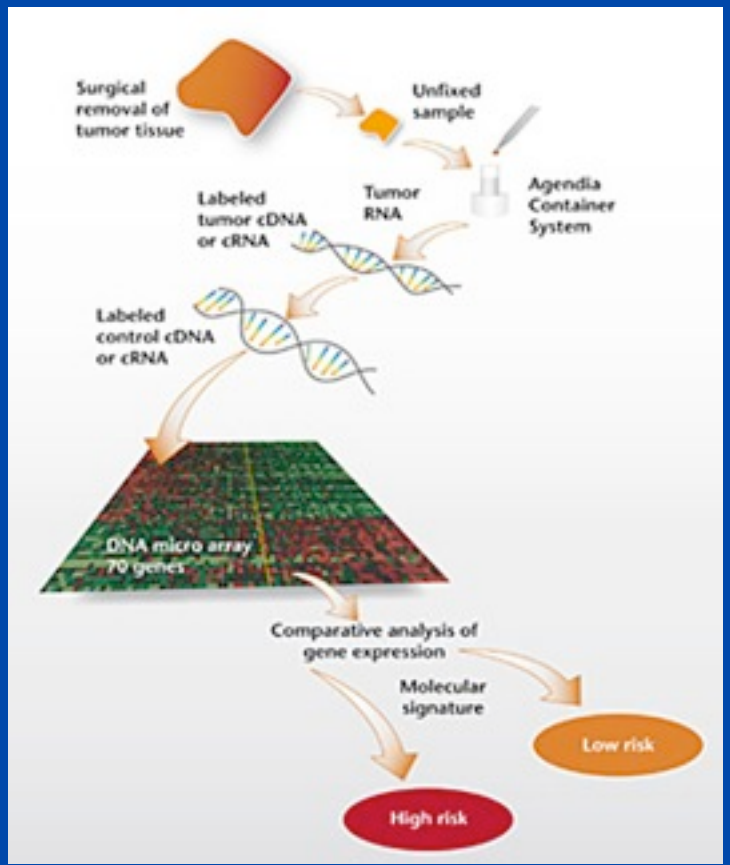
外科病理的演進

- Era of Autopsy Pathology – Curious physicians (1700 – early 1900s)
- Era of Surgical Pathology – Branched out from Surgery (early to mid-1900s)
- Era of Personalized Medicine – Integrated Anatomic and Clinical Pathology (turn of the century)

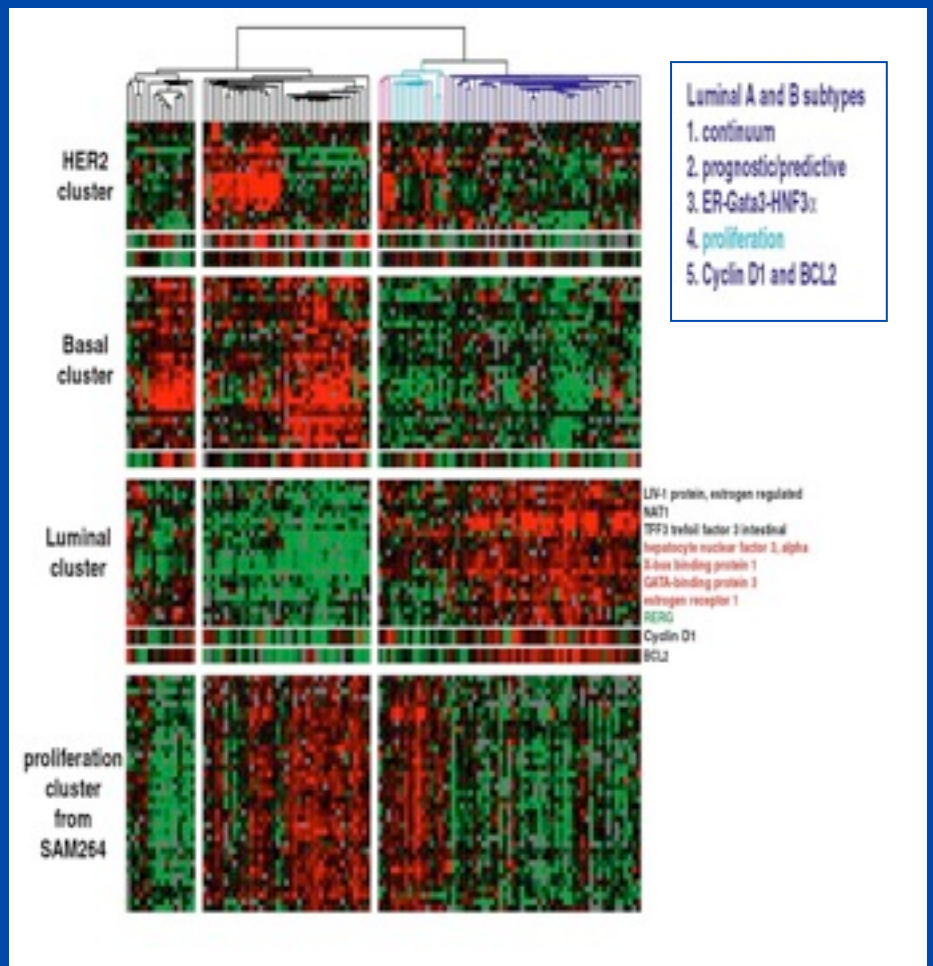
- **Tumors genetic signature stratifies patients risk for metastasis (OncodxTM, MamoprintTM etc)**





