# HA Convention 2013

## Corporate Scholarship Presentation

# Cancer Biology: Predictive Biomarkers for Tailored Therapies

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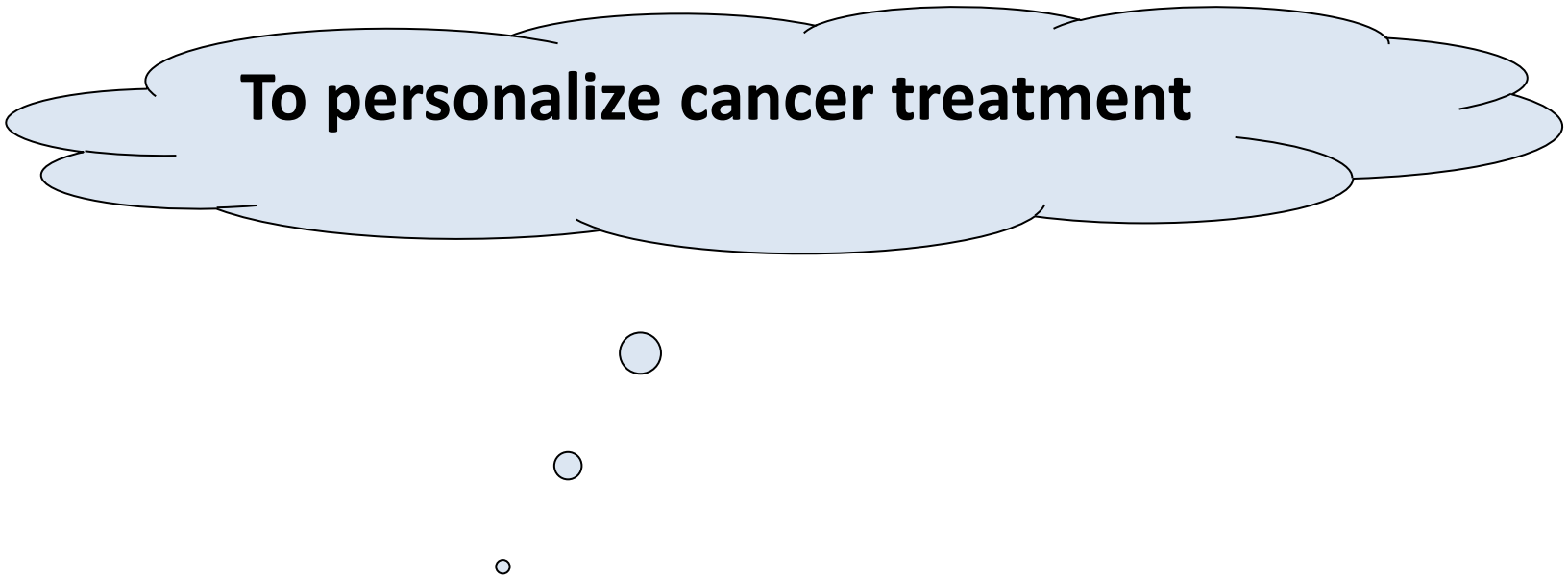
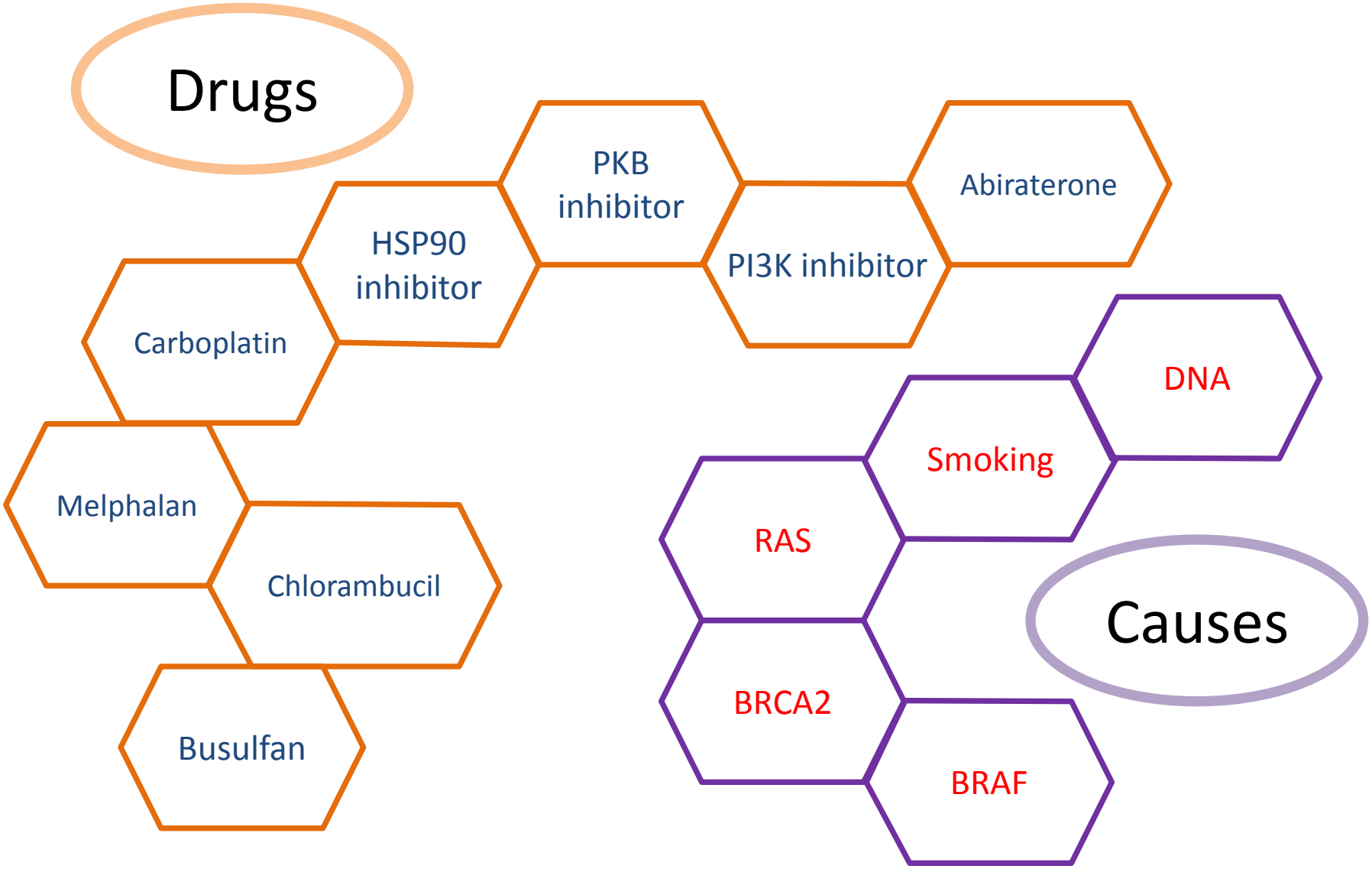
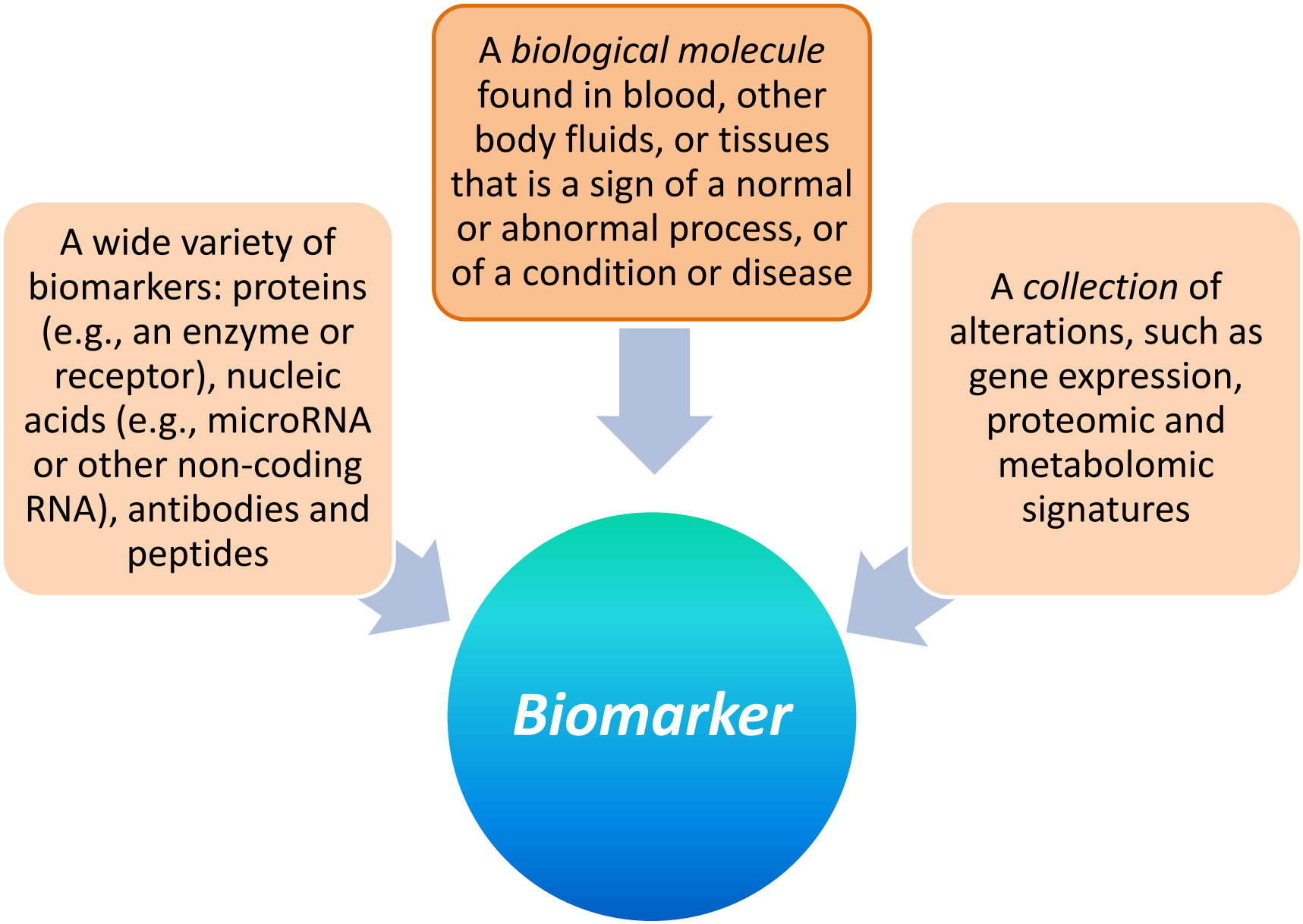

