Delivering on the Promise of Personalised Healthcare

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EBF 6th Open Symposium, Barcelona, 20 Nov 2013

AstraZeneca

Presentation Outline

- Introduction
- Drug-Diagnostic Co-development – Key steps
- Challenges and Opportunities
- An illustrative example
- Bioanalytical Perspective
- Summary

Introduction

All Drugs Don’t Work in All Patients

“The vast majority of drugs - more than 90 per cent – only work in 30 or 50 per cent of the people” *Allen Roses (GSK)*

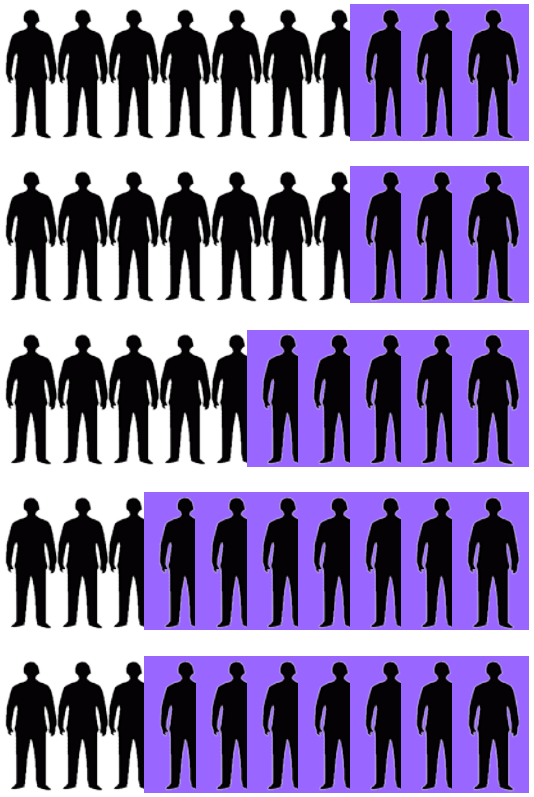
Hypertension Drugs
10-30% ACE Inhibitors

Heart Failure Drugs
15-25% Beta Blockers

Anti Depressants
20-50%

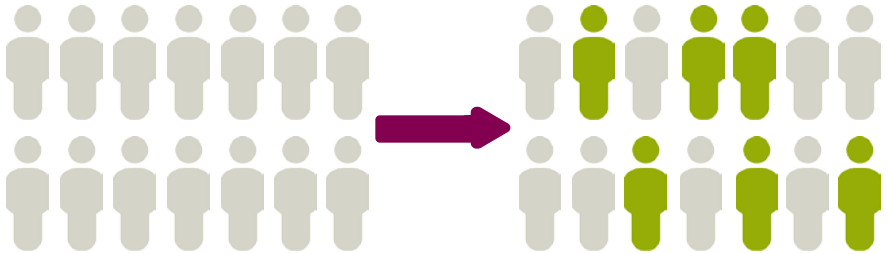
Cholesterol Drugs
30-70% Statins

Asthma Drugs
40-70% Beta-2-agonists



What is Personalised Healthcare ?

Delivering the
right treatment
to the right patient
at the right dose



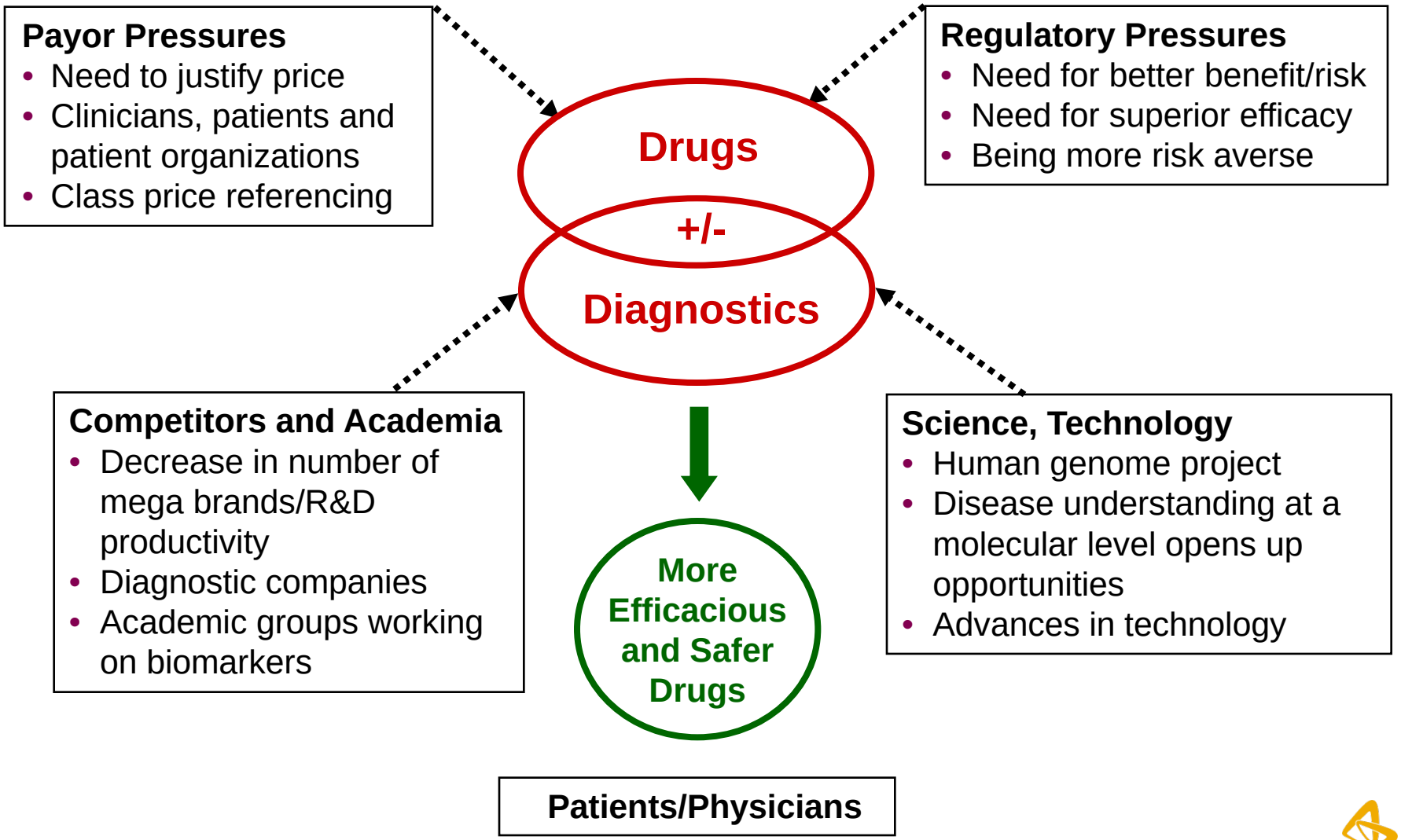
Who could argue with this as a worthwhile objective?