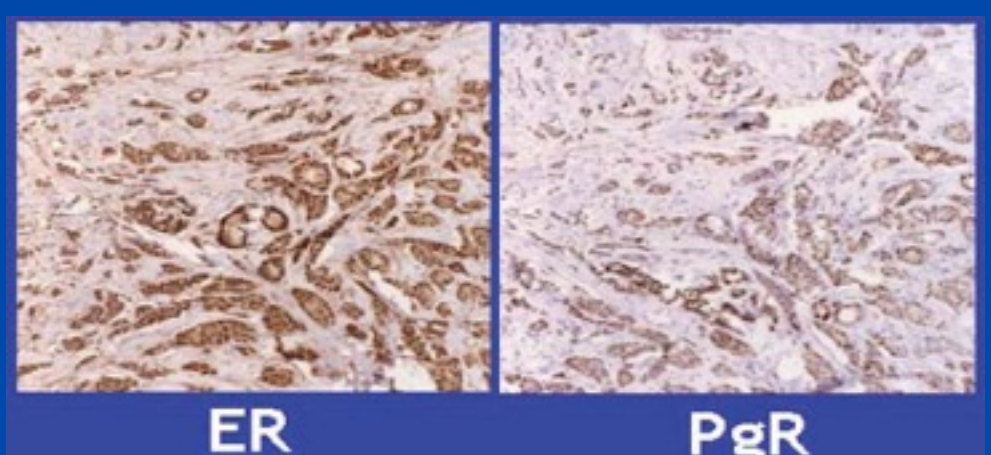


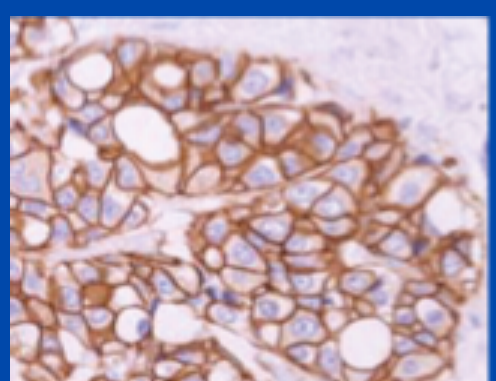
Breast Cancer is Not ONE Disease



IHC-based subtypes

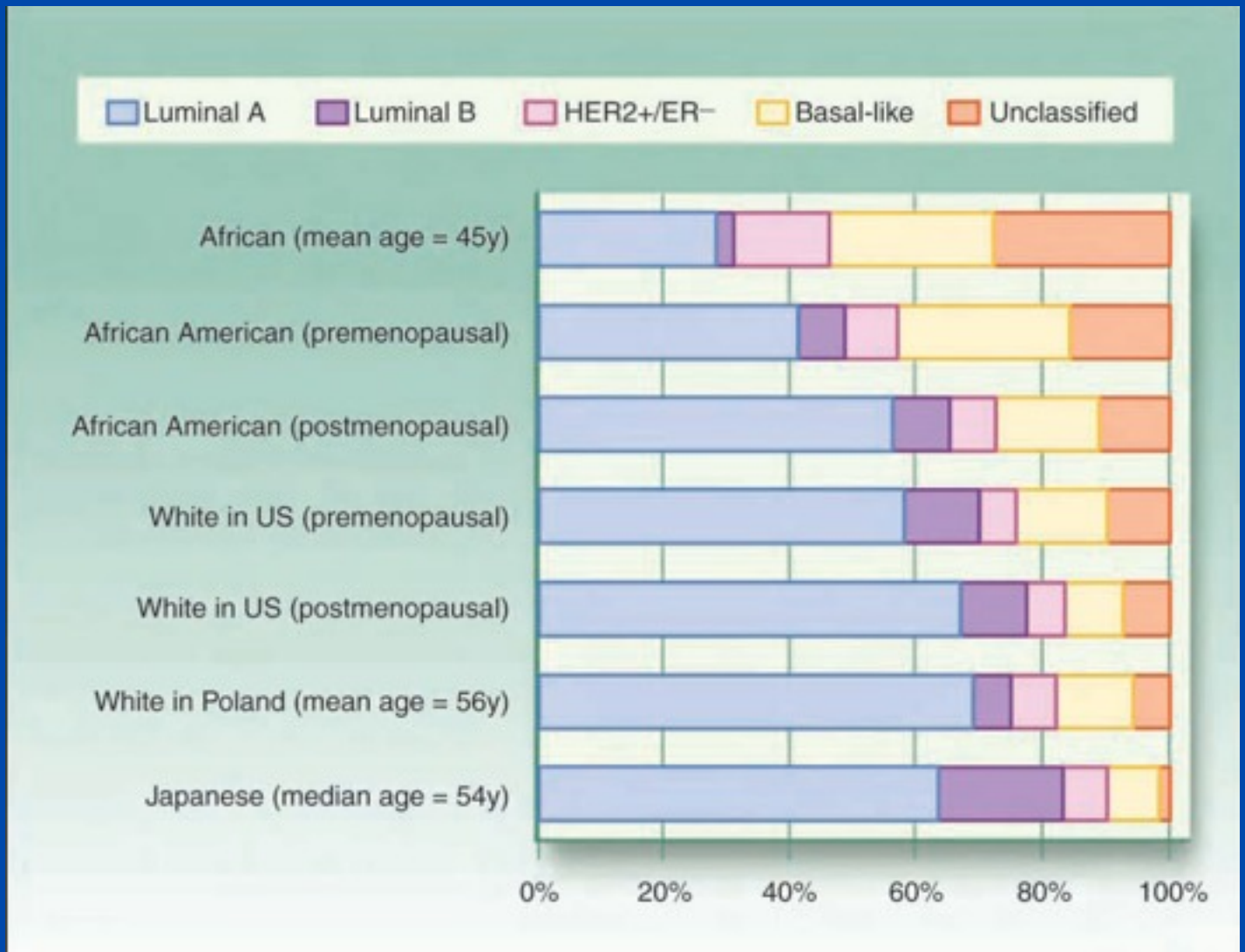
- Luminal A: ER+ and/or PR+, HER2-
- Luminal B: ER+ and/or PR+, HER2+
- Basal-like: ER-, PR-, HER2-, CK 5/6+ and/or EGFR+
