

HTA of Companion Diagnostics

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Workshop on Pharmacogenomics: from science to clinical care
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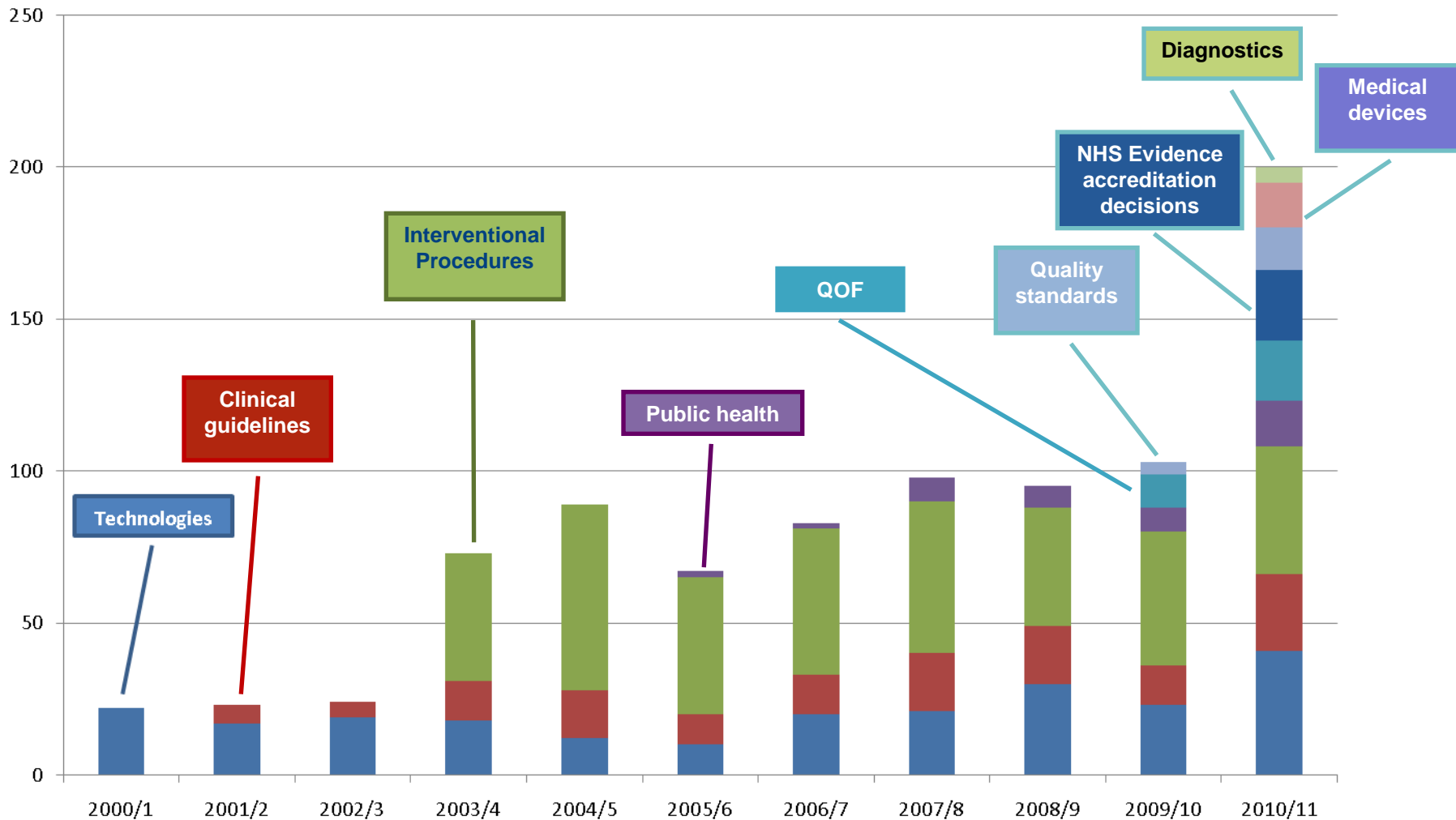
Outline