Why Personalised Healthcare ?

Patients	**Best treatment**	
Prescribers	**Delivering the best patient outcome**	
Payers	**Right Value**	

Because Personalised Health Care is the right thing to do

Companion Diagnostics – Key Drivers



But….. it can look complex (and costly)

Historic pharma industry success based on blockbusters

- Simple to recognise the patients
- Medicines which are easy to prescribe

Personalised Medicines can look difficult and costly to develop

- Complexity of simultaneous development and regulatory approval of drug and diagnostic
- Clinical trials seen as more complex

Personalised Medicines can look complicated to sell

- Increased cost for payer due to testing
- Testing adds a barrier to prescription
- Testing reduces the number of accessible patients

Where Are We Today..

- Growing portfolio of drugs with companion diagnostics
  - "Required" testing
  - "Recommended" testing
  - "Informational" testing

- Trastuzumab – HER2 testing
- Maraviroc – Trofile

- Irinotecan – UGT1A1
- Warfarin – CYP2C9, VKORC1 etc

- Abacavir – HLA-B 5701b
- Imatinib – Ph+ CML

Table 2 A growing personalized medicine cabinet

Drug/indication	Drug developer	Test/selected product developers	Comments
Testing required by FDA			
Erbitux/colon cancer	Imclone	EGFR pharmDX/DAKO Cytomation	IHC to determine EGFR presence or absence. Test also recommended, but not required, for use with Erbitux in head and neck cancer
Selzentry/HIV AIDS	Pfizer	Trofile (CCR5 tropism)/ Monogram Biosciences	Amplification of patient HIV genome, creation of artificial viral particles and infection assay
Vectibix[a]/colon cancer	Amgen	EGFR expression KRAS/DxS	The test is required in Europe. KRAS mutations may be relevant in a variety of other cancers
Herceptin/breast cancer	Genentech/Roche	HER2 overexpression/various	Can be done by FISH or IHC but apparently variation in accuracy is possible between labs. Test also useful for prescribing GSK's Tykerb (lapatinib)
Testing recommended by FDA			
Imuran (azathioprine)/autoimmune diseases and transplants	GSK	Thiopurine methyltransferase variants/various	Enzyme activity and/or genotyping
Tegretol (carbamazepine)/epilepsy and bipolar disorder	Various	HLA-B 1502 variant found in people of Asian ancestry/various	Boxed warning recommends that patients with Asian ancestry receive a genetic test before starting treatment, because their risk of serious adverse reactions is 10 times that (1 to 6 per 10,0000) of European ancestry
Tarceva (erlotinib)/NSCLC	Genentech/OSI	EGFR pharmDX/DAKO Cytomation	Impact of testing on treatment still unclear because too few patients were tested in trials
Camptosar (irinotecan)/colon cancer	Pfizer	UTG1A1 variants/Third Wave	Third Wave has a marketing relationship with Genzyme Genetics for this test
Elitek (rasburicase)/cancer	Sanofi-Aventis	G6PD deficiency/various	Beutler fluorescent-spot test
Coumadin/anticoagulant	Various	CYP2C9 and VKOR (vitamin K epoxide reductase) variant genotyping/Clinical Data, Genelex (Seattle) and Roche	There is much debate about whether and how to test
Selected drugs for which informational tests are available			
Ziagen (abacavir)/HIV AIDS	GSK	HLA-B 5701b/various	Predictive value for hypersensitivity reaction
Strattera (atomoxetine)/attention deficit hypersenitivity disorder (ADHD)	Eli Lilly	CYP2D6/various	Variants can impede metabolism of the drug, leading to high blood levels
Xeloda (capecitabine)/cancer	Roche	Dihydropyrimidine dehydrogenase deficiency/various	Related to severe toxicity
Prozac (fluoxetine)/depression	Eli Lilly	CYP2D6 with alternate context/various	Fluoxetine, and a wide range of similar agents, inhibits the activity of P450 2D6, and thus may make normal metabolizers resemble 'poor metabolizers'
Gleevec/various cancers including CML and gastrointestinal stromal tumor (GIST)	Novartis	Philadelphia chromosome, c-KIT, platelet-derived growth factor (PDGF) receptor/various	The drug was developed specifically to target Philadelphia Chromosome+ CML, but has been shown to be useful for a growing number of cancers, including GIST
VFEND (voriconazole)/fungal infections	Pfizer	CYP2C19/Gentris, Roche	A variety of other drugs, including, Prilosec (omeprazole), Protonix (pantoprazole), Nexium (esomeprazole) and Valium (diazepam) are also affected by variation in same gene

[a]Required by the European Medicines Agency.

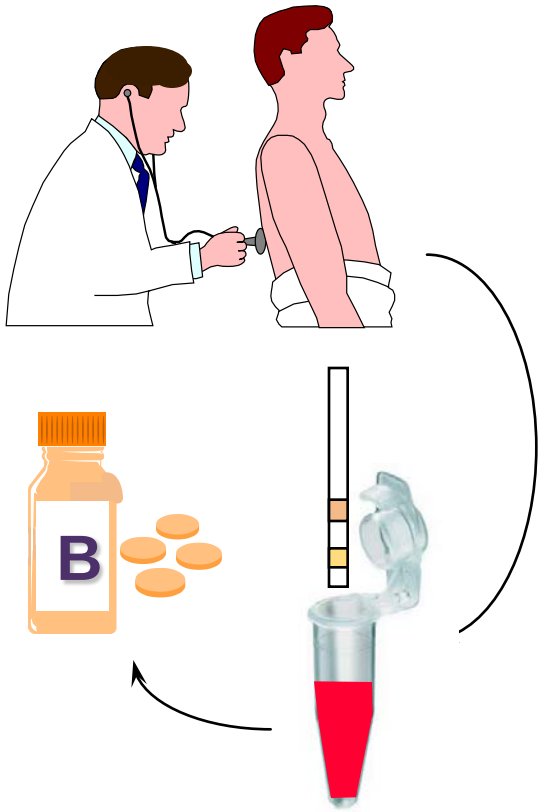
Source: US FDA and company materials

...and on the increase

Nature Biotechnology, Volume 26 (5) May 2008

Companion Diagnostic

- A test or method designed to determine if a patient will respond to treatment with a particular drug or not



Is this drug effective and safe for this patient (personalised healthcare)?