- HER2+/ER-
- Unclassified: negative for all five markers





JAMA 295:2492, 2006

人種的不同也有乳癌次分類的不同



Personalized Medicine

Old Paradigm: Trial and Error Medicine

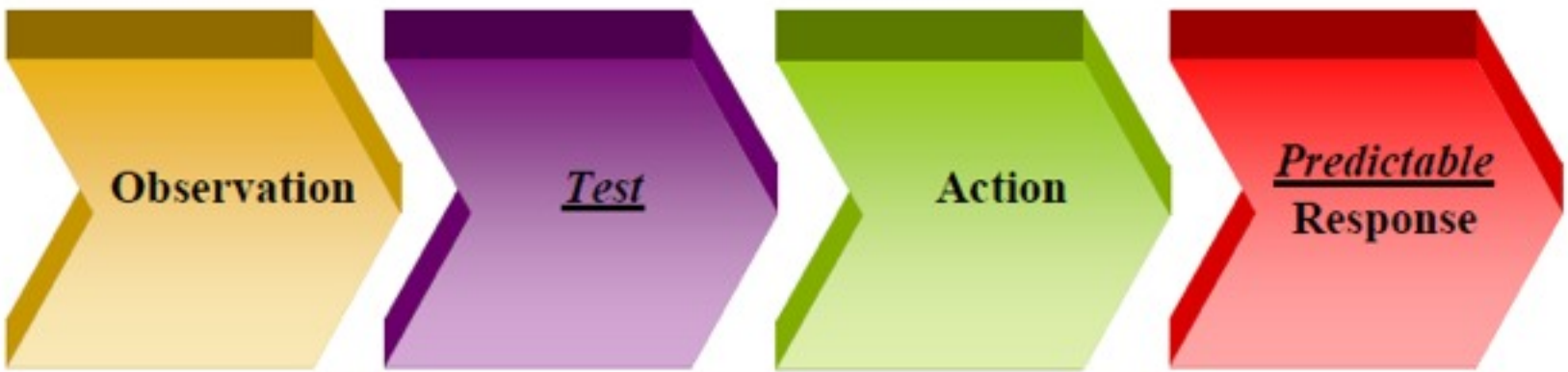
Successful When it Leads to Innovation and Improves Standard of Care.

