Future challenges to HTA

Policy challenges

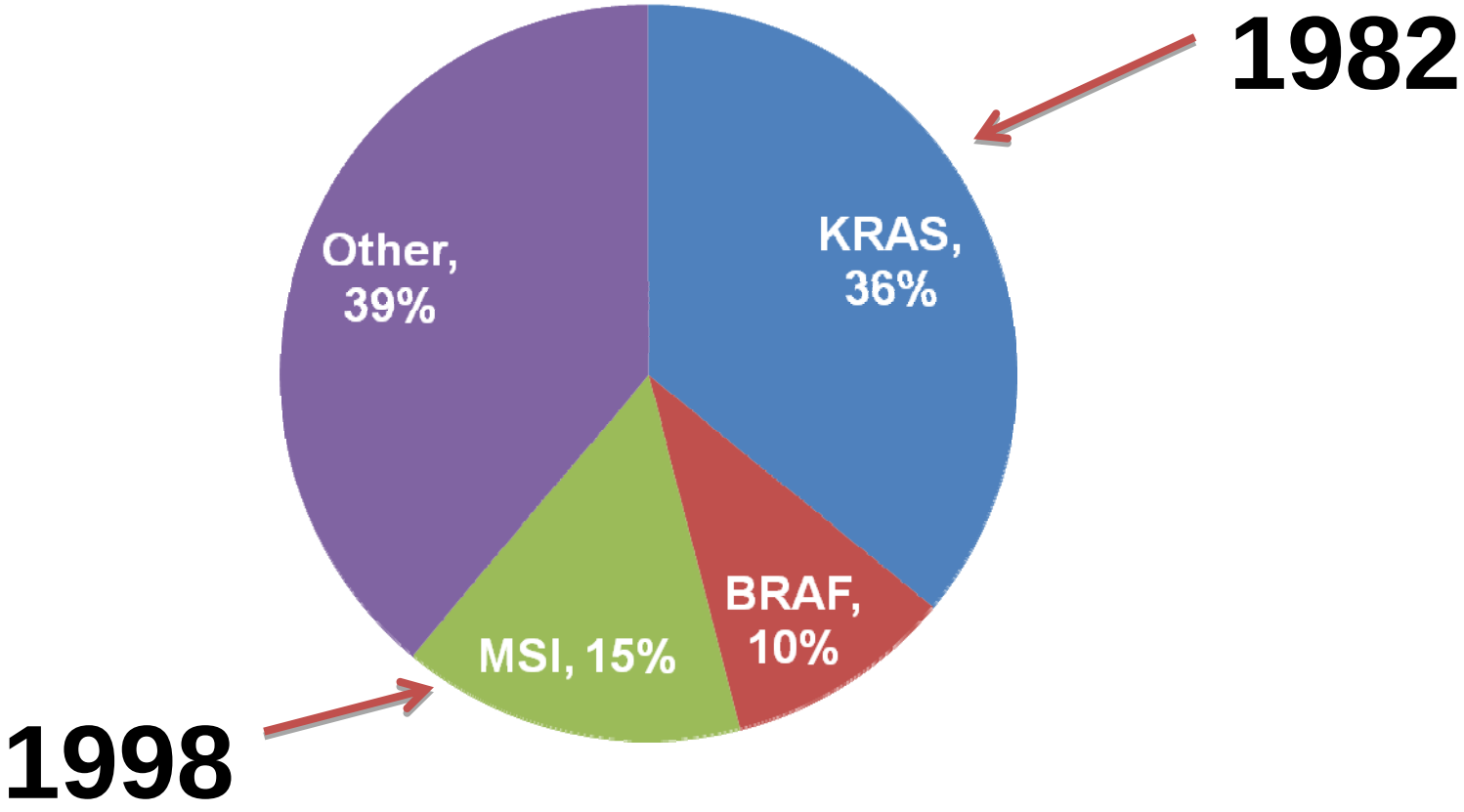
Co-dependent technologies

- Test + Targeted drug
- Cancer as an exemplar
- Aka personalised medicine
  (21,600,000 hits in 10 secs on Google)

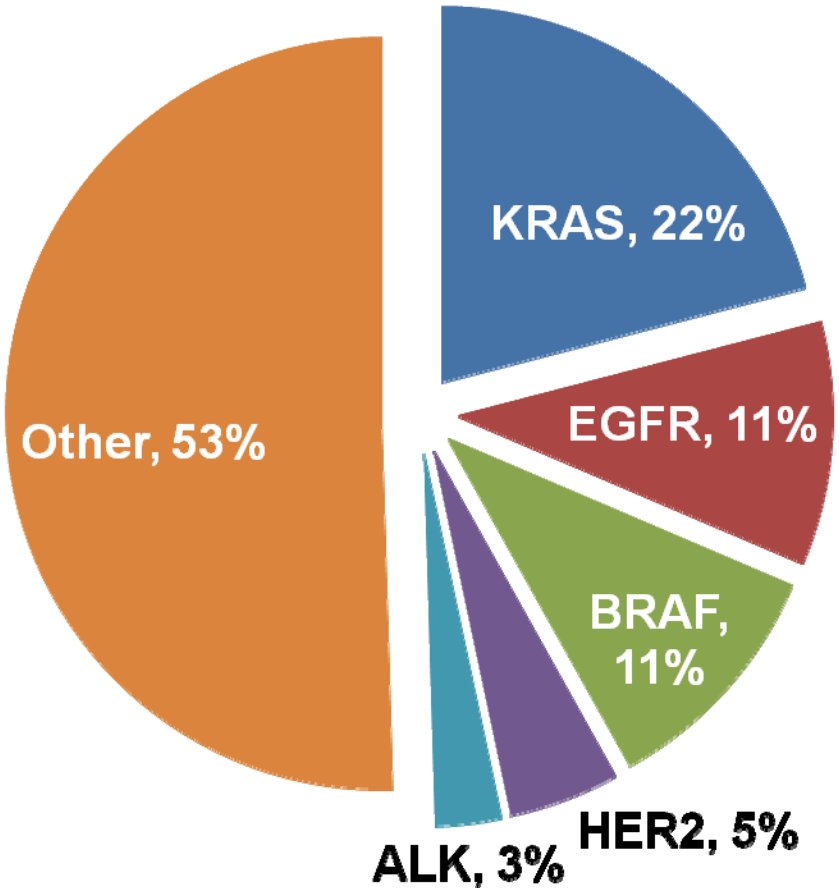
Issues

- Bang for the health care buck
- Test and drug exist in separate worlds

Molecular subtypes of colorectal cancer



Molecular subtypes of non-small cell lung cancer



Kryptonite made relevant by Superman
Molecular subtyping of cancer made relevant by drugs