Vemurafenib and *BRAF*/Melanoma

- Zelboraf™ (vemurafenib) is an orally available serine-threonine kinase inhibitor of the mutated form of *BRAF*
- The drug is indicated for the treatment of *BRAF* mutation positive melanoma. Zelboraf™ is not recommended for use in patients with wild-type *BRAF* melanoma
- Roche Molecular Systems have developed a companion diagnostic - Cobas® 4800 *BRAF* V600 Mutation Test. Test is designed to detect *BRAFV600E* mutations in DNA isolated from formalin fixed, paraffin-embedded human melanoma tissue
- Simultaneous approval of the drug and the companion diagnostic in the US (ahead of the scheduled PDUFA and MDUFMA dates)

ZELBORAF™
(vemurafenib) tablets

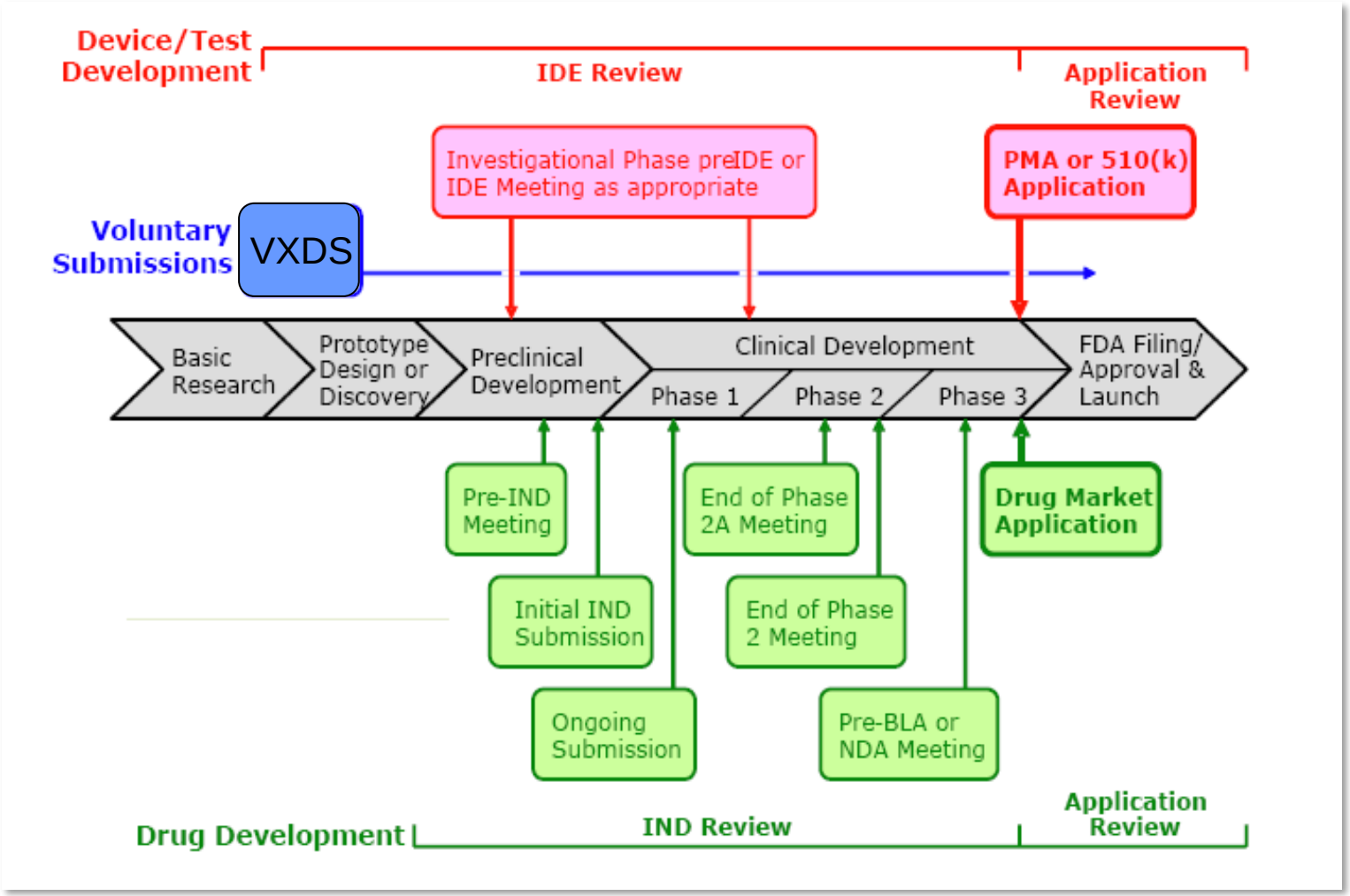
Crizotinib and *ALK Positive*/NSCLC

- Xalkori (crizotinib) is an orally available kinase inhibitor of ALK, HGFR, c-Met
- Indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive
- Abbott Molecular have developed a companion diagnostic - Vysis ALK Break-Apart FISH Probe Kit
- Test uses DNA probes with attached fluorescent dyes to detect the presence of chromosomal rearrangements of the ALK gene, located on chromosome 2, in non-small cell lung cancer (NSCLC) tissue
- Simultaneous approval of the drug and the companion diagnostic in the US (ahead of the scheduled PDUFA and MDUFMA dates)

Drug–Diagnostic Co-Development

Key Steps

Overview of Drug/Diagnostic Co-Development



Putting the Pieces Together

Scientific Understanding

+

Diagnostic Platform Availability and Utility

+

FDA

emea

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Ministry of Health, Labour and Welfare

Regulatory Acceptance

Putting it into Practice

Patient & Physician Value

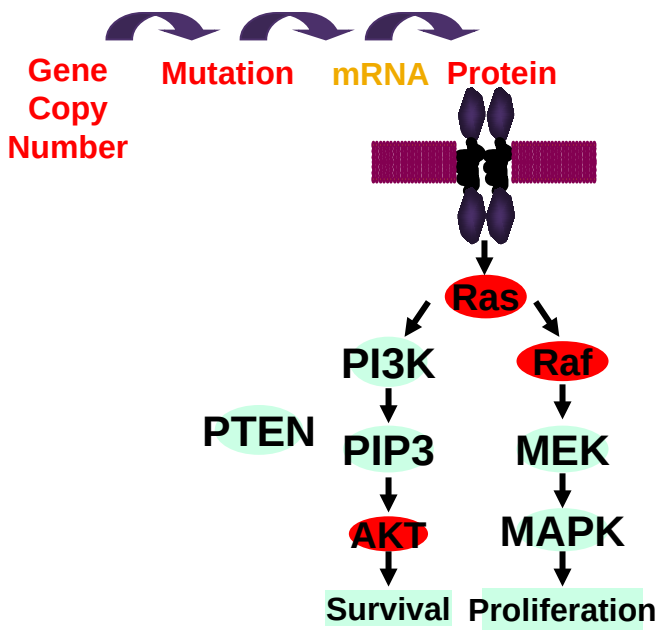
Assay Availability Assay Reimbursement

Clinical Guidelines & Practice

Scientific Understanding

- Choosing the right biomarker requires in-depth understanding of:
  - the mode of action of your drug
  - the biology of the disease you are trying to treat
- To be successful – start early!