To personalize cancer treatment

# Institute of Cancer Research




Drugs
PKB inhibitor
Abiraterone
HSP90 inhibitor
PI3K inhibitor
Carboplatin
DNA
Smoking
Melphalan
RAS
Chlorambucil
Causes
BRCA2
Busulfan
BRAF

# Biomarker development & problems

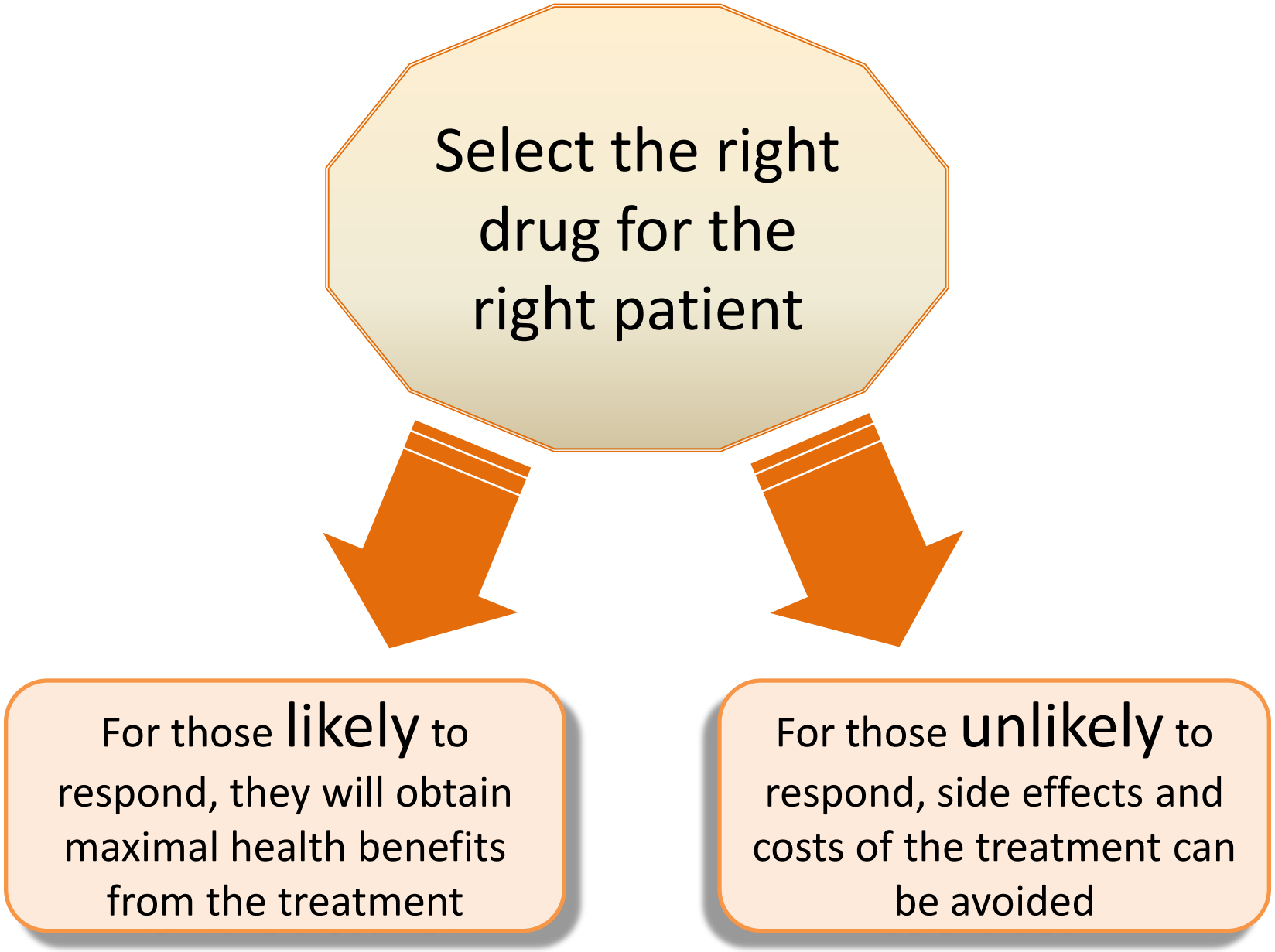

A *biological molecule* found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease
A wide variety of biomarkers: proteins (e.g., an enzyme or receptor), nucleic acids (e.g., microRNA or other non-coding RNA), antibodies and peptides
A *collection* of alterations, such as gene expression, proteomic and metabolomic signatures
Biomarker