Title of the Session:

Pharmacogenomics: impact and needs from health care view point to facilitate patients' access

- Current situation
 - How NICE facilitates patient access
 - Companion diagnostics - strategies for assessment
 - Pharmacogenomics and NICE
 - Genetic diagnostics – case studies
- Next steps/ implementation

NICE publications



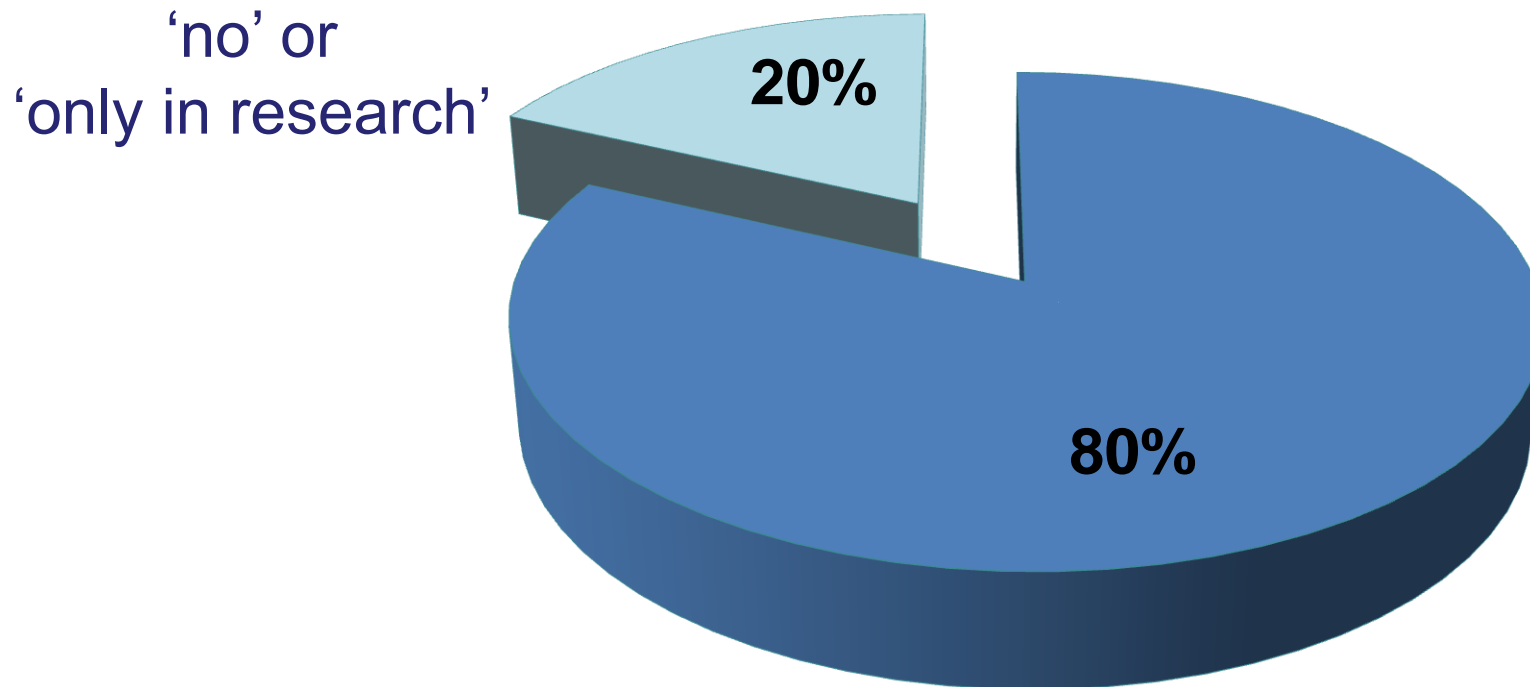
Guiding principles for NICE guidance

- Robust
 - underpinned by a sound evidence base, explicit methods and criteria
- Inclusive
 - involvement of and contributions from stakeholders
- Transparent
 - evidence and conclusions in the public domain
- Independent
 - developed by external advisory committees
- Regular review
 - Maximising value with limited resources
 -in a consistent way