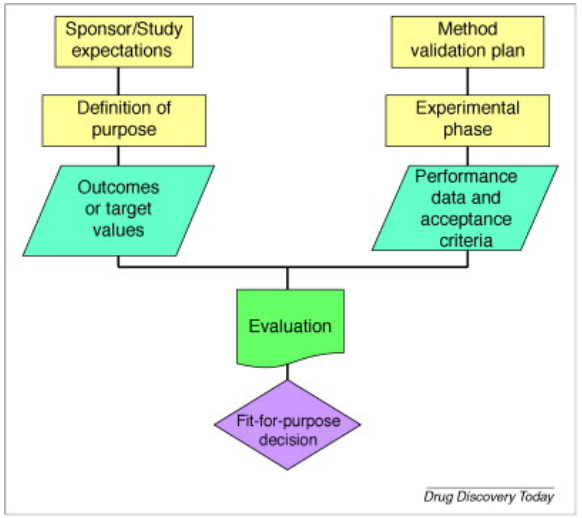
Gefitinib Biomarker Considerations



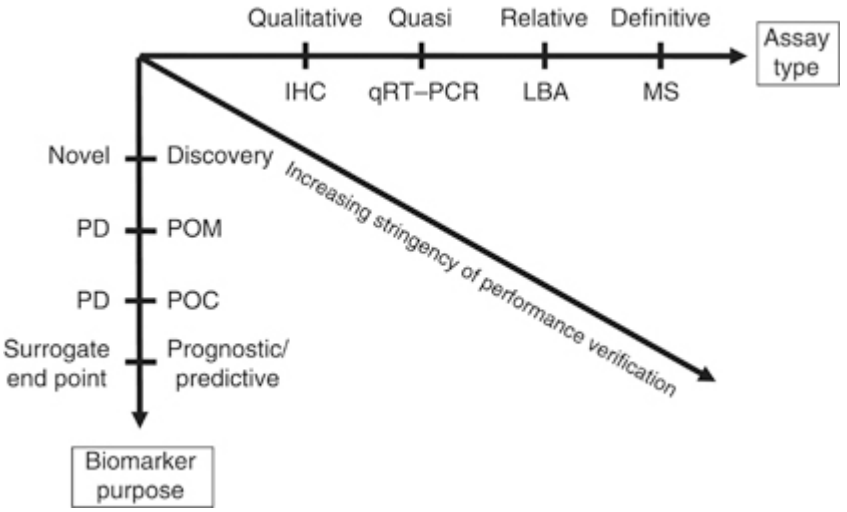
- ►EGFR mutation
- ►EGFR gene copy number
- ►EGFR protein expression
- ►Other.....

Developing the Assay

- What is the “intended use” of the assay?
- Ensure assay meets design requirements
  - Analytical validation
  - Clinical validation
  - Manufacturing
- Diagnostic partner engagement