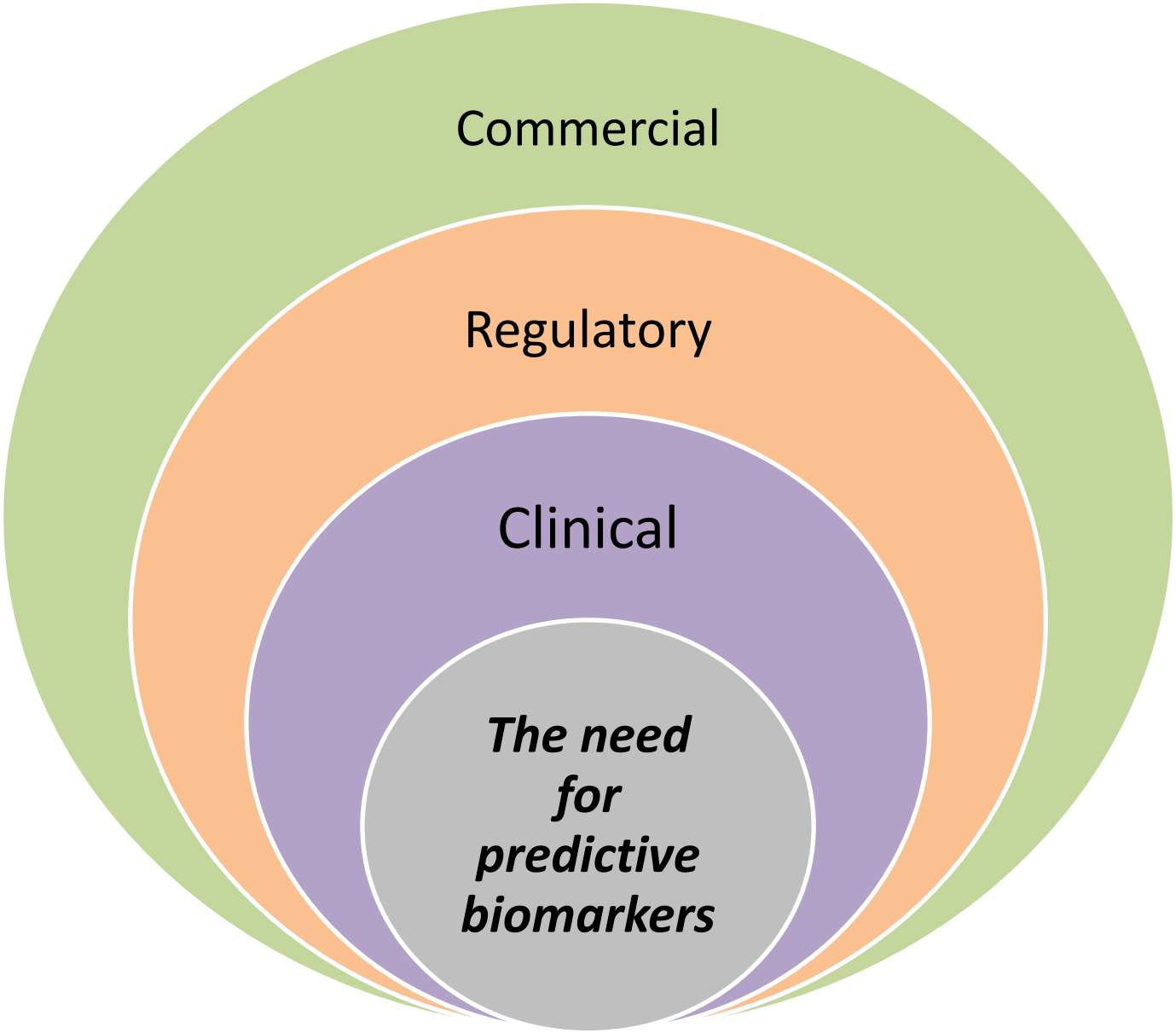
## Predictive biomarker

It is a biomarker used to assess the likelihood that the tumor will respond to the drug, i.e. to *predict response* to a particular treatment

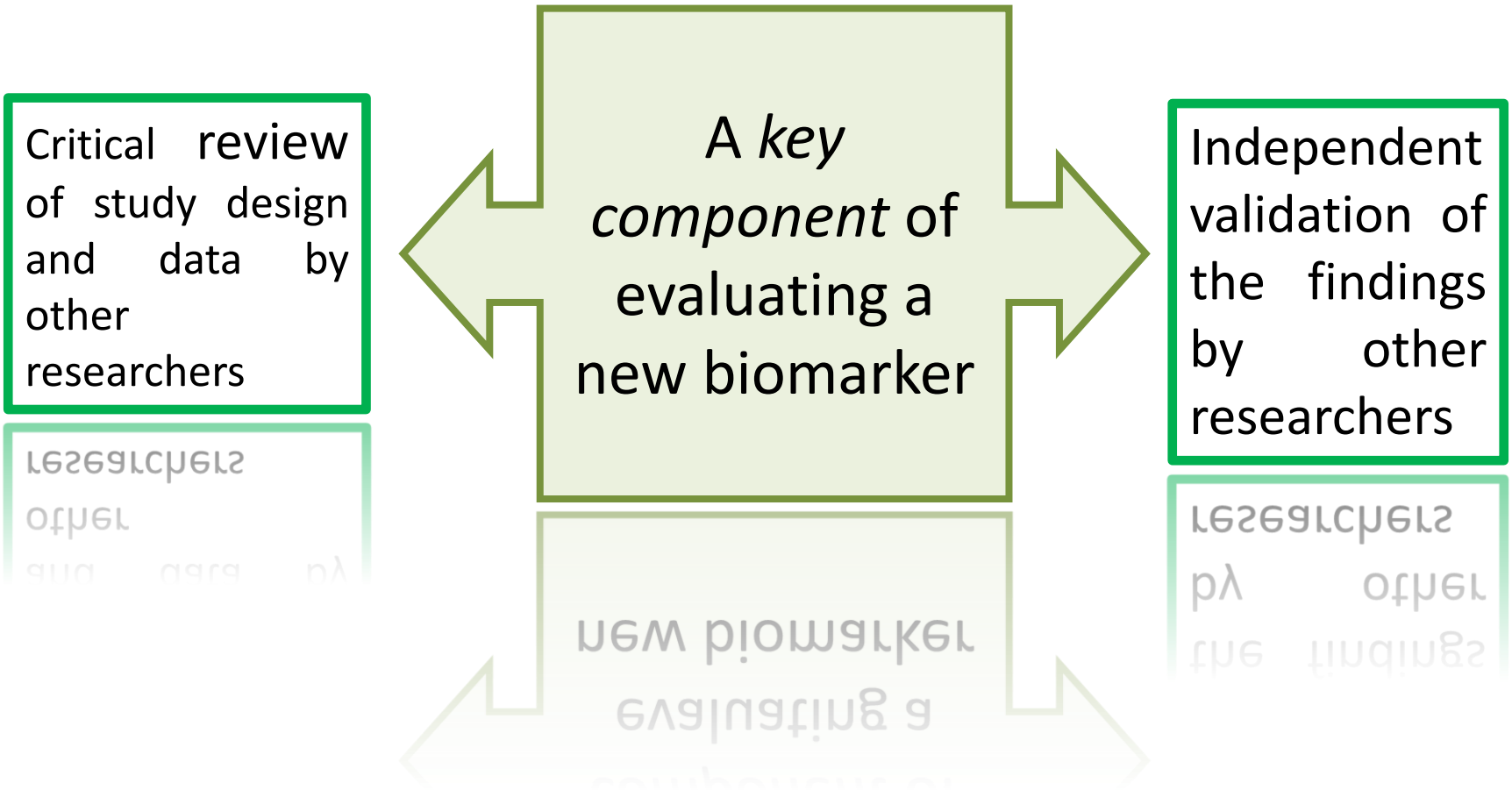
Treating cancer has progressed from a 'one drug fits all' approach to a more 'personalized' strategy where treatment regimens are driven by *biomarker expression profiles*