Fails When We Settle for "Trial and Error" Medicine *AS* the Standard of Care.

Personalized Medicine

New Paradigm: Personalized Medicine

Linking Tests to Action and Therapy



Breaking The Cycle of Trial and Error Medicine

Symptoms vs. Genetic-based Medicine

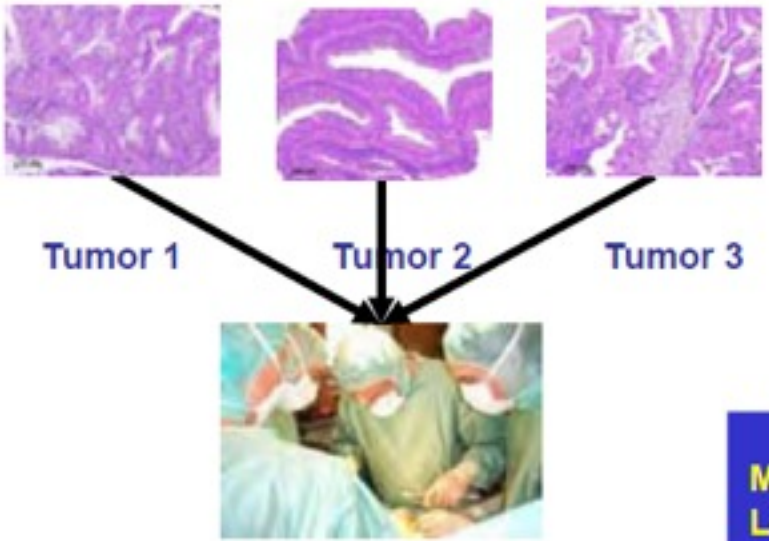
Symptoms-based

- Symptomatic diagnosis, prescription & monitoring
- Treatment Targets selected based on largest population
- Blockbuster drug for all patients effective in only 40-60% and can have adverse drug reactions (ADR)
- Reactive

Symptoms vs. Genetic-based Medicine

- ***Genetic-based***
- Molecular Diagnosis
- Risk-stratification by molecular
- Drug-targeted therapy
- Less or no ADR
- Molecular monitoring of disease
- Preventive

Today



Standard Therapy

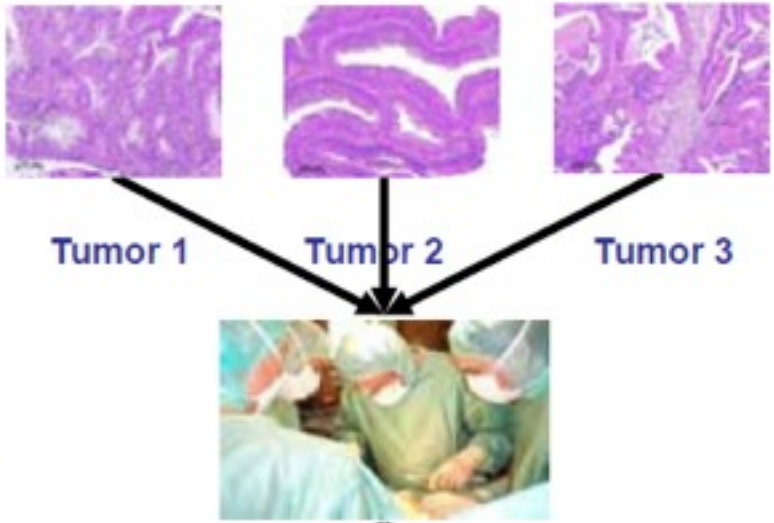
In 2001, only one of three patients benefited from cancer drug treatment