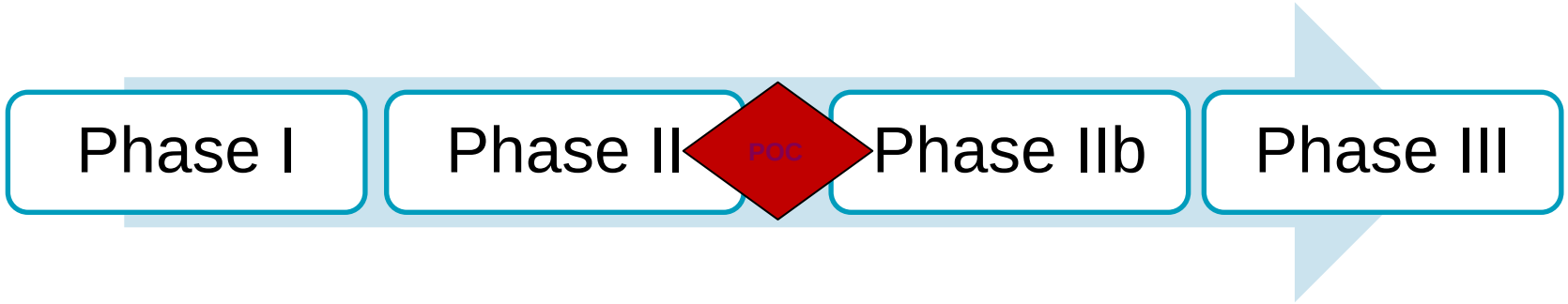


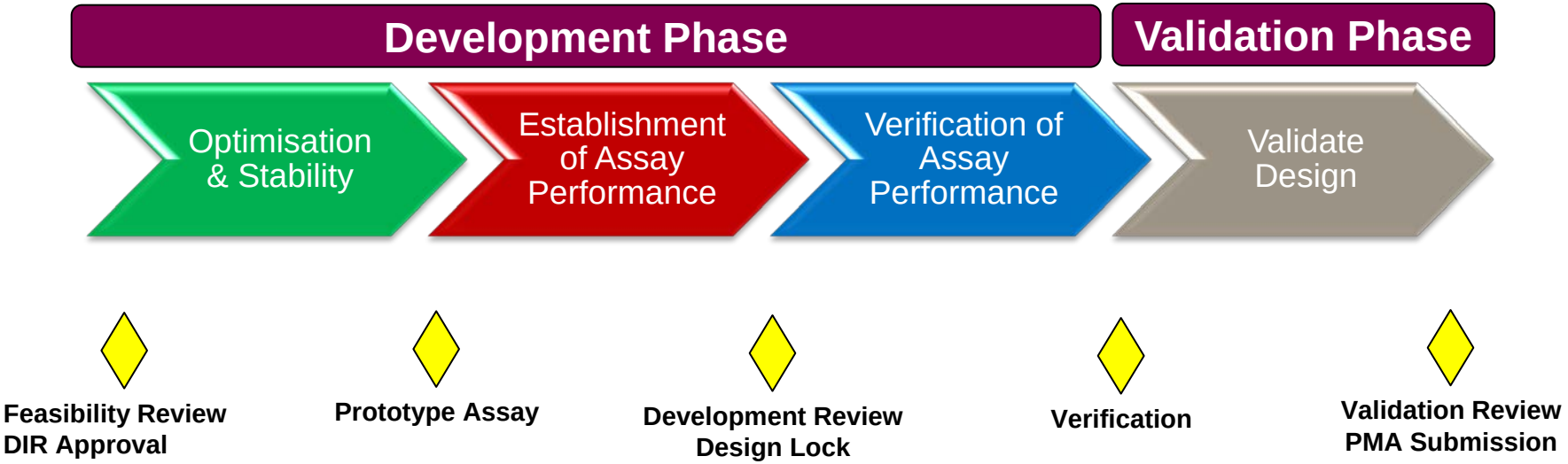
Drug Discovery Today (2010) 15,816-825



Cummings et al., *British Journal of Cancer* (2010) 103, 1313–1317

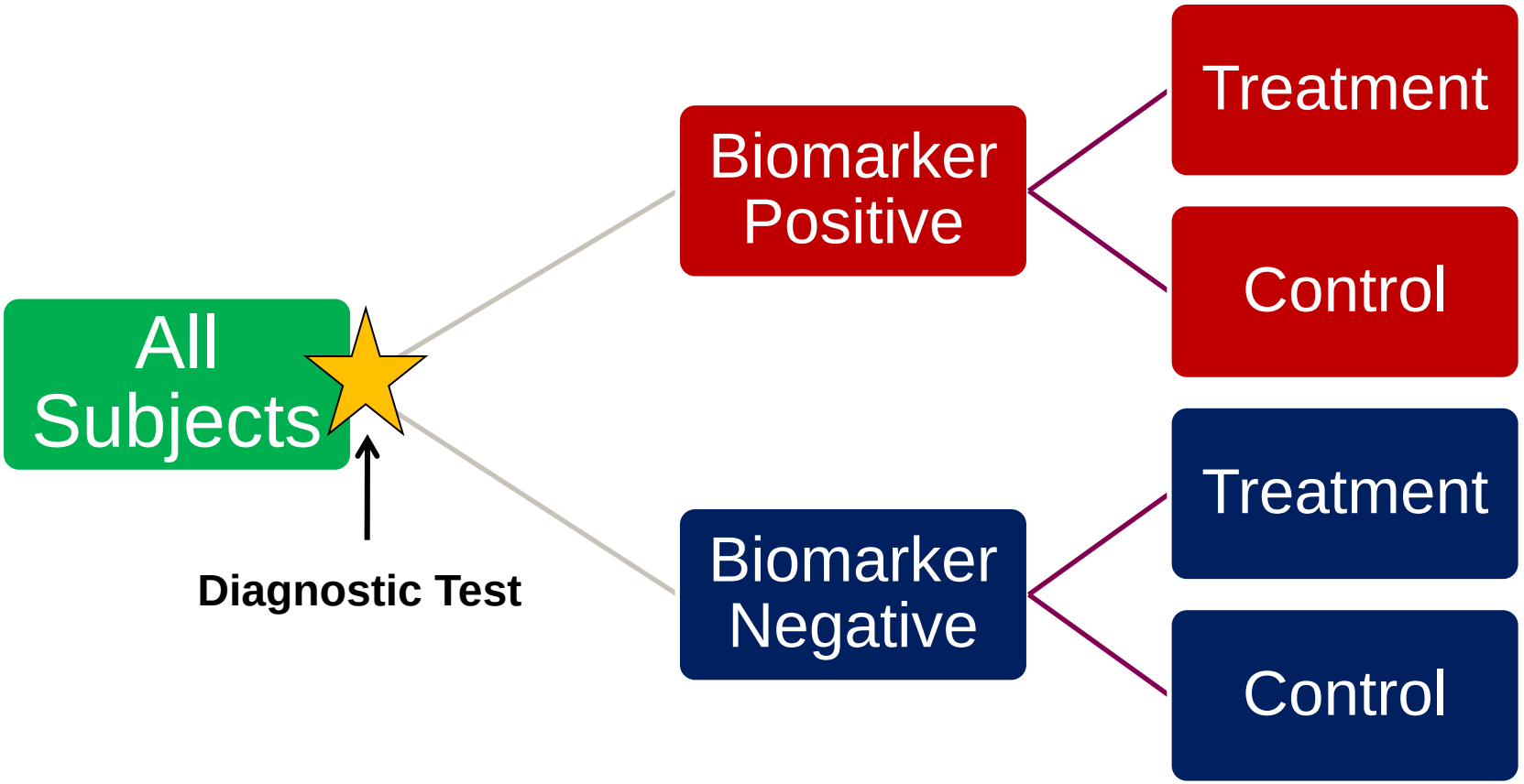
Developing the Assay





Proving Biomarker/Diagnostic Utility

- Data from pivotal trial must support drug and diagnostic submission



Regulatory Approval

- Companion diagnostics considered high risk and therefore likely to need to meet the highest regulatory hurdles in the US [Class III, Pre Market Approval (PMA) required]

- Regulatory approvals across multiple territories required

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 14, 2011

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709, or ocod@fda.hhs.gov; for questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research

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Ministry of Health, Labour and Welfare

FDA Premarket Approval - PMA

- Contents Specified in 21 CFR 814.20
- General Information Section
- Assay Development / Analytical Validation Section
- Manufacturing and Quality System Section
- Clinical Investigations Section
- Labeling Section

- Process is 180 days….but routinely takes much longer

- Modular PMA

A compilation of sections or "modules" submitted at different times that together become a complete PMA application

21

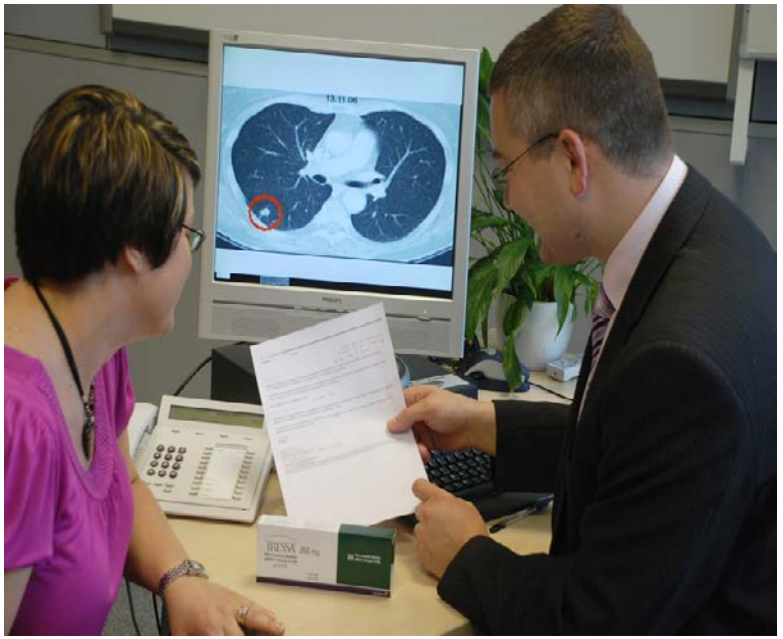
Some potential pitfalls en route to PMA

- Poor communication between Rx and Dx companies and Regulators
- Not establishing assay with real clinical samples from intended use population
- Analytical performance not validated & standardized prior to use in clinical trials
- Not addressing ‘all-comers’ or developing biological rationale for a targeted program
- Bias introduced by only testing a subset of intended use population – and/or pre-screening
- Multiple tests (with different performance?) and/or local labs used in clinical trials
- Bridging studies from CTA to companion Dx are risky; they need high sample ascertainment (> 90%recommended)