Drugs that have dragged their targets from obscurity

Drug	Disease	Target
Imatinib	CML, ALL	BCR-ABL translocation
Imatinib	GIST	KIT & PDGFR
Panitumumab & cetuximab	CRC	KRAS mutation
Trastuzumab	Breast, gastric, GO	HER2
Gefitinib & erlotinib	Lung	EGFR mutation
Crizotinib	Lung	EML4-ALK translocation
Vemurafenib	Melanoma	BRAF V600E

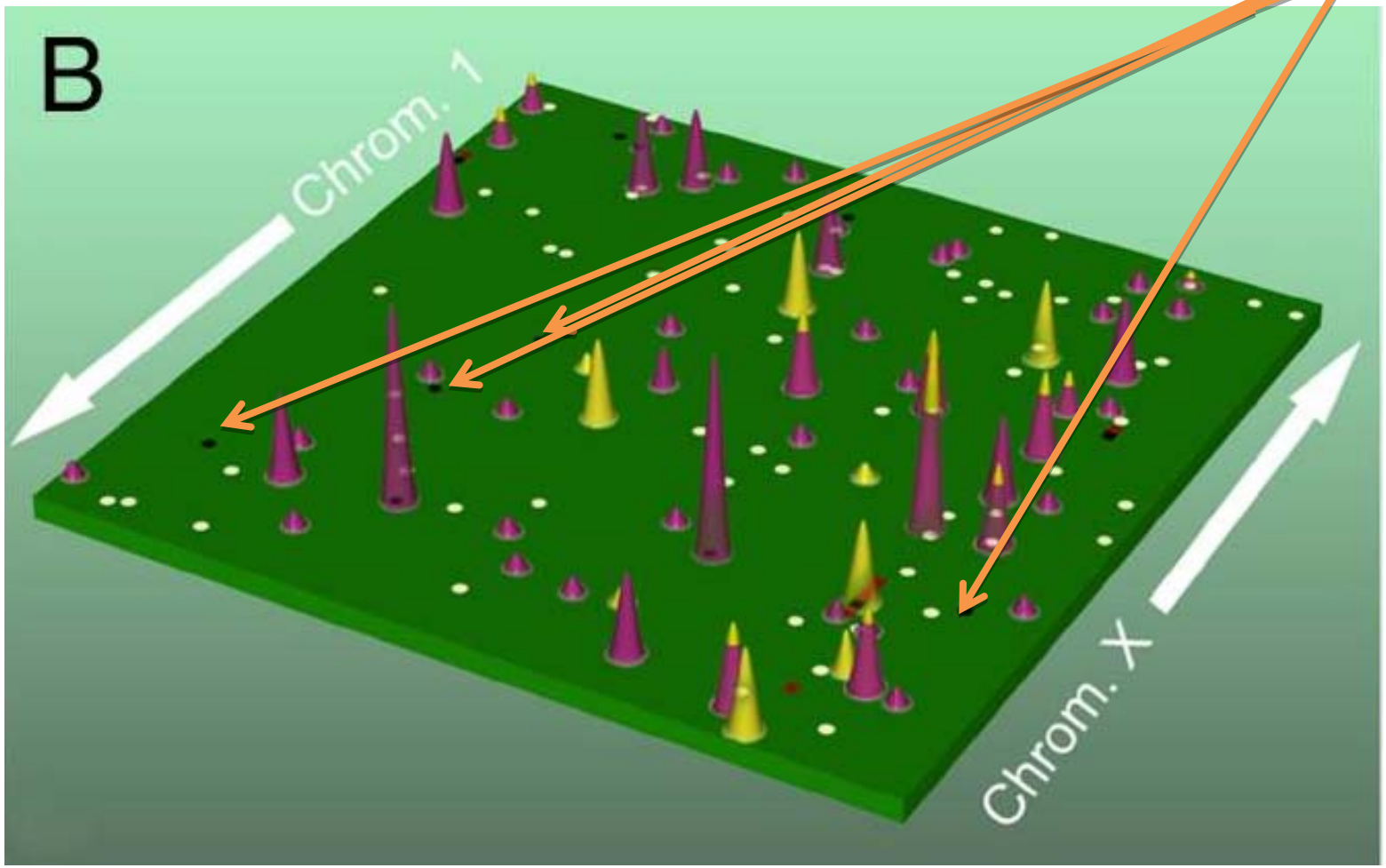
Challenges associated with a co-dependency claim

- Molecular labelling – simplistic interpretation of complex biology
- Consequences of diagnostic inaccuracy
- The test in practice - who, when and what
- Burden of statistical proof

Challenge 1: Molecular labelling of tumours – shifting the paradigm

- molecular alterations are shared in several cancers
- so label cancers on the basis of their molecular alterations
- ...one targeted drug can be used for many different cancers