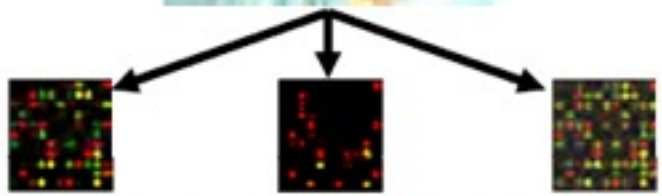
(Spear et al. (2001) Trends Molec. Med. 7, 201-203)

More effective
Less toxic
Less costly

Future

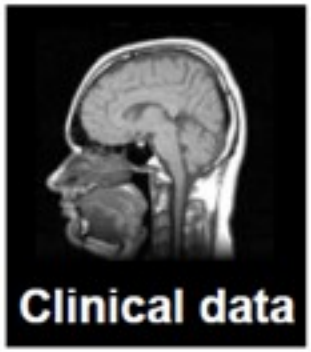
f Biorepositories
specimen Research



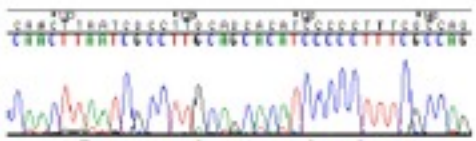


Molecular diagnosis

Compliments of Dr. Hartmut Juhl, Indivumed GmbH, Hamburg

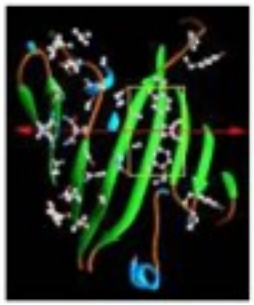


Clinical data



Genetic variation

Genetic expression



Proteomic expression

Personalized Healthcare

The patient has disease X, subclass Y, which will likely respond to drug Z

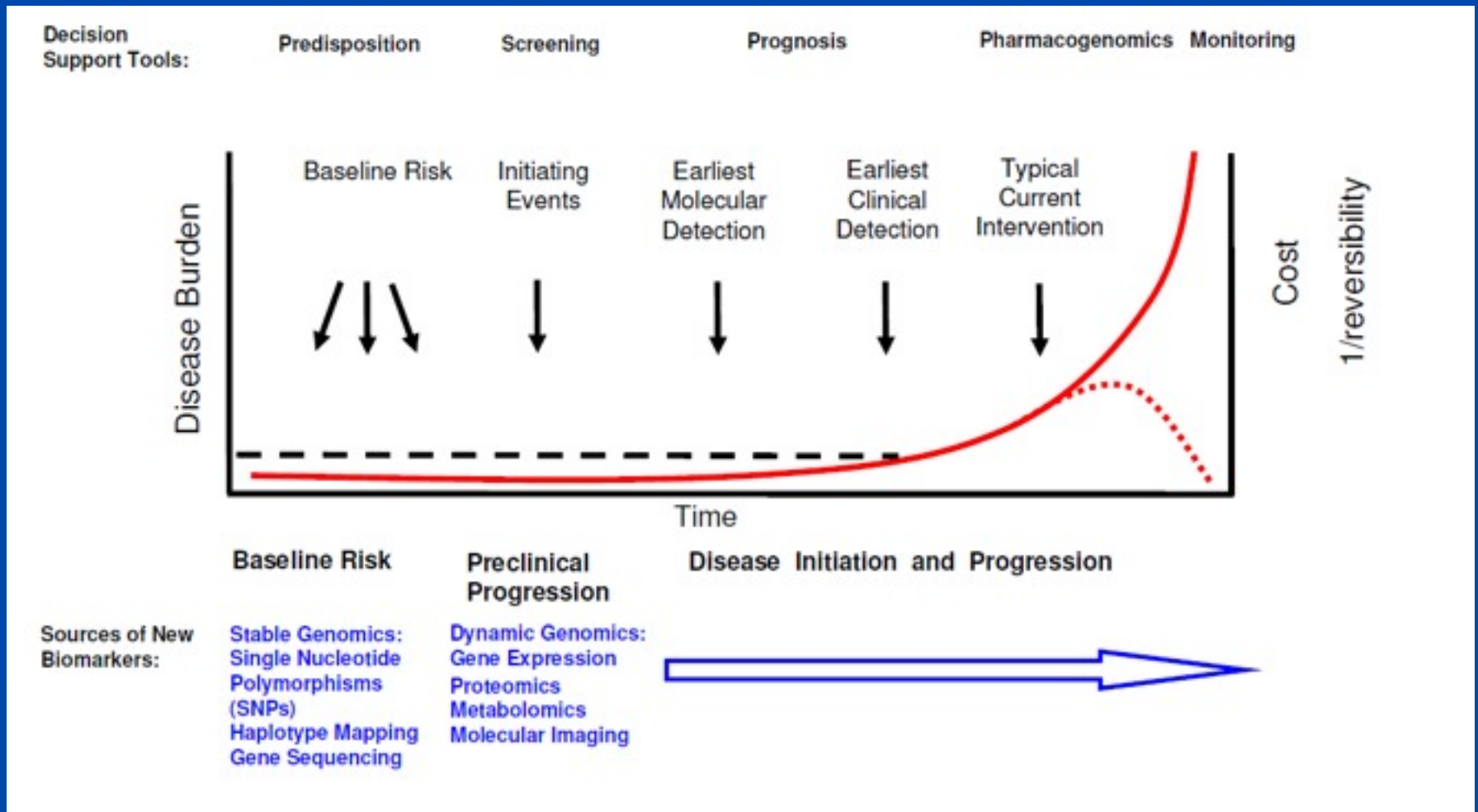
Genetics and Genomics in Clinical Medicine