Breakdown of Technology Appraisal recommendations

263 appraisals published up to Sept 2012

490 individual decisions

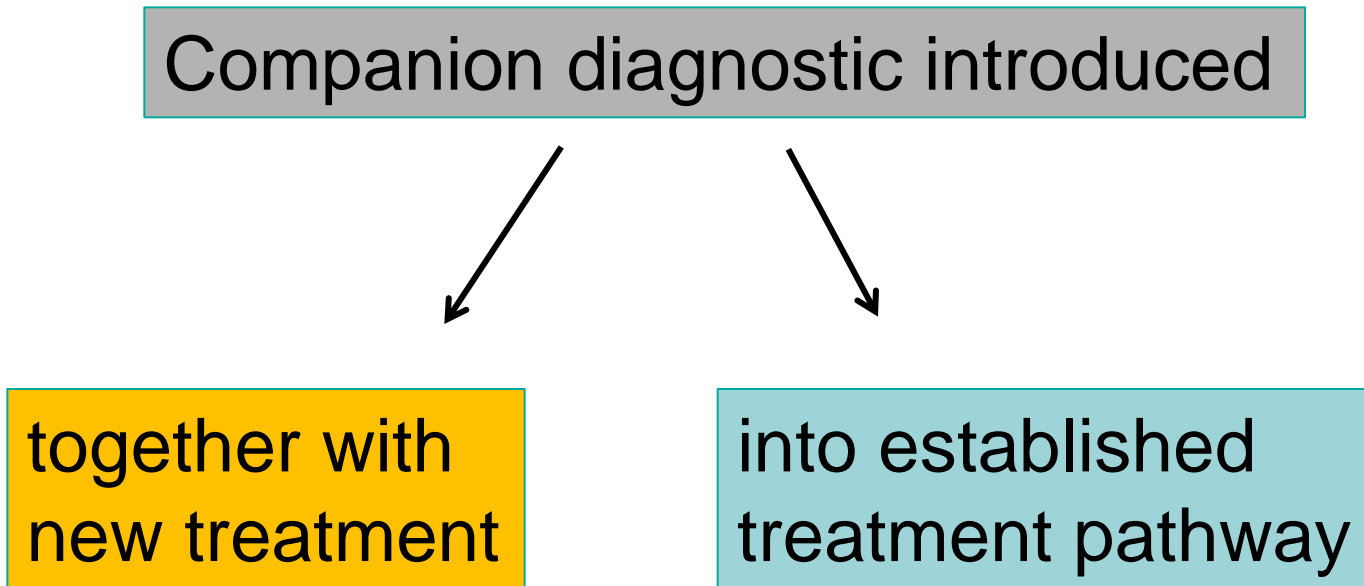


recommended for routine use
or under specific circumstances

Companion diagnostics

- Diagnostic test specifically carried out for a particular treatment decision
- Identifies sub-populations of patients for whom treatment is likely to be more effective or safer
 - Improved clinical outcomes - focusing treatment in patients who can benefit most - avoiding adverse effects in patients unlikely to benefit
 - Cost savings - avoiding treatment in patients who are unlikely to benefit – avoiding costs for managing adverse events
- FDA definition: *An IVD companion diagnostic device is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic*