Genomic landscape of one colorectal cancer



PNAS, 2008;105:16224-16229

Most of the genomic alterations in cancers are bystanders or passengers

Handful of genomic alterations in cancers are drivers

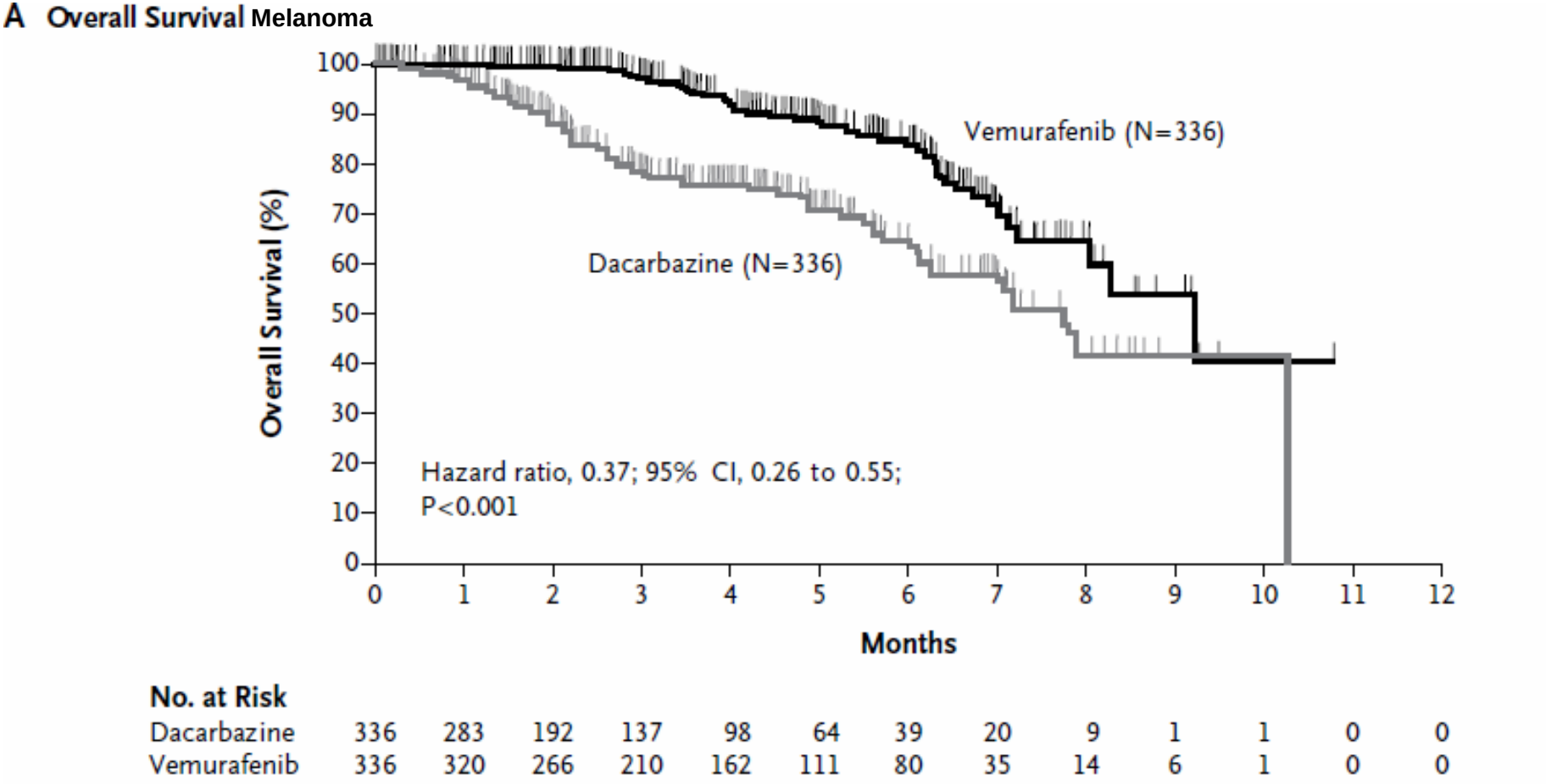
Handful of genomic alterations in cancer are permissive

Tumour heterogeneity

Drivers, permissive mutations and passengers vary between tumours and between individuals with the same tumour

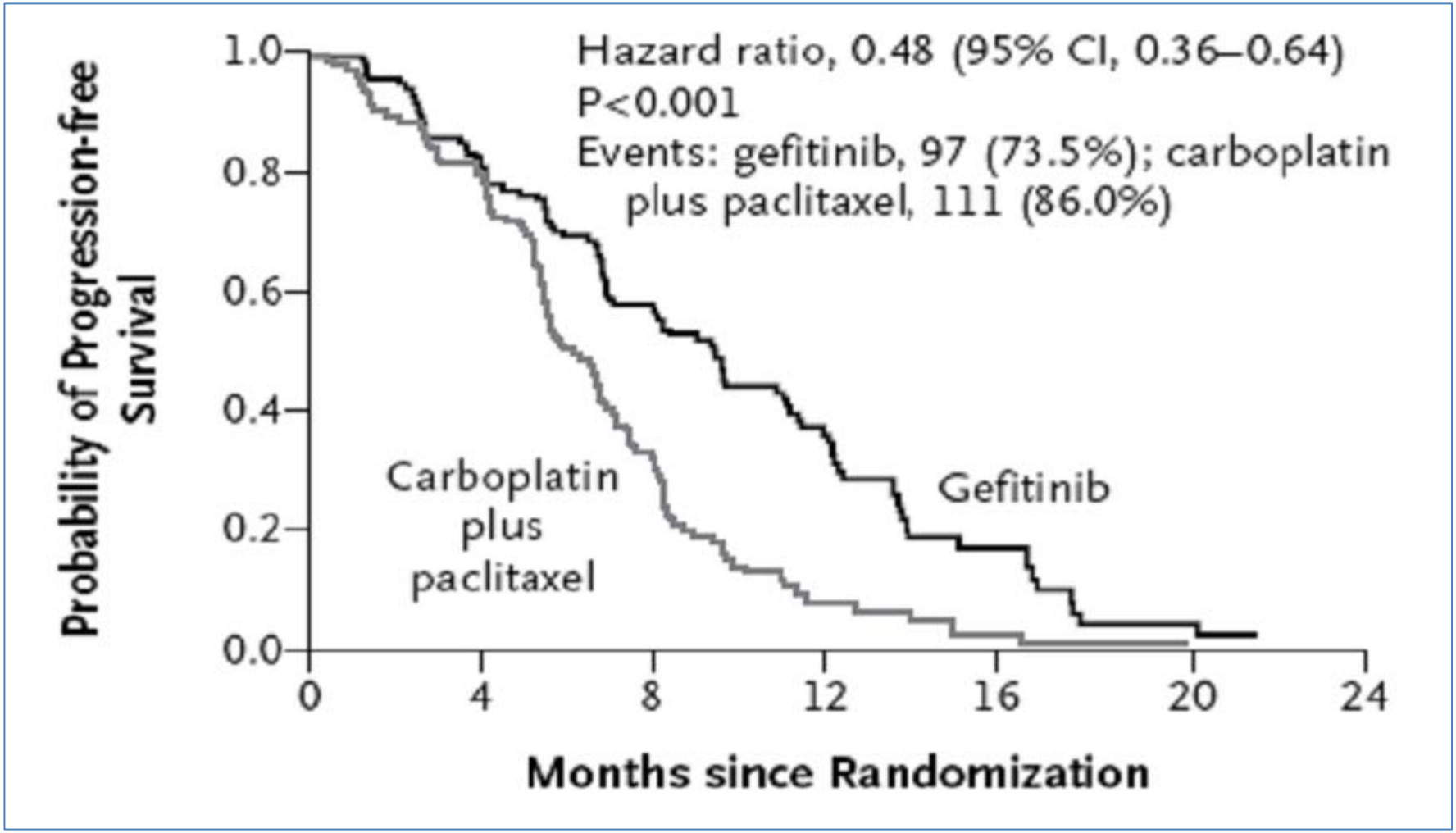
BRAF inhibitor works in BRAF mutant melanoma