- **Assessment of risk** (eg., Breast cancer and Colon cancer)
- **Pharmacogenomics** – Efficacy of drugs based on genomic changes
- **Pharmacogenetics** – Efficacy of drugs based on genetic differences

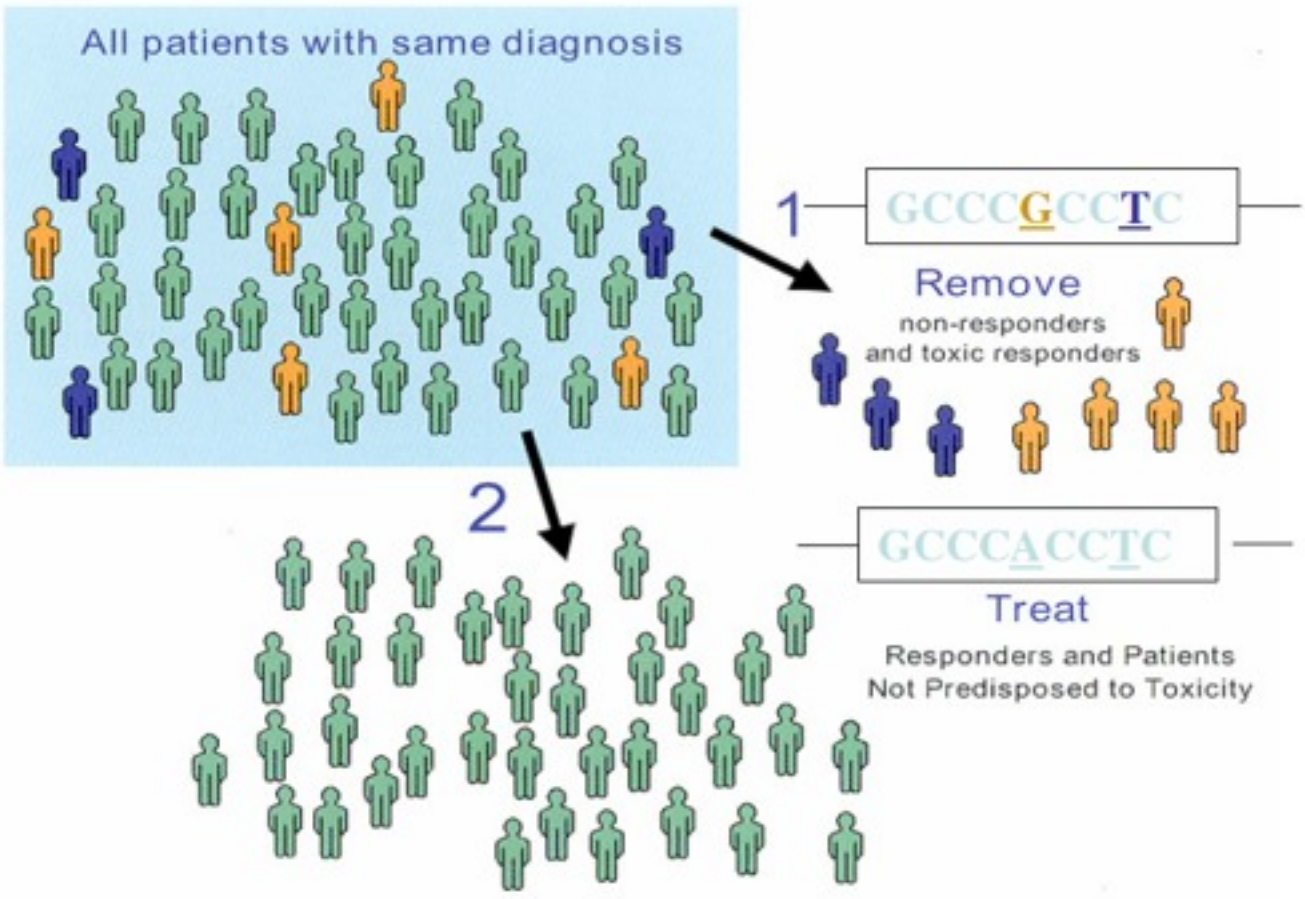
Personalized Medicine involve

- Risk stratification
- Inform treatment selection
- Inform dosage
- Prognostic testing
- Treatment monitoring
- Improve or optimize clinical treatment pathways
- ---------