This will allow a level of *personalization* to be introduced into the treatment regimen


Select the right drug for the right patient
For those likely to respond, they will obtain maximal health benefits from the treatment
For those unlikely to respond, side effects and costs of the treatment can be avoided


Commercial
Regulatory
Clinical
*The need for predictive biomarkers*

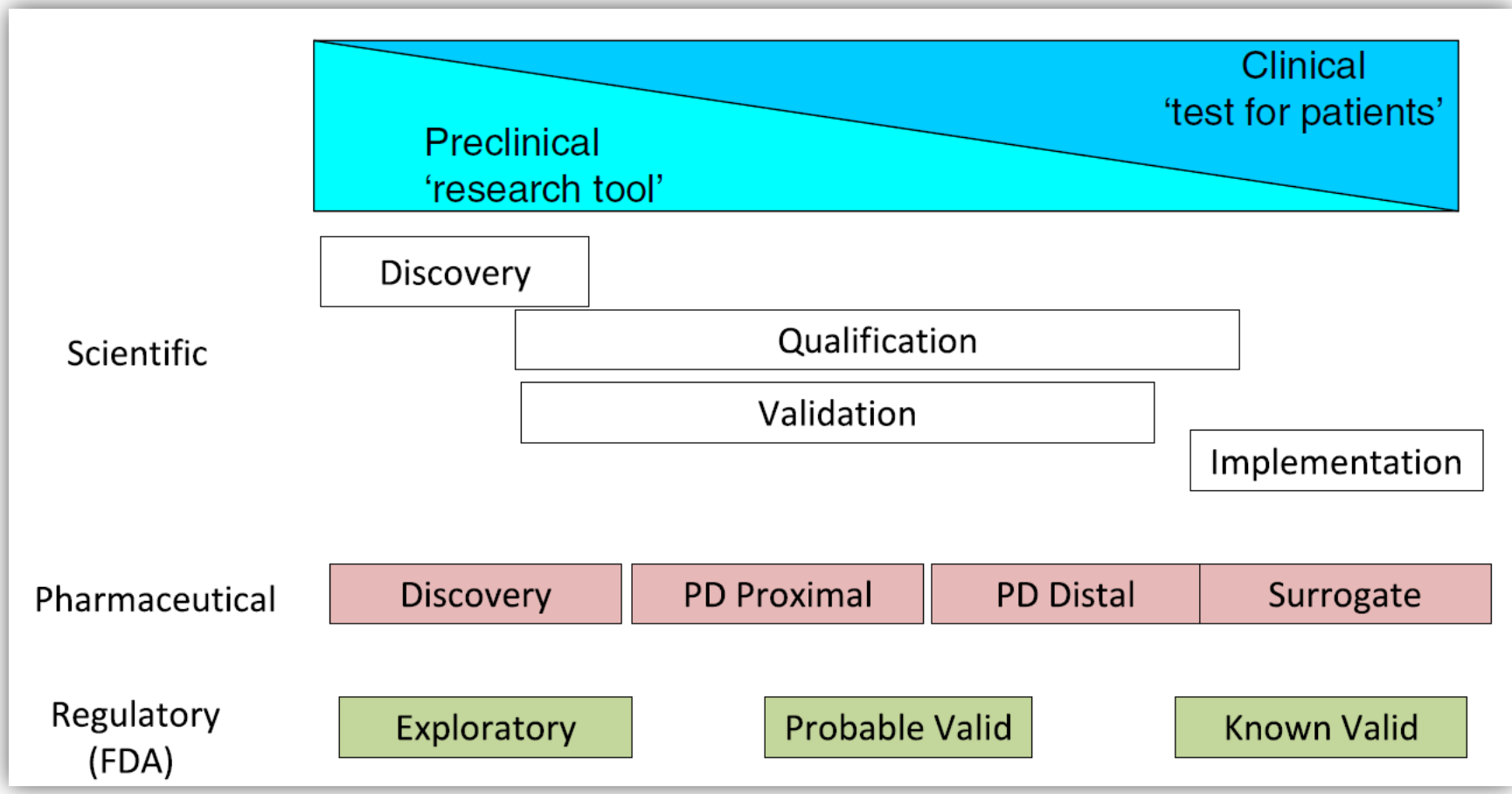
# Reporting the results of biomarker studies



# Guidelines for reporting and evaluating biomarker studies

| Guidelines | Developed for | Contents |
|---|---|---|
| Biospecimen Reporting for Improved Study Quality (BRISQ) | Reporting the details of pre-analytical and analytical issues related to potential prognostic factor studies | |
| REporting recommendations for tumor MARKer (REMARK) prognostic studies | | Promote transparent and full reporting in prognostic studies<br>Comprise specific recommendations with respect to the reporting of patients, their treatment, characteristics of specimens used, assay method employed, design of the study and statistical analysis |
| STAndards for Reporting of Diagnostic accuracy (STARD) | Publishing diagnostic tests | Guide authors in the description of key elements of biomarker study design and execution, including descriptions of the method of patient recruitment, the diagnostic test, the use of a reference standard and statistical analyses |
| Minimum Information About a Microarray Experiment (MIAME) guideline | Reporting microarray research | |

# Biomarker development



Identification of a potential biomarker

Classic approach

Discovery approach

A key decision in biomarker discovery

*What to biomark?*

Underlying disease biology

Molecular characterisation of the clinical end-point

Solid tumour

Inadequate understanding of the biology underlying disease pathogenesis or clinical outcome

Hypothesis-generating approaches using *'omic' platforms*

**Validation of a biomarker**:- *systematic evaluation* to assure that the technique used to assay the biomarker is *reliable* to perform its task

Guided by the established principles of *bio-analytical method validation*

In UK, guidance is provided by the British Association for Research into Quality Assurance (BARQA) in the guidelines for Good Clinical Laboratory Practice

The principles of bio-analytical method validation have been termed Good Laboratory Practice (GLP), but these are not always applicable in validating biomarkers.