but not BRAF mutant CRC



Single agent Gefitinib effective in EGFR M+NSCLC

but not EGFR M+ colorectal cancer



Simplistic pairing of molecular test with proposed drug falls down because;

- BRAF mutant CRC ≠ BRAF mutant melanoma
- HER2+ gastric cancer ≠ HER2+ breast cancer
- KRAS positive CRC ≠ KRAS positive lung cancer

TIME

THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?

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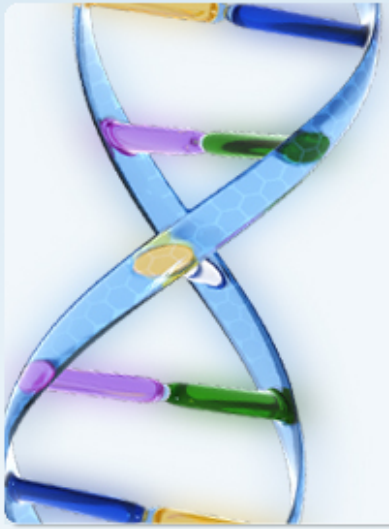

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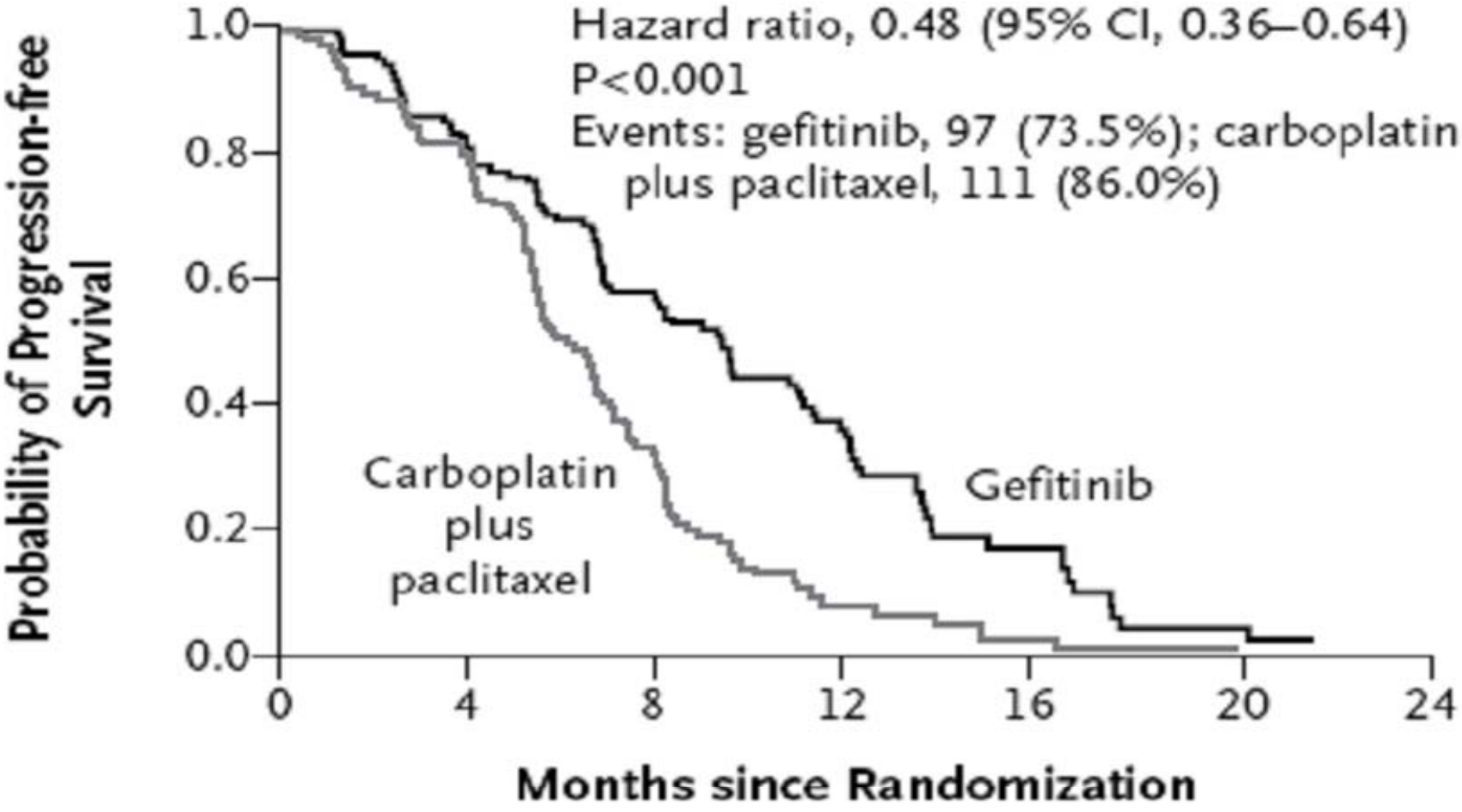
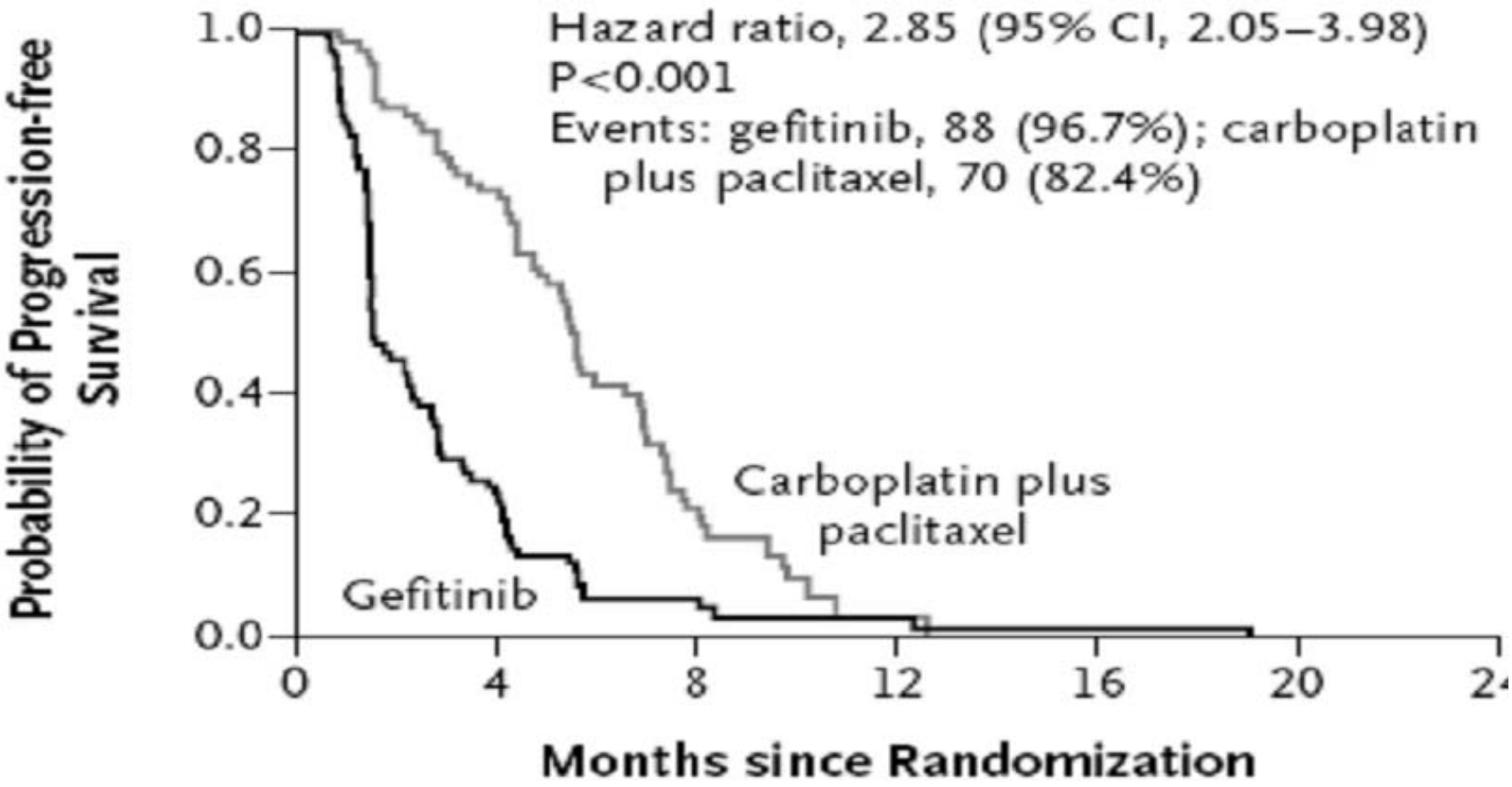
Challenge 2: Consequences of diagnostic inaccuracies