Companion diagnostic – strategies for assessment



Companion diagnostic – RCT strategies

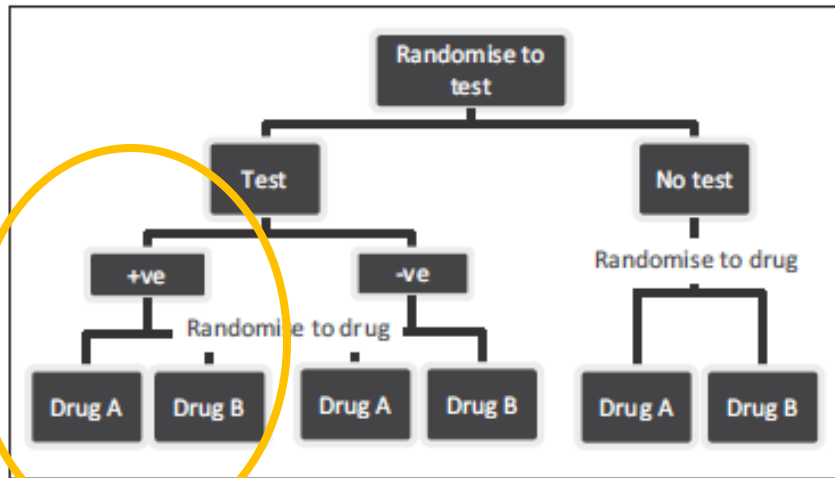


Figure 1 Double-randomized controlled trial.

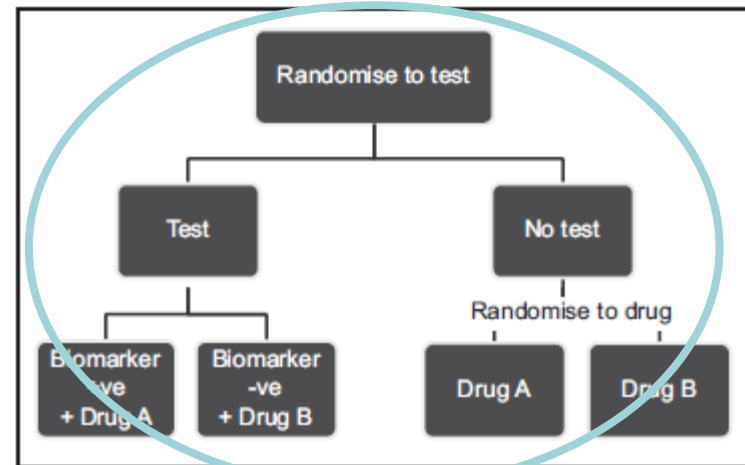


Figure 2 Single-randomized controlled trial (targeted treatment)-
Note: This design cannot explain test (biomarker)-drug relationship.
Additional evidence would need to be provided to show whether the biomarker is a treatment-effect modifier or a prognostic factor.

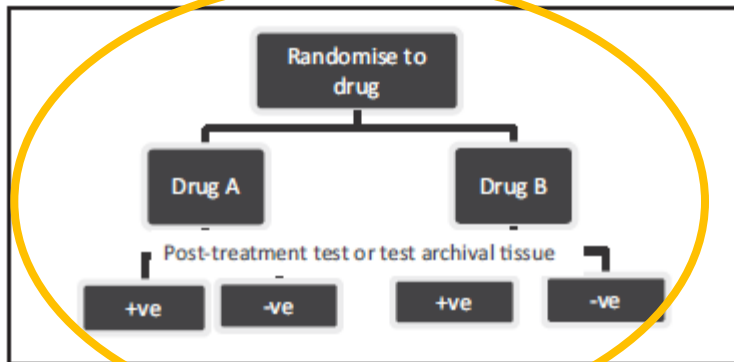


Figure 4 Biomarker-stratified design via subgroup analysis.

Figures taken from Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing personalized medicines in Australia: A national framework for reviewing codependent technologies. Medical Decision Making, August 15, 2012. <http://mdm.sagepub.com/content/early/2012/08/20/0272989X12452341>

Pharmacogenetics and NICE

Diagnostic linked to new drug



Technology Appraisal
part of the appraisal
of the new drug

Diagnostic linked to
established drug
or non drug treatment



Diagnostics Programme

NICE technology appraisals of drugs with companion diagnostics

Treatment	Condition	Marker	NICE technology appraisal
Imatinib	chronic myeloid leukaemia GIST	Philadelphia chromosome (bcr-abl) Kit (CD 117)	50, 70, 241, 251 86, 196, 209
Trastuzumab	breast cancer metastatic gastric cancer	HER-2 (protein)	107, 257 208
Bevacizumab	breast cancer	HER 2 (protein) (negative)	242, 263
Cetuximab	metastatic colorectal cancer	KRAS	218, 176, 242
Gefitinib	non-small-cell lung cancer	EGFR TK mutations	192
Erlotinib			258
Vemurafenib	malignant melanoma	BRAF V600 mutation	TBC
Crizotinib	non-small-cell lung cancer	anaplastic lymphoma kinase fusion (ALK) genes	TBC