The pivotal validation study should investigate Dx use in the claimed clinical population using the final Dx configuration

The Commercial World

- Key considerations
  - Diagnostic must be available at time of drug launch
  - Strategies to drive test adoption
  - Strategies to remove barriers to testing
  - Reimbursement for diagnostic testing



Challenges & Opportunities

Some Challenges

- **Scientific understanding advanced but much more to learn…..**
- **Don’t always understand why drug works differently in some patients**
- **Identifying and developing a biomarker can be difficult**
- **Tools and technologies don’t yet exist (or not good enough)**
- **A test is never 100% predictive**
- **Challenging to develop biomarker in time for co-launch with drug (Co-ordination of test development with drug development)**
- **Clinical trials more complicated – Inclusion of test +ve and -ve patients (utility)**
- **Slower recruitment due to testing**
- **The regulatory path**
- **Smaller market**

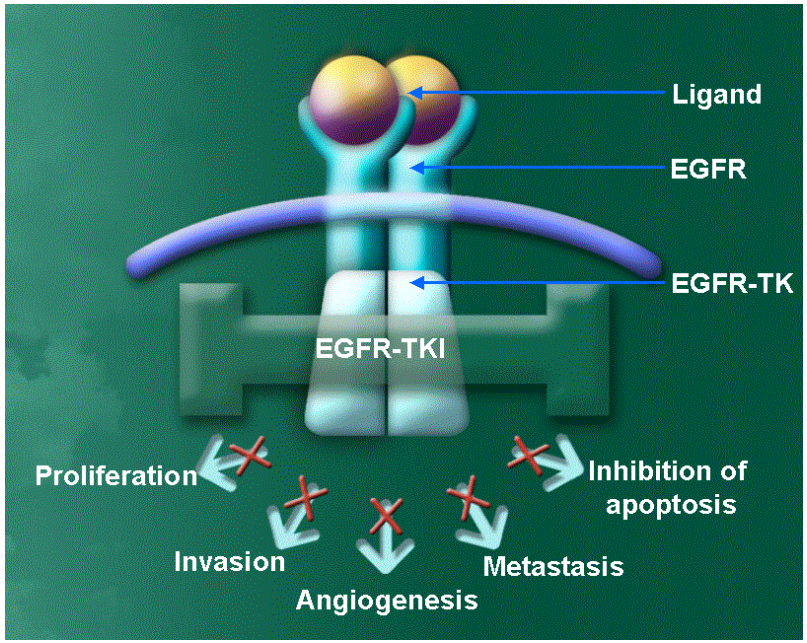
Some Opportunities

- **Clear benefits to patients, clinical community and payers**
- **Better benefit/risk – price**
- **Faster development if clear rationale & evidence**
- **Potential opportunities to move straight into first line therapy**
- **Potential for product rescue**
- **Faster uptake once launched**
- **If we don’t do it someone else will!**

Gefitinib – An Example

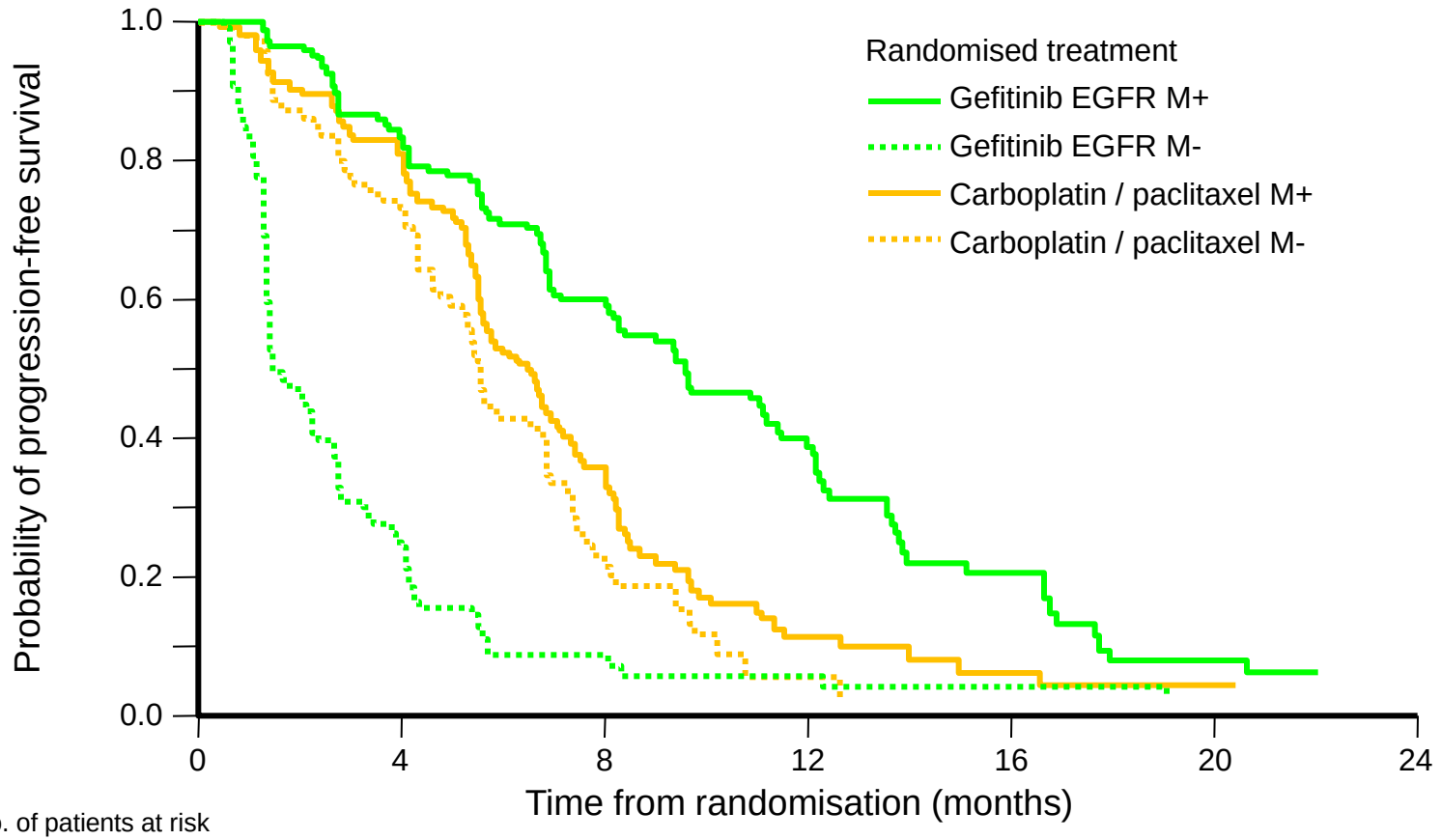
Gefitinib Early Development

- Gefitinib is an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor
- Phase I: encouraging antitumour activity seen in NSCLC
- Phase II (IDEAL 1 and 2): promising activity observed and well-tolerated
  - EGFR expression levels did not correlate with response