Genomic Tools for Prediction and Personalized Care

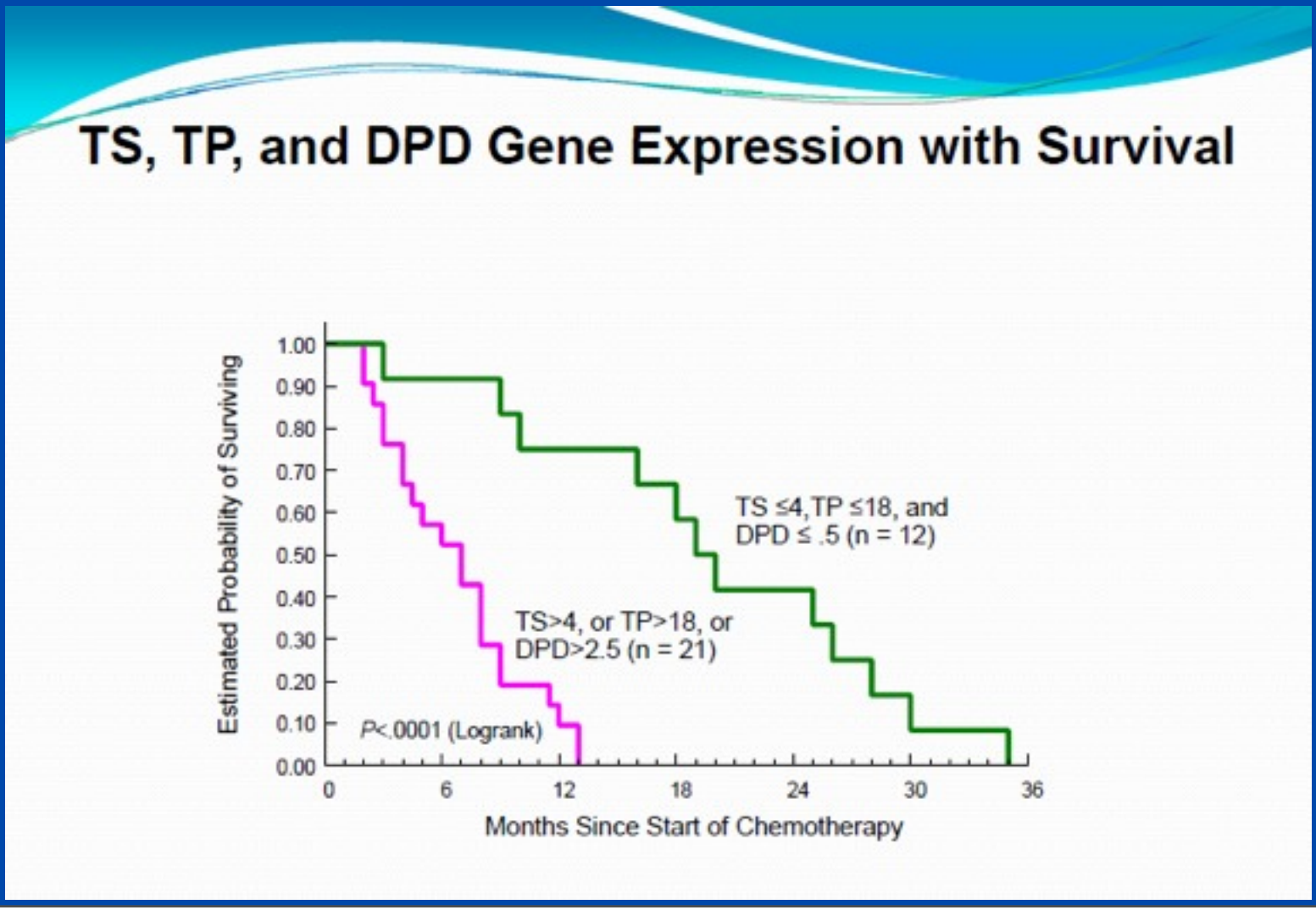


Pharmacogenomics Strategy



From McLeod and Evans, Ann Rev of Pharmacol and Toxicol, 2001: 41,101-121

大腸直腸癌藥物治療的預後與相關代謝的基因表現相關



個人化癌症藥物治療

- Which drug should I use?
  - Tamoxifen(ER), Herceptin(Her-2),Glivec(CML Bcr-Abl),Erbitux (EGFR),Tarceva(EGFR)
- How much of the drug do I need?
  - Camptosar(UGT1A1)
- Is the drug working ?
  - Glivec(CML QT-PCR for Bcr-Abl)

Personalized Medicine: Fears

- Pharma
- Payers
- Doctors
- Patients
- Regulators
- Diagnostics

- Reduce market
- Add cost without return