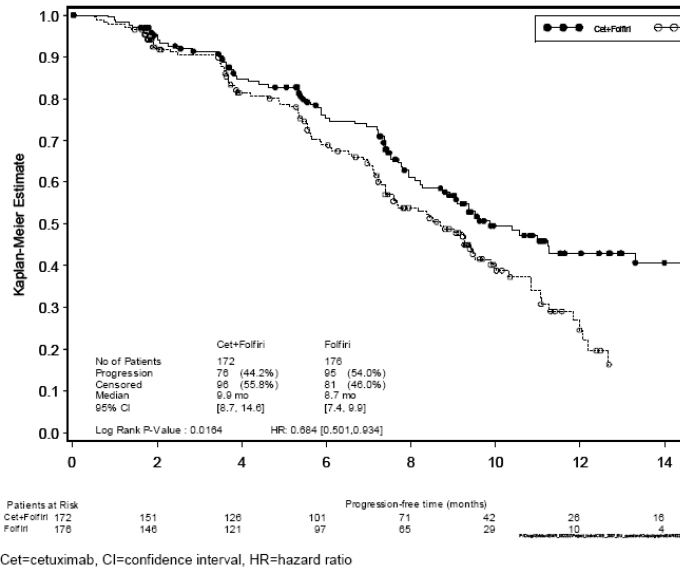
Example 1

TA176 Cetuximab for colorectal cancer (2009)

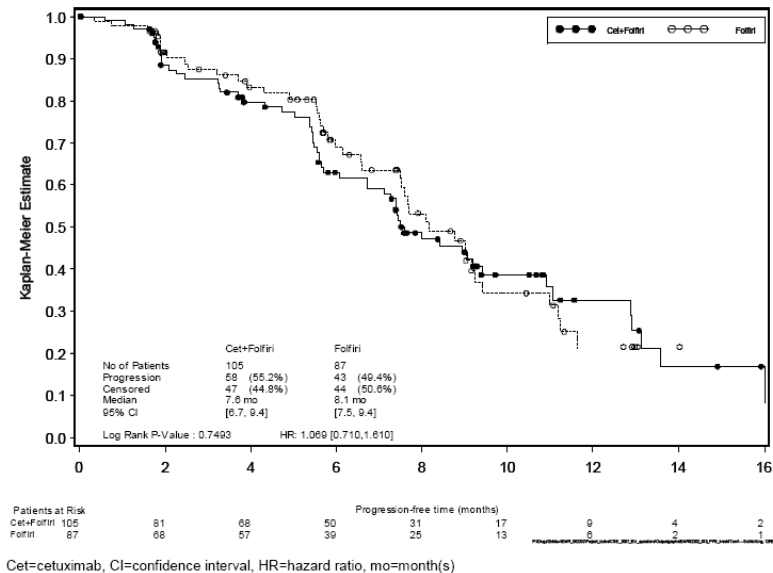
- Cetuximab is indicated for the treatment of patients Kirsten rat sarcoma (KRAS) wild-type metastatic colorectal cancer in combination with chemotherapy
- KRAS: wild-type in ~35%
 - KRAS not mentioned in trial protocol
 - Asked for by EMA, i.e. post hoc

TA176 Cetuximab for colorectal cancer

CRYSTAL study KRAS wildtype



CRYSTAL study KRAS mutant



http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000558/WC500029117.pdf

Recommended by NICE for the treatment of people with metastases in the liver only

Example 2

TA192 Gefitinib for lung cancer (2010)

- UK marketing authorisation for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations of EGFR-TK
- Innovative - oral and targeted treatment
- Evaluation of efficacy by baseline EGFR-TK biomarker status was a planned exploratory objective, but not stratified for the marker
- 29 EGFR-TK mutations, trial population enriched for biomarker