net benefits of a co-dependent test and drug are negated if incorrect test assignment exposes patients to inferior treatments

Gefitinib improves survival in patients with EGFR mutant tumours



Gefitinib reduces survival in patients with EGFR wild tumours

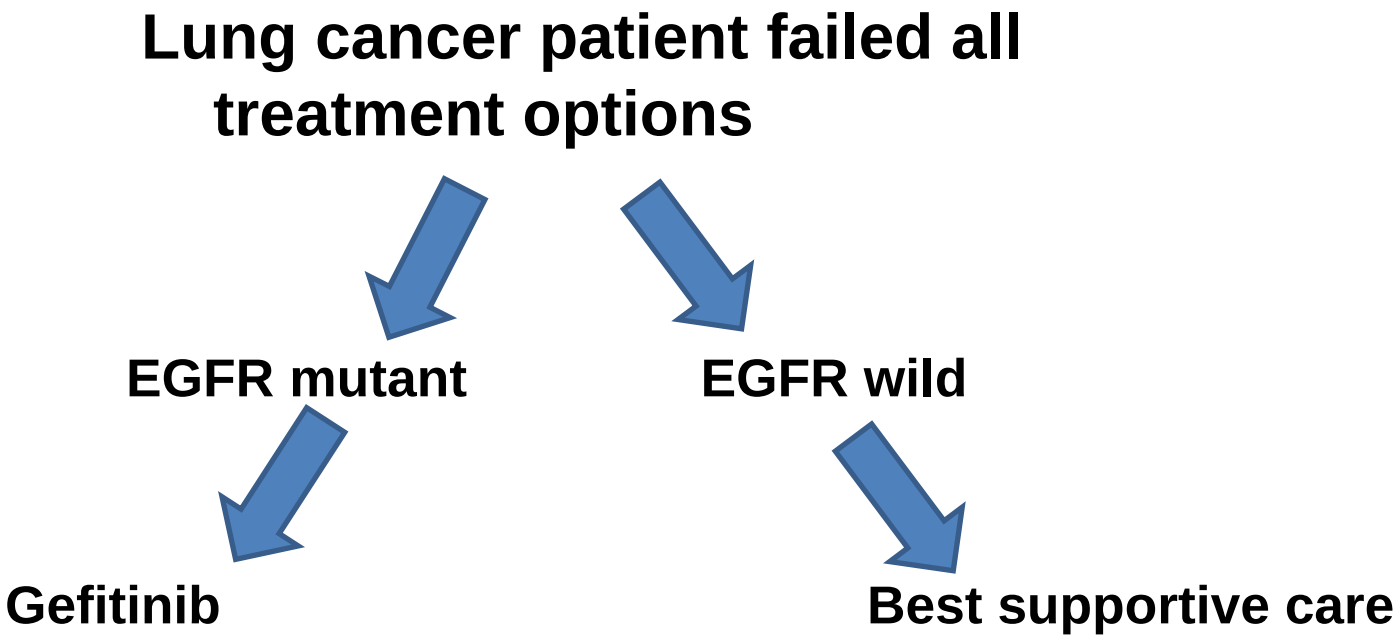


Consequences of incorrect assignment of EGFR status in **first line** NSCLC

Result reported	Actual result	Treatment given	Consequence	Change in survival
EGFR mutant	Wild	Gefitinib	Denied standard chemotherapy	PFS falls from 6 months to 1.5 mths
EGFR wild	Mutant	Standard chemotherapy	Denied gefitinib	PFS falls from 9 to 6 months

Either way – incorrect test results leads to suboptimal care

Incorrect test assignment in third line setting has minimal adverse consequences because there are no other active treatment options



April 19, 2010 APRIL 19, 2010

Cancer Fight: Unclear Tests for New Drug

Two patients with ambiguous results – the first – part negative part positive; the second – tumour tested 4 times – results +ve, -ve, +ve, -ve.

GSK noted there still seemed to be a 20% discordant result for HER testing between labs.

Dr Wolff, Johns Hopkins – if testing is incorrect Herceptin could be "a toxic and expensive placebo"

These examples show that the consequences of incorrect assignment of test results may depend on disease stage or other clinical variables

Challenge 3: The place of the test in practice - who, when and what

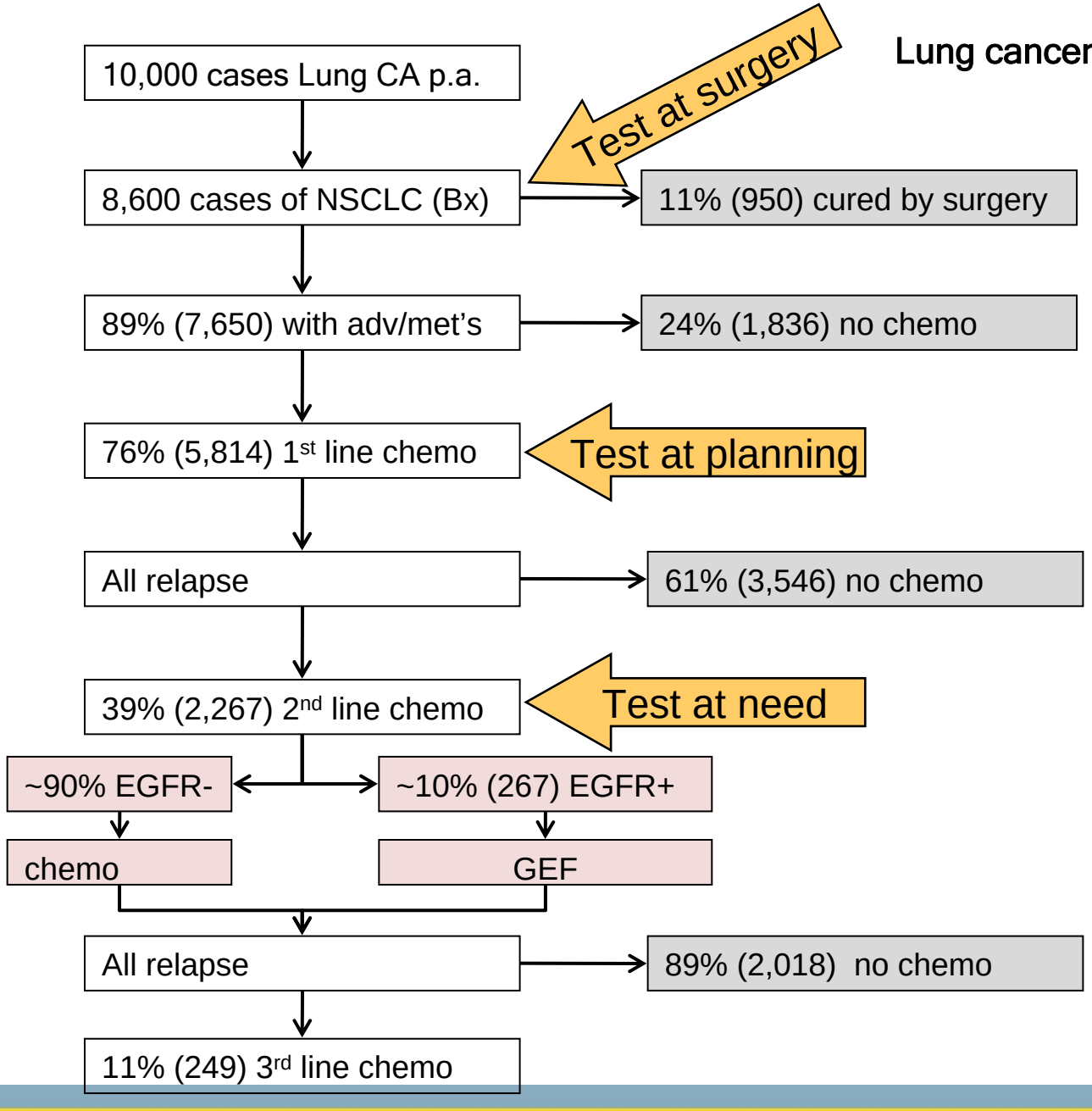
TEST - reference standard, effective analytic validity

What are the consequences on treatment outcomes of a delay in obtaining the results of a test?

Is the test result stable over time?

Is the test result affected by prior therapy?