Biomarkers must be qualified for a *specified purpose* prior to clinical implementation

Aim of biomarker **qualification**

To define its sensitivity and specificity for clinical end-point determination

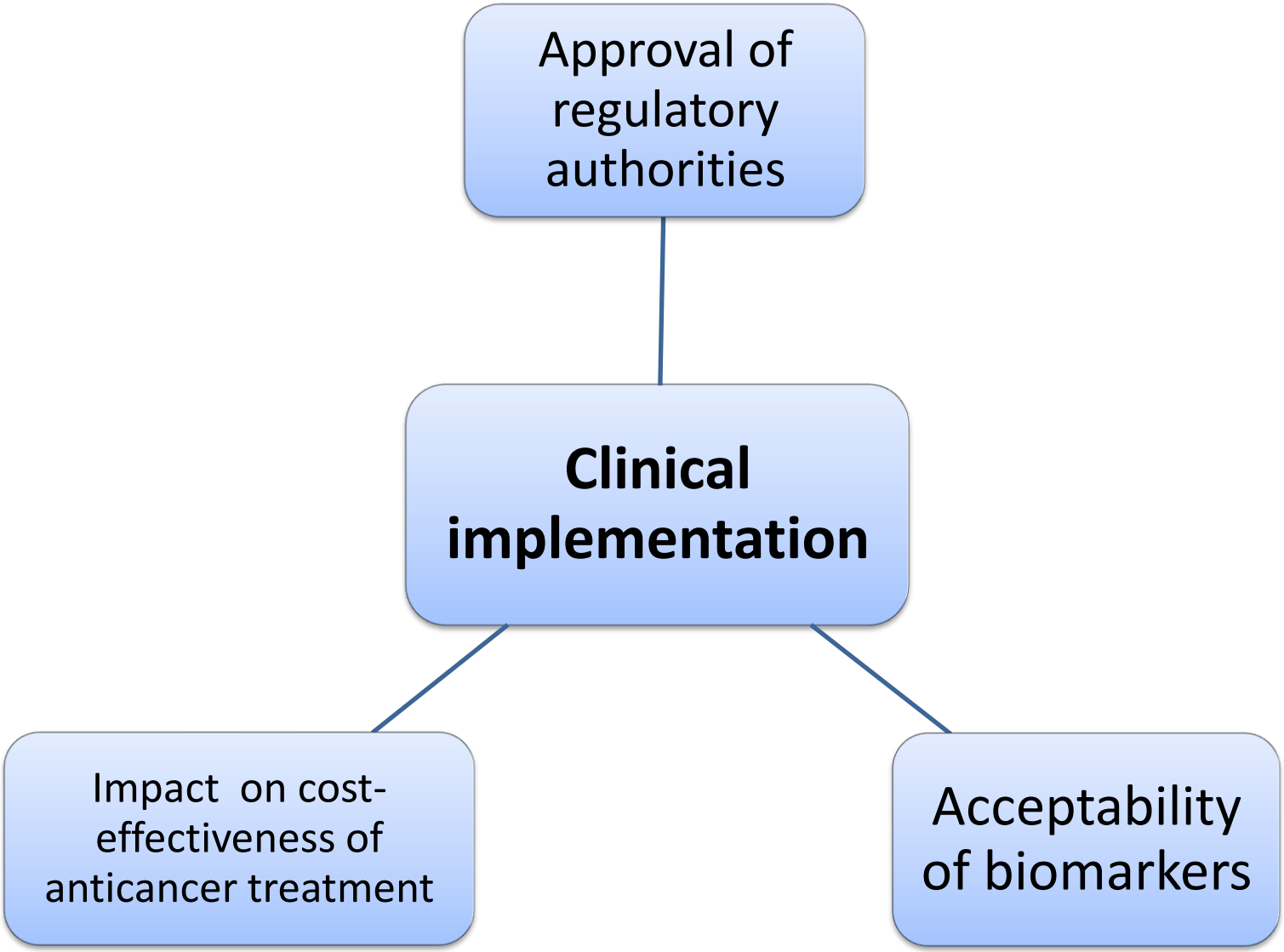
To prove its clinical utility

A challenging and relatively underdeveloped process

Optimal study design

Retrospective
Prospective

Tumour Marker Utility Grading System (TMUGS):- designed to assess the evidence associated with a biomarker in order to conclude on its impact for improved patient outcomes


Approval of regulatory authorities
Clinical implementation
Impact on cost-effectiveness of anticancer treatment
Acceptability of biomarkers

# Successful biomarkers

| Biomarker | Cancer type | Drug therapy | Drug target |
|---|---|---|---|
| **HER2 (gene amplification)** | Breast | Trastuzumab | HER2 |
| **ER (protein expression)** | Breast | Tamoxifen | ER |
| **BCR–ABL (gene translocation)** | CML | Imatinib, dasatinib, nilotinib | BCR–ABL |
| **KIT (mutation)** | GIST | Imatinib | KIT |
| **EGFR ± KRAS (KRAS mutation)** | CRC | Cetuximab, panitumumab | EGFR |
| **EGFR (kinase domain mutation)** | NSCLC | Erlotinib, gefitinib | EGFR |
| **PML–RAR (gene translocation)** | APL | All trans retinoic acid | PML–RAR |
| **BRCA1/2 (mutation)** | Breast | Olaparib, veliparib | PARP |
| **BRAF V600E (mutation)** | Melanoma | Vemurafenib | BRAF |
| **ALK (rearrangements)** | NSCLC | Crizotinib | ALK |

# Potential predictive biomarkers

Not all patients with ERBB2+ve breast cancer respond to trastuzumab. Why?

Oncogene (2013), 1–13

www.nature.com/onc

**ORIGINAL ARTICLE**

# Integrative molecular and functional profiling of *ERBB2*-amplified breast cancers identifies new genetic dependencies

K-K Shiu[1], D Wetterskog[1], A Mackay[1], R Natrajan[1], M Lambros[1], D Sims[1], I Bajrami[1], R Brough[1], J Frankum[1], R Sharpe[1], C Marchio[2], H Horlings[3], F Reyal[3], M van der Vijver[3], N Turner[1], JS Reis-Filho[1], CJ Lord[1] and A Ashworth[1]

**METHODS.** To study samples from 58 patients with HER2-positive breast cancer, 14 commercially available ERBB2-amplified cell lines and 9 non-ERBB2-amplified controls using an integrated genomic, gene expression and functional analysis to determine whether the genes present within amplicons are critical for the survival of ERBB2+ve breast tumour cells.

**TFAP2C** amplification and overexpression represents a genetic dependency in ERBB2+ve breast cancer.

Not all ERBB2+ve breast cancer rely on the ERBB2 receptor for their survival.

By finding out more genes involved in helping tumours to survive, we can work out strategies to overcome drug resistance in these patients.

British Journal of Cancer (2011) 105, 1230 – 1234

www.bjcancer.com



BJC OPEN

# *BRCA2* is a moderate penetrance gene contributing to young-onset prostate cancer: implications for genetic testing in prostate cancer patients

**Z Kote-Jarai*[,1], D Leongamornlert[1,6], E Saunders[1,6], M Tymrakiewicz[1], E Castro[1], N Mahmud[1], M Guy[1], S Edwards[1,5], L O'Brien[1], E Sawyer[1], A Hall[1], R Wilkinson[1], T Dadaev[1], C Goh[1], D Easton[2], The UKGPCS Collaborators[7], D Goldgar[3] and R Eeles[1,4]**

*[1]Oncogenetics Team, The Institute of Cancer Research, Sutton SM2 5NG, UK; [2]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, Strangeways Laboratory, Cambridge CB1 8RN, UK; [3]Department of Dermatology, University of Utah, Salt Lake City, Utah 84132, USA; [4]The Royal Marsden NHS Foundation Trust, London SM2 5NG, UK*

**BACKGROUND.** A family history of prostate cancer (PrCa) is a strong risk factor for the disease, indicating that inherited factors are important in this disease. We previously estimated that about 2% of PrCa cases diagnosed ≤55 years harbour a BRCA2 mutation and PrCa among BRCA2 carriers has been shown to be more aggressive, with poorer survival.