Gefitinib mechanism of action

IPASS: PFS by Mutation Status



No. of patients at risk

Months	0	4	8	12	16	20	24
Gefitinib M+	132	108	71	31	11	3	0
Gefitinib M-	91	21	4	2	1	0	0
Carboplatin / paclitaxel M+	129	103	37	7	2	1	0
Carboplatin / paclitaxel M-	85	58	14	1	0	0	0

Iressa™ (Gefitinib)

IRESSA (Gefitinib) Receives Marketing Authorisation for the Treatment of Non-Small Cell Lung Cancer in Europe

AstraZeneca announced today that the European Commission has granted marketing authorisation for the oral anti-cancer drug, IRESSA for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) ***with activating mutations of EGFR-TK*** (epidermal growth factor receptor-tyrosine kinase) across all lines of therapy. The authorisation is based on a submission package including two pivotal Phase III studies comparing IRESSA with chemotherapy, IPASS and INTEREST

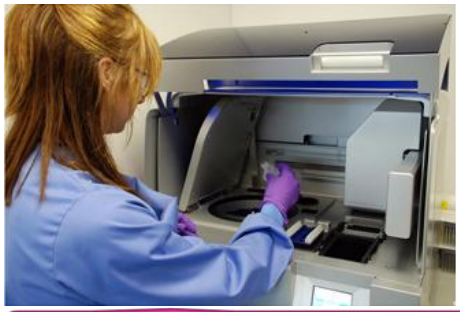
Working with different partners is key….