Lung cancer testing for EGFR mutations



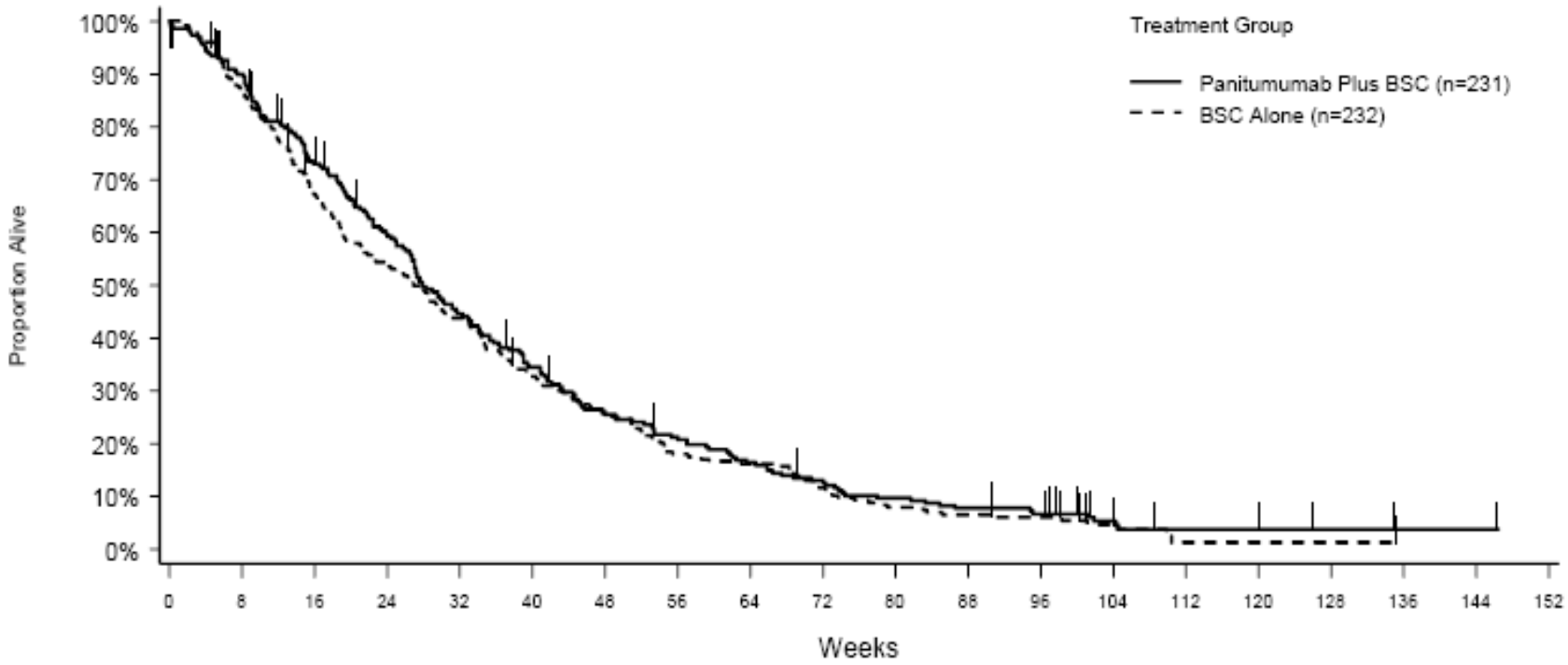
Colorectal cancer testing for KRAS mutations

Stage	I	II	III	IV
% of cases	15%	35%	29%	21%
% developing met's	12%	29%	61%	100%
No. needed to test	18	7	3	2
Cost per treated patient	$4,403	$1,794	$850	$521

Challenge 4: Burden of statistical proof

- Demonstrating test predicts response to drug
- Example - post-hoc target identification - KRAS mutational status a genetic predictor of responsiveness to EGFR antibodies

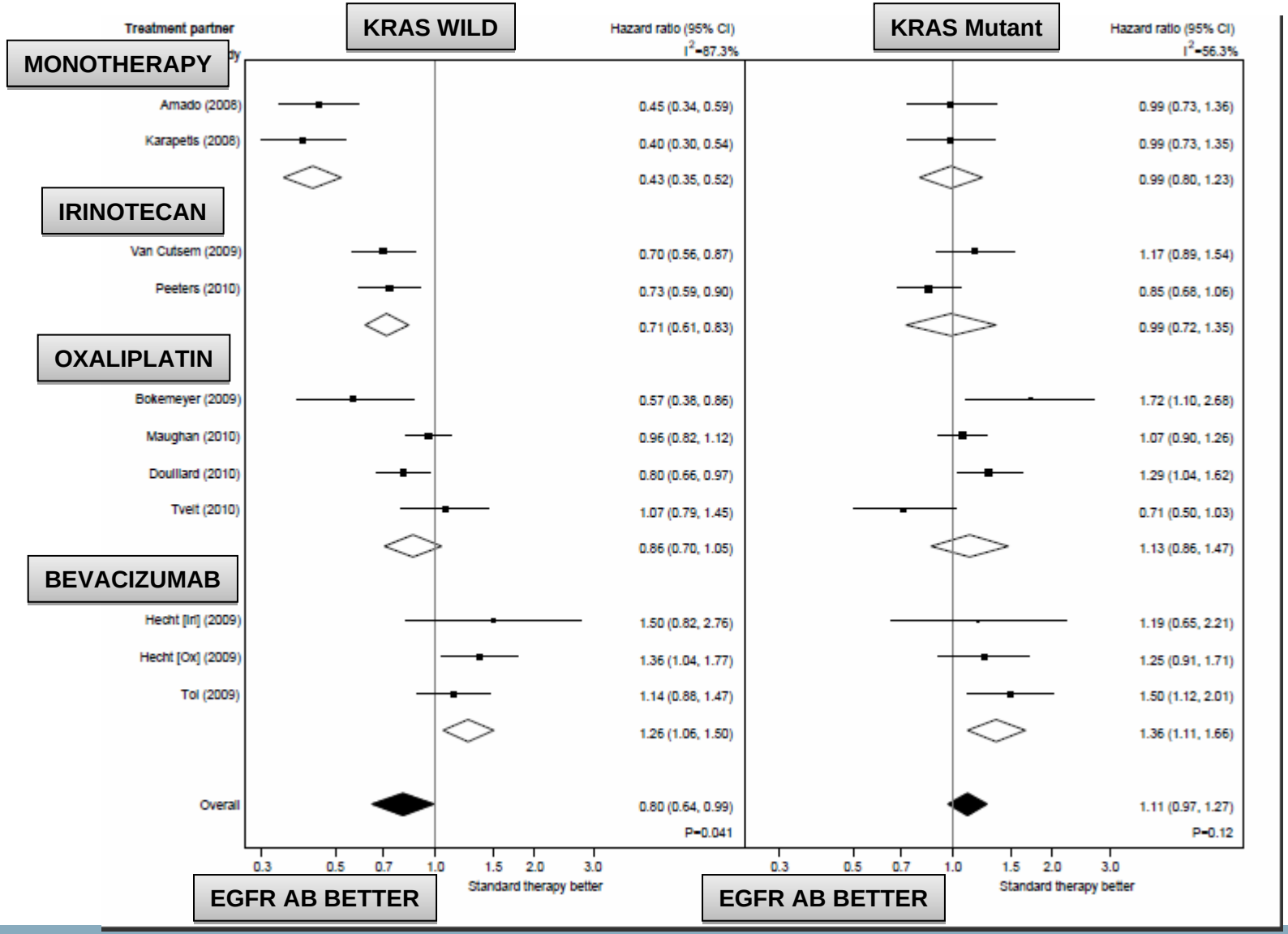
Study 408 – Open-label phase III trial of panitumumab plus BSC compared BSC alone in patients with chemotherapy-refractory metastatic CRC