**METHODS.** To further evaluate the role of BRCA2 in PrCa predisposition, we screened 1864 men with PrCa aged between 36 and 88 years. We analysed the BRCA2 gene using a novel high-throughput multiplex fluorescence heteroduplex detection system developed for the ABI3130xl genetic analyzer.

**RESULTS.** We identified 19 protein-truncating mutations, 3 in-frame deletions and 69 missense variants of uncertain significance (UV) in our sample set. **All the carriers of truncating mutations developed PrCa at ≤65 years**, with a prevalence of BRCA2 mutation of 1.20% for cases in this age group.

**CONCLUSION.** Based on the estimated frequency of BRCA2 mutations in UK, we estimate that germline mutations in the BRCA2 gene confer an **~8.6-fold increased risk of PrCa by age 65**, corresponding to an absolute risk of ~15% by age 65. These results suggest that routine testing of early onset PrCa cases for germline BRCA2 mutations will further help to refine the prevalence and risk associated with BRCA2 mutations and may be useful for guiding management options.

# The Role of Lysyl Oxidase in SRC-Dependent Proliferation and Metastasis of Colorectal Cancer

Ann-Marie Baker, Thomas R. Cox, Demelza Bird, Georgina Lang, Graeme I. Murray, Xiao-Feng Sun, Stacey M. Southall, Jon R. Wilson, Janine T. Erler

Manuscript received April 23, 2010; revised September 27, 2010; accepted December 19, 2010.

**Correspondence to:** Janine T. Erler, PhD, Section of Cell and Molecular Biology, Cancer Research UK Tumor Cell Signalling Unit, The Institute of Cancer Research, London, SW3 6JB, UK (email: janine.erler@icr.ac.uk).

J Natl Cancer Inst 2011;103:407–424

**BACKGROUND.** Emerging evidence implicates lysyl oxidase (LOX), an extracellular matrix–modifying enzyme, in promoting metastasis of solid tumors. We investigated whether LOX plays an important role in the metastasis of colorectal cancer (CRC).

**METHODS.** We analyzed LOX expression in a patient CRC tissue microarray consisting of normal colon mucosa (n = 49), primary (n = 510), and metastatic (n = 198) tissues. **LOX was overexpressed in CRC cell line SW480 (SW480+LOX)**, and the **expression was knocked down in CRC cell line SW620 using LOX-specific short hairpin RNA (SW620+shLOX)**. Effect of LOX manipulation on three-dimensional cell proliferation and invasion was characterized in vitro. Effect of LOX manipulation on tumor proliferation and metastasis was investigated in a subcutaneous tumor mouse model (n = 3 mice per group) and in an intrasplenic metastatic mouse model (n = 3 mice per group). The mechanism of LOX-mediated effects via v-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog (avian) (SRC) was investigated using dasatinib, an inhibitor of SRC activation. All statistical tests were two-sided.

**RESULTS.** Compared with normal colon tissue, LOX expression was statistically significantly increased in tumor tissues of CRC patients ($P < .001$), and a greater increase was observed in metastatic tissue. SW480+LOX cells showed a statistically significantly increased three-dimensional proliferation ($P = .037$) and invasion ($P = .015$), whereas SW620+shLOX cells showed reduced proliferation ($P = .011$) and invasion ($P = .013$) compared with controls. Subcutaneous tumor growth in mice was statistically significantly increased in SW480+LOX tumors ($P = .036$) and decreased in SW620+shLOX tumors ($P = .048$), and metastasis was statistically significantly increased in SW480+LOX tumors ($P = .044$) and decreased in SW620+shLOX tumors (SW620 control vs SW620+shLOX, mean = 1.0 luminescent signal, 95% CI = 0.3 to 1.7 luminescent signal, vs mean = 0.3 luminescent signal, 95% CI = 0.1 to 0.5 luminescent signal; $P = .035$) compared with controls. LOX-mediated effects on tumor progression were associated with SRC activation, and these effects were inhibited by dasatinib.

**CONCLUSIONS.** *LOX showed an important role in CRC cell proliferation and metastasis and was dependent on the activation of SRC.* These results have the potential to identify patients with high SRC activity, who may benefit from dasatinib treatment.

*Therapeutics, Targets, and Chemical Biology*

Cancer Research

# MGMT-Independent Temozolomide Resistance in Pediatric Glioblastoma Cells Associated with a PI3-Kinase–Mediated *HOX*/Stem Cell Gene Signature

Nathalie Gaspar[1,2,3], Lynley Marshall[1,2,4], Lara Perryman[1], Dorine A. Bax[1], Suzanne E. Little[1], Marta Viana-Pereira[1,5], Swee Y. Sharp[2], Gilles Vassal[4], Andrew D.J. Pearson[1,3], Rui M. Reis[5], Darren Hargrave[3], Paul Workman[2], and Chris Jones[1]

*Cancer Res; 70(22); 9243–52.* 

**BACKGROUND.** Sensitivity to temozolomide is restricted to a subset of glioblastoma patients, with the major determinant of resistance being a lack of promoter methylation of the gene encoding the repair protein DNA methyltransferase MGMT, although other mechanisms are thought to be active. There are, however, limited preclinical data in model systems derived from pediatric glioma patients.

**METHODS.** We screened a series of cell lines for temozolomide efficacy in vitro, and investigated the differential mechanisms of resistance involved.

**RESULTS.** In the majority of cell lines, a lack of MGMT promoter methylation and subsequent protein overexpression were linked to temozolomide resistance. An exception was the pediatric glioblastoma cell line KNS42. Expression profiling data revealed a coordinated **upregulation of HOX gene expression** in resistant lines, especially KNS42, which was **reversed by PI3K pathway inhibition**. High levels of HOXA9/HOXA10 gene expression were associated with a shorter survival in pediatric high-grade glioma patient samples. Combination treatment in vitro of pathway inhibition and temozolomide resulted in a highly synergistic interaction in KNS42 cells. The resistance gene signature further included contiguous genes within the 12q13-q14 amplicon, including the Akt enhancer PIKE, significantly overexpressed in the KNS42 line. These cells were also highly enriched for CD133 and other stem cell markers.

**CONCLUSIONS.** We have shown an in vitro link between PI3K–mediated HOXA9/HOXA10 expression, and a drug-resistant, progenitor cell phenotype in MGMT-independent pediatric glioblastoma.

*Tumor and Stem Cell Biology*

Cancer Research

# *FGFR1* Amplification Drives Endocrine Therapy Resistance and Is a Therapeutic Target in Breast Cancer

Nicholas Turner[1,2], Alex Pearson[1], Rachel Sharpe[1], Maryou Lambros[1], Felipe Geyer[1], Maria A. Lopez-Garcia[1], Rachael Natrajan[1], Caterina Marchio[1], Elizabeth Iorns[1], Alan Mackay[1], Cheryl Gillett[3], Anita Grigoriadis[3], Andrew Tutt[3], Jorge S. Reis-Filho[1], and Alan Ashworth[1]

*Cancer Res; 70(5); 2085–94.* 

**BACKGROUND.** Amplification of fibroblast growth factor receptor 1 (*FGFR1*) occurs in ~10% of breast cancers and is associated with poor prognosis. However, it is uncertain whether overexpression of FGFR1 is causally linked to the poor prognosis of amplified cancers.