Respiratory physician/ surgeon

Pathologist

Diagnostic company

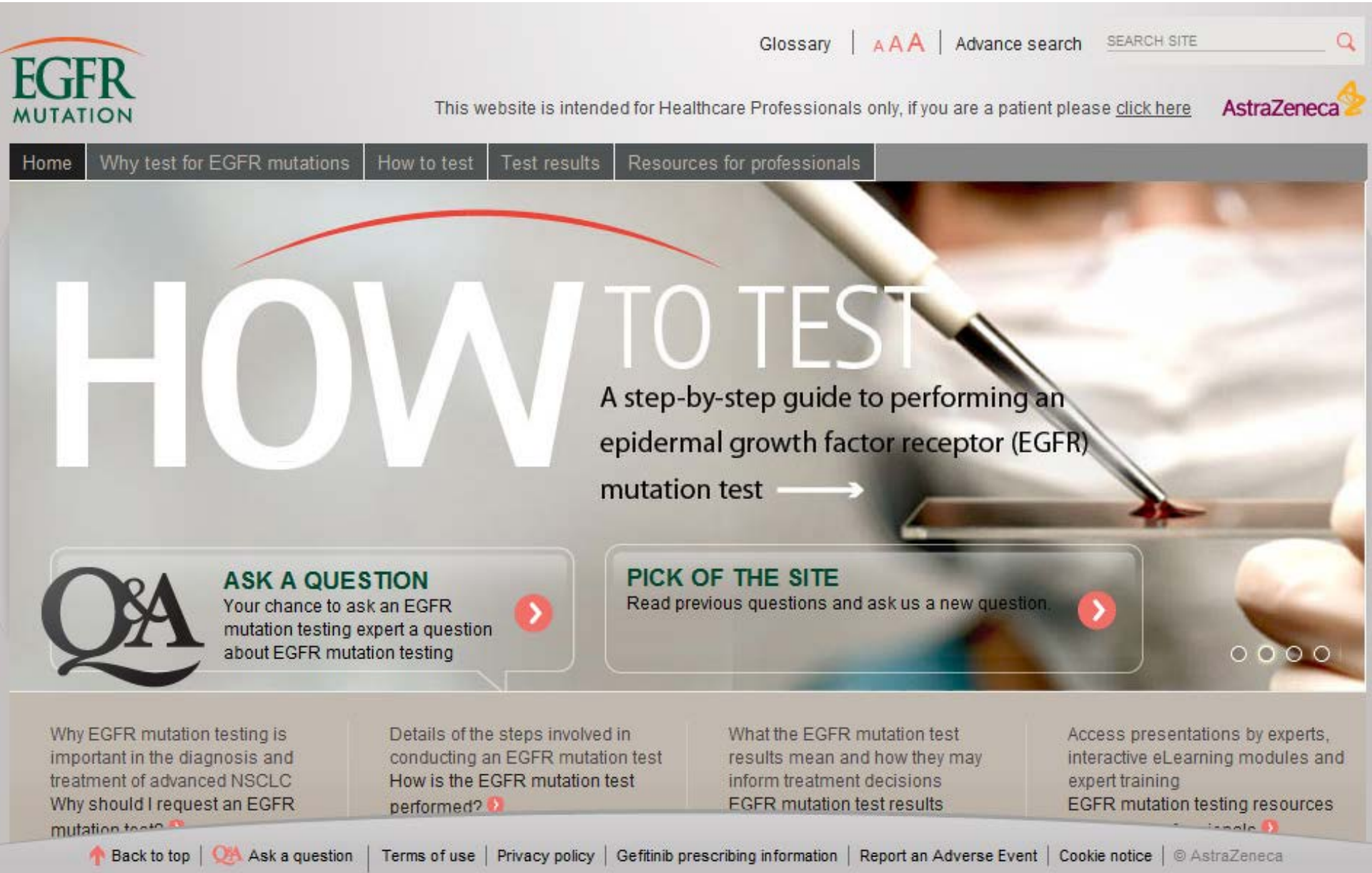
Oncologist



Lab service provider/Molecular Biologist

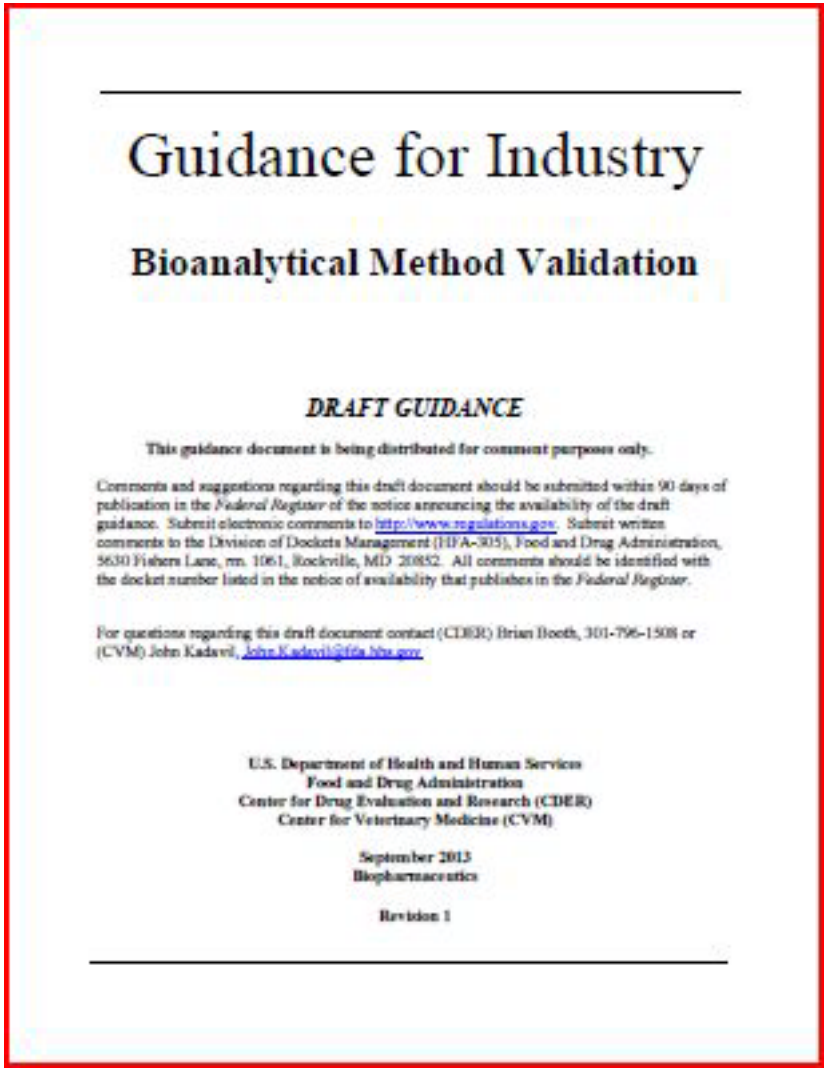
Diagnostic platform provider

What success looks like



Bioanalytical Perspective

Regulated Bioanalysis



Guidance for Industry

Bioanalytical Method Validation

DRAFT GUIDANCE

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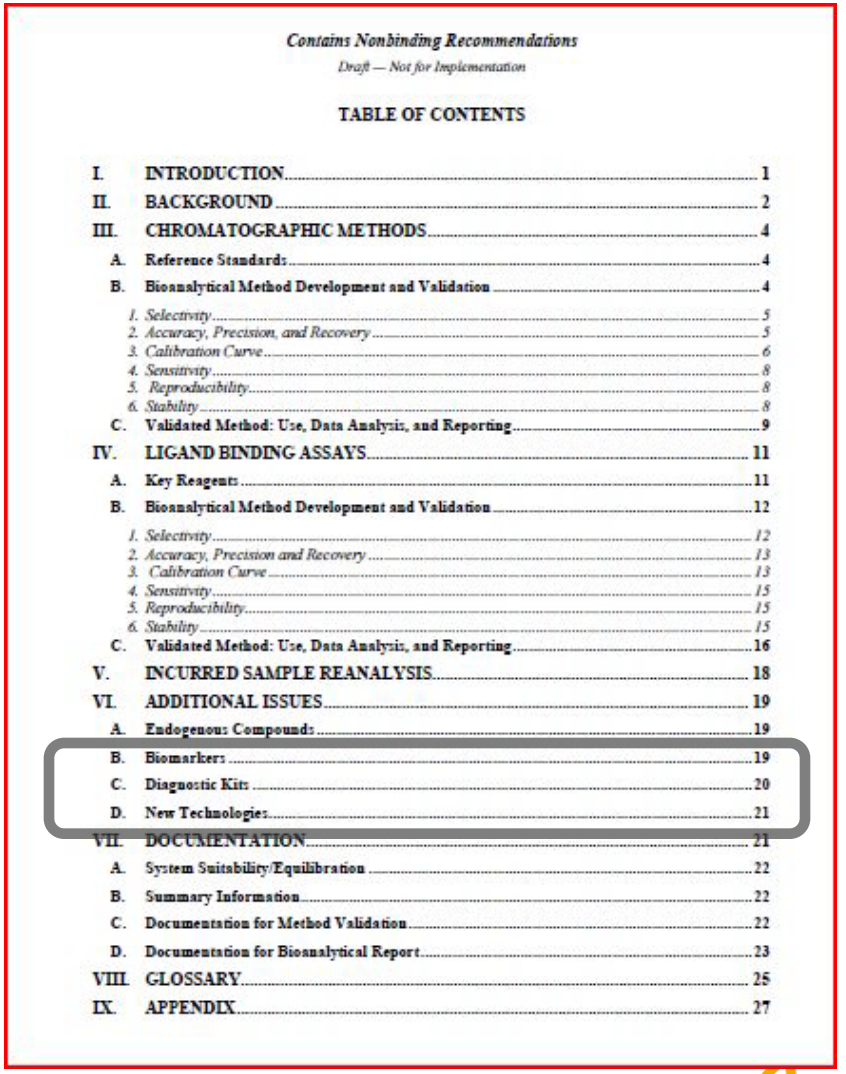
For questions regarding this draft document contact (CDER) Brian Booth, 301-796-1508 or (CVM) John Kadavil, John.Kadavil@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

September 2013
Biopharmaceutics

Revision 1



Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

Regulated Bioanalysis

- **Focus on validation**
  - **Accuracy, precision, selectivity, sensitivity, reproducibility, stability**

- **Biomarker data used to support a regulatory action (pivotal determination of drug safety/effectiveness, labeled dosing) – full validation required**

- **For CDx development (treatment decision) – CDRH guidance**

- **New technologies – any data submitted should be supported by data from current gold standard**

Summary

Summary

- Companion diagnostics are a reality
- Companion diagnostics are a necessity
- The path to drug-test co-development is challenging
- Personalised healthcare offers much promise - potential to benefit everyone in the healthcare system

Thank You!