- Too prescriptive
- Will I be denied access to new drugs?
- How do handle new complexities?
- More tests with poor reimbursement

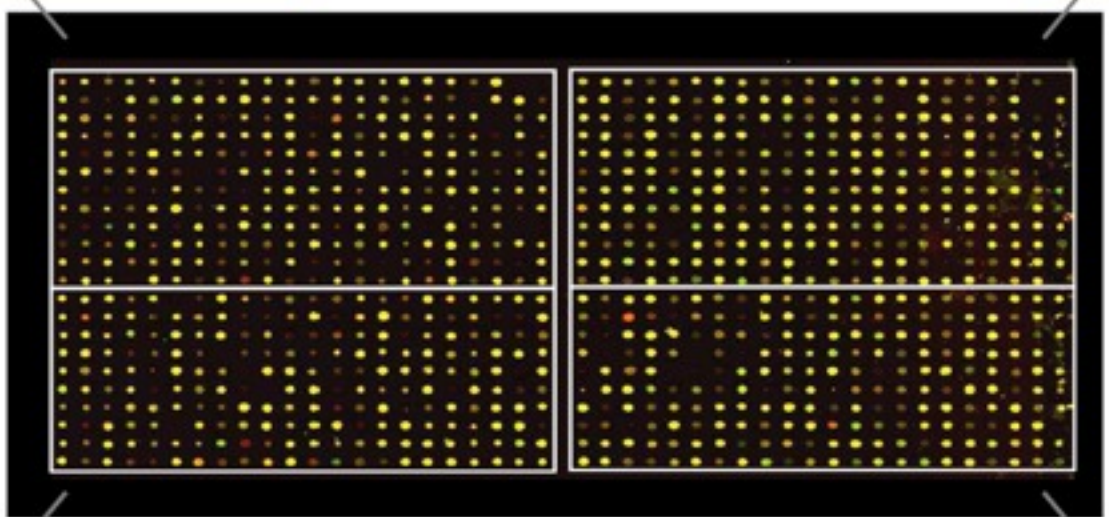
Personalized medicine:

multiple pathways analyzed on a single microarray

Will tumor come back? (prognosis)

(Is BRCA1 mutated?)

Will tumor respond to PARPi?



Will tumor respond to EGFR drug?

(Is PI3K pathway active?)

Will tumor respond to hormonal therapy?

(Is ER pathway active?)

Personalized Medicine

The right drug or treatment, at the right time, for the right patient, at the right cost

對的治療　對的時間

對的患者　對的代價