**RESULTS.** We show that *FGFR1* overexpression is robustly associated with *FGFR1* amplification in two independent series of breast cancers. Breast cancer cell lines with *FGFR1* overexpression and amplification show enhanced ligand-dependent signaling, with increased activation of the mitogen-activated protein kinase and PI3K–AKT signaling pathways in response to FGF2, but also show basal ligand-independent signaling, and are dependent on FGFR signaling for anchorage-independent growth.

**RESULTS.** *FGFR1*-amplified cell lines show **resistance to 4-hydroxytamoxifen**, which is reversed by small interfering RNA silencing of FGFR1, suggesting that FGFR1 overexpression also promotes endocrine therapy resistance. FGFR1 signaling **suppresses progesterone receptor (PR) expression** *in vitro*, and likewise, amplified cancers are frequently PR negative, identifying a potential biomarker for FGFR1 activity. Furthermore, we show that amplified cancers have a high proliferative rate assessed by Ki67 staining and that *FGFR1* amplification is found in 16% to 27% of luminal B–type breast cancers.

**CONCLUSIONS.** Our data suggest that amplification and overexpression of *FGFR1* may be a major contributor to poor prognosis in luminal-type breast cancers, driving anchorage-independent proliferation and endocrine therapy resistance.

# Role of HA

# Hospital Authority

## Annual Plan 2013-2014

## An Overview

醫院管理局
HOSPITAL AUTHORITY

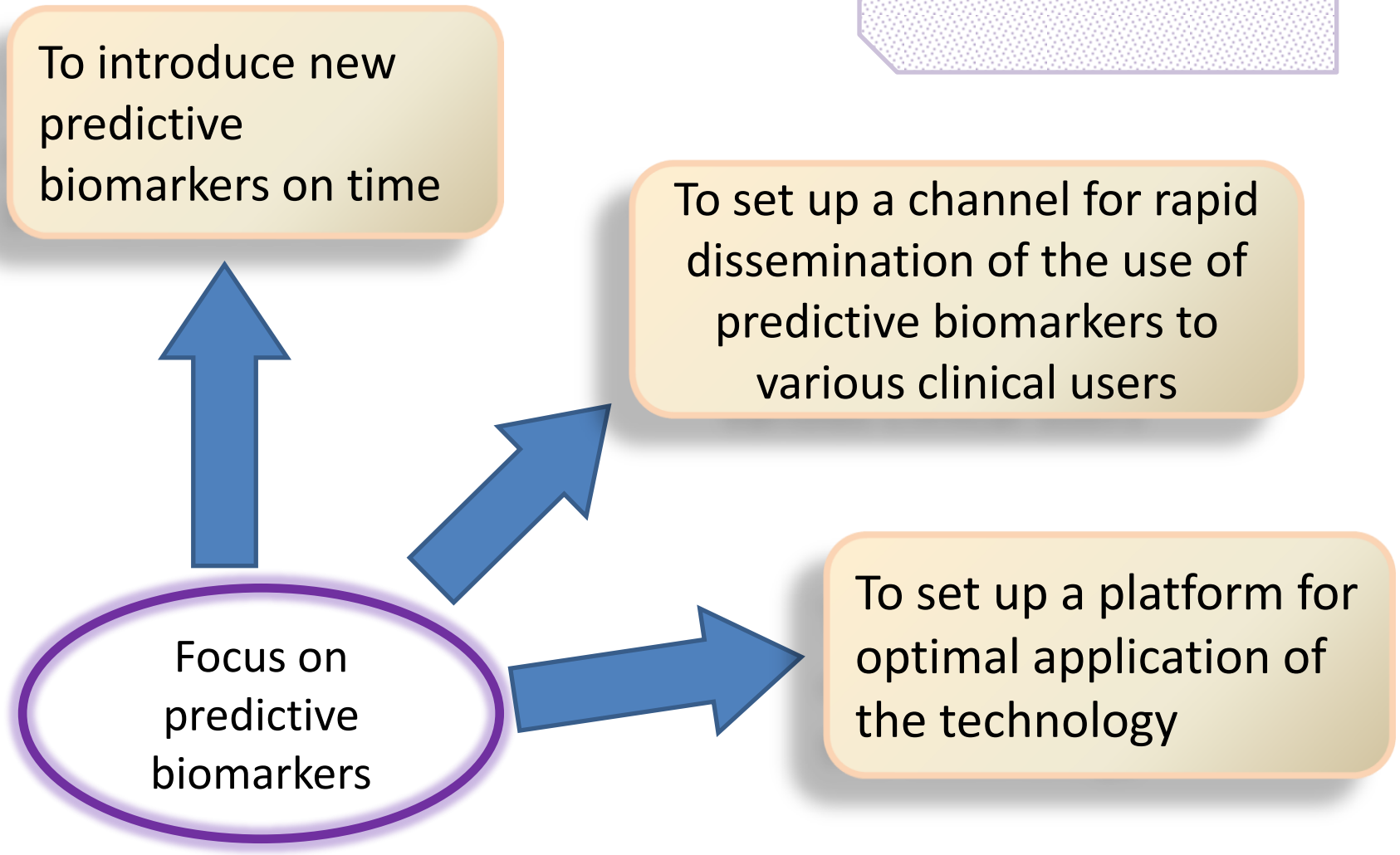
Keeping
HealthcAre In Sync

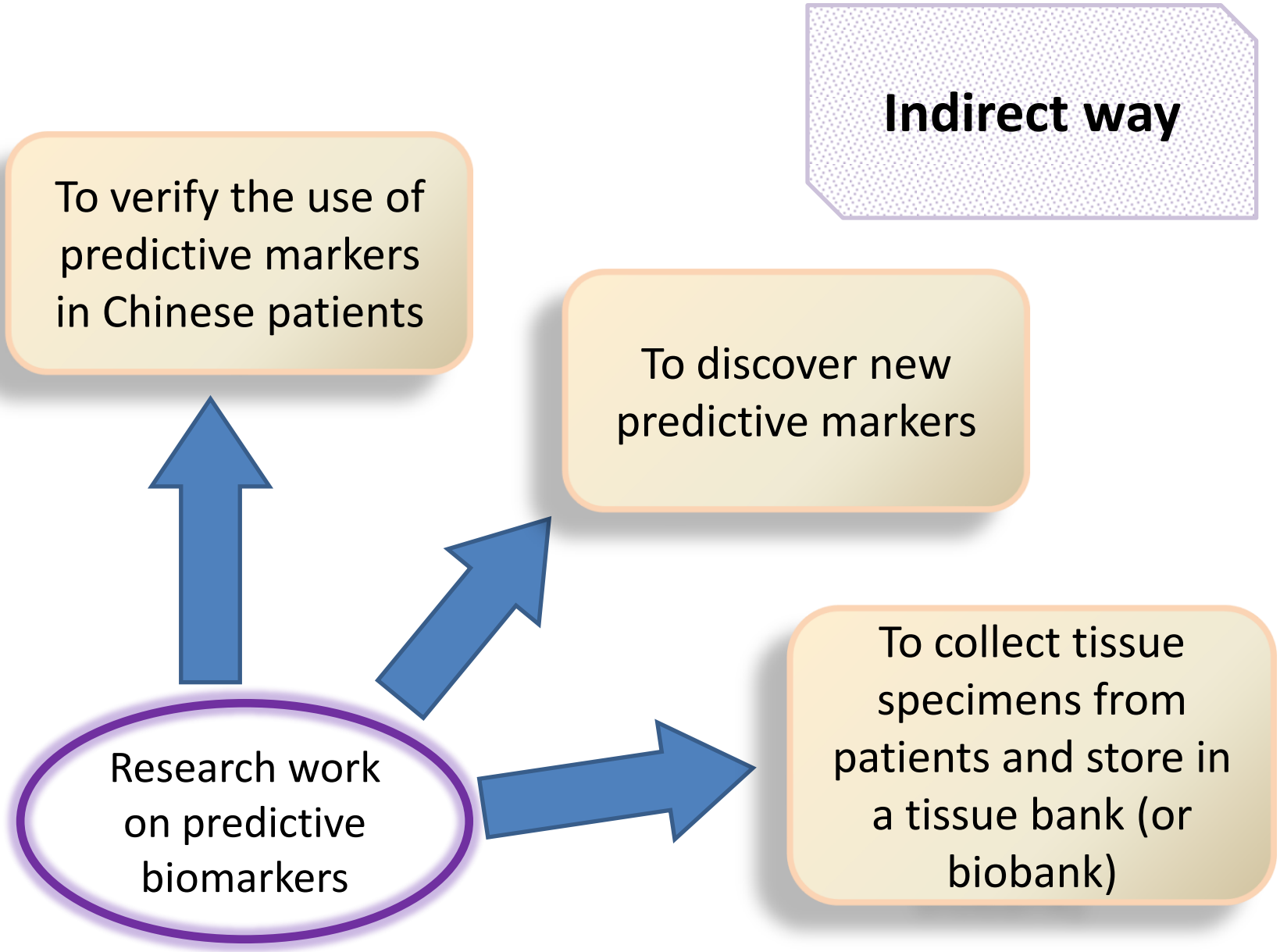
# Ensure Service Quality and Safety

We will implement measures to build safety culture, develop safer service models, and adopt modern technology and new treatment options. Actions include:

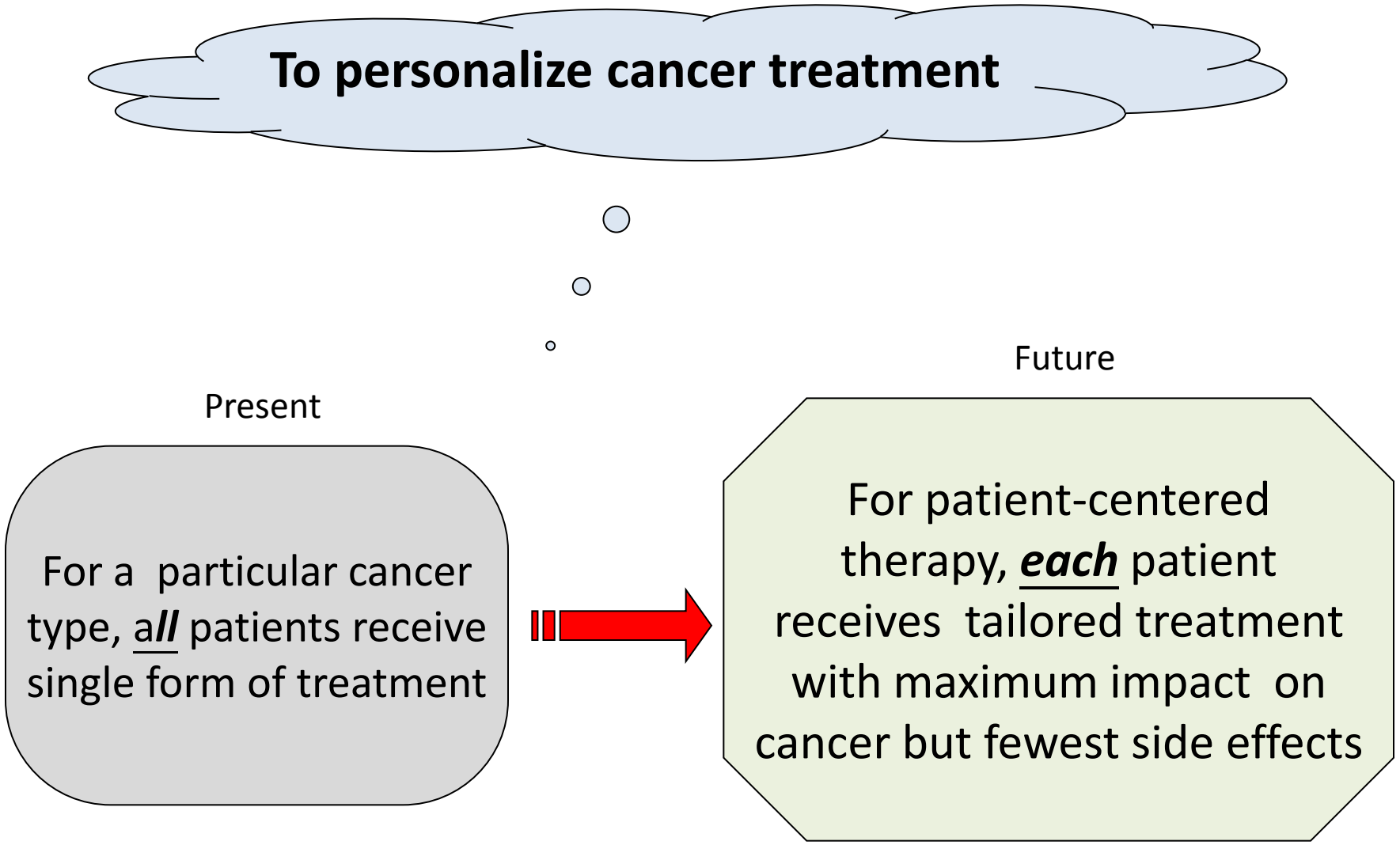
- Foster psychological services for healthcare staff to strengthen the preparedness and emergency response for disasters and crisis intervention
- Strengthen pharmacy support for hospitalised children to enhance the quality and safety of medication use for paediatric patients
- Broaden the scope of HA Drug Formulary to include two new cancer drugs as Special Drugs and widen the clinical applications of two therapeutic groups of drugs for Parkinson's disease and cancer
- Modernise the diagnostic services for cancer patients by expanding the cytogenetic services and predictive molecular testing services
- Adopt Minimally Invasive Surgery technique in hysterectomy surgeries for suitable gynaecological patients

**Direct way**


To introduce new predictive biomarkers on time
To set up a channel for rapid dissemination of the use of predictive biomarkers to various clinical users
Focus on predictive biomarkers
To set up a platform for optimal application of the technology


Indirect way
To verify the use of predictive markers in Chinese patients
To discover new predictive markers
To collect tissue specimens from patients and store in a tissue bank (or biobank)
Research work on predictive biomarkers


Single institution
Multiple institutions
Centralised structure
clinicians
Scientists
Academia
Local
Regional
International


To personalize cancer treatment
Present
For a particular cancer type, all patients receive single form of treatment
Future
For patient-centered therapy, each patient receives tailored treatment with maximum impact on cancer but fewest side effects

# The end