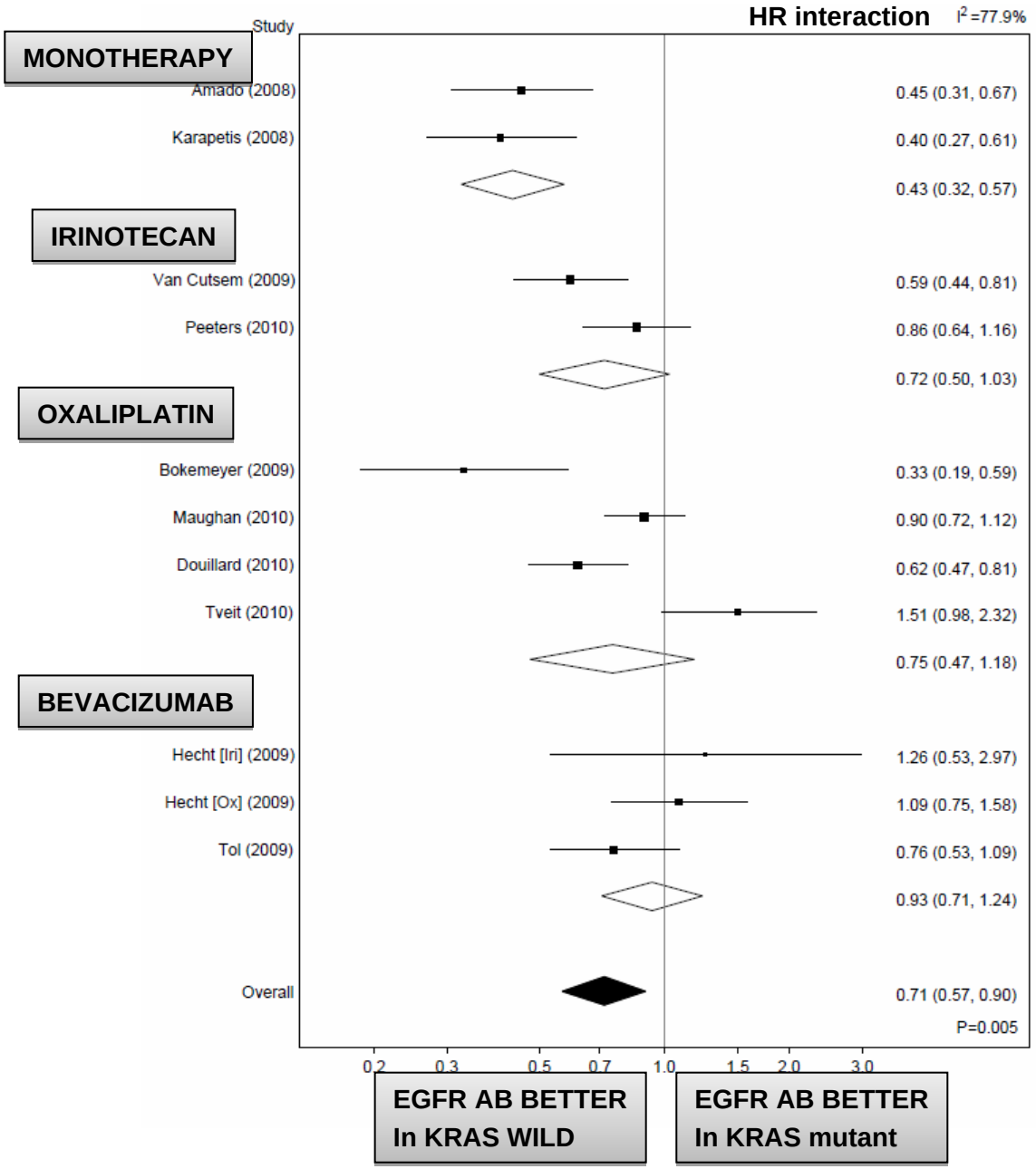
Subjects at risk:

Panitumumab Plus BSC	231	205	162	130	97	74	55	44	34	27	20	16	13	7	4	4	2	1	1	0
BSC Alone	232	199	152	123	99	75	57	40	36	25	17	14	12	6	1	1	1	0	0	0

Progression free survival according to KRAS status



Treatment effect interaction by KRAS status



Other practical challenges

Major reforms occurring across all process as well as those for managing co-dependent technologies

Applicants are seeking concurrent assessment by different committees while processes are being phased in

HTA committees have different evidentiary requirements

Different assessment time frames

PBAC is cost recovered, MSAC is not

Responding to the challenges

- Early engagement – single HTA entry point
- PASC define the question(s) for public funding of a proposed new intervention prior to lodgement
- Guidelines – transparency, reduces uncertainty, defines the goal posts
- Engagement with the colleges, general public, others
- Coordination - single exit point – consolidated advice to government from its HTA committees
- Transitional arrangements in place

Summary of challenges discussed today

- Molecular labelling – simplistic interpretation of complex biology
- Consequences of diagnostic inaccuracy
- The test in practice - who, when and what
- Burden of statistical proof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