IPASS	EGFR TK M+		EGFR TK M-	
	Gefitinib (n=132)	Pac/Carb (n=129)	Gefitinib (n=91)	Pac/Carb (n=85)
Median PFS	9.5 m	6.3 m	1.5 m	5.5 m
HR (95% CI)	0.48 (0.36-0.64)		2.85 (2.05-3.98)	
Median OS	NR	19.5 m	12.1 m	12.6 m
HR (95% CI)	0.78 (0.50-1.20)		1.38 (0.92-2.09)	

Example 3

Vemurafenib for metastatic melanoma

- Oral tyrosine kinase inhibitor of the oncogenic BRAF V600 protein kinase
- UK marketing authorisation: for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'.
- Drug developed alongside the Roche cobas 4800 BRAF V600 mutation test, which is commercially available in the European Union.
- The manufacturer of vemurafenib is currently making BRAF V600 mutation testing free of charge by funding 3 BRAF reference testing centres in the UK

Challenges in the NICE appraisals

- Target population is a post hoc subgroup
 - Issues with power, randomisation; biologically plausibility
- Comparator data
 - If relevant comparator is not from the respective clinical trial, comparator data usually not available for the specific target population
- Availability of the test
 - Informed by clinical specialists
- Accuracy of the test
 - Informed by clinicians statements not evidence on performance of the test
 - Serious for false positives (gefitinib) and false negative (cetuximab)
- Identification of additional mutations

NICE Diagnostis programme – pharmacogenomics guidance

- Elucigene FH20 and LIPOchip for the diagnosis of familial hypercholesterolaemia (DG2, Dec 2011)
 - Elucigene FH20 and LIPOchip not recommended; comprehensive genetic analysis and targeted sequencing more appropriate.
- Gene expression profiling and expanded immunohistochemistry tests to guide selection of chemotherapy regimes in breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat
 - Diagnostics consultation document, Feb 2012
 - More work currently being undertaken

NICE Diagnostics programme

Companion diagnostics

- Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer
- Scope and protocol published
- Currently in the assessment phase
- Guidance expected mid 2013 (public Committee meetings in March and May 2013)
- <http://guidance.nice.org.uk/DT/11>

EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC - scope

Decision question	Which technologies / methodologies for EGFR-TK mutation testing in adults with chemotherapy naive, locally advanced or metastatic NSCLC are clinically effective and cost-effective for informing first line treatment decisions as currently recommended by NICE, in the NHS in England?
Interventions	<ul style="list-style-type: none"> • Therascreen EGFR RGQ PCR Kit / EGFR Pyro Kit • Cobas EGFR Mutation Testing Kit • Sanger sequencing (exons 18-21)/Therascreen EGFR RGQ PCR Kit of samples with >30% and <30% tumour cells, resp. • Sanger sequencing (exons 18-21)/ cobas EGFR Mutation Testing Kit of samples with >30% and <30% tumour cells, resp. • Sanger sequencing (exons 18-21) followed by fragment length analysis (exon 19 deletions) / PCR (to detect L858R) of negative samples • Pyrosequencing (to detect T790M, L858R, L861Q, G719X and S768I) and fragment length analysis (to detect exon 19 deletions and exon 20 insertions) • Single strand conformation polymorphism analysis (exons 18-21) • HRM analysis (exons 18-21) • Next generation sequencing (exons 18-21)

EGFR-TK mutation testing in adults with locally advanced or metastatic NSCLC - scope

Comparator	Although not a gold standard, Sanger sequencing (exons 18-21) is the comparator for the purpose of the economic modelling.
Outcomes	<p>Number of true/ false positives; true/ false negatives for the prediction of treatment benefit</p> <p>Minimum % tumour cells in biopsy sample needed (limit of detection)</p> <p>Failure rate, turnaround time</p> <p>Survival (overall and progression free)</p> <p>Objective tumour response rate</p> <p>Adverse events , health related quality of life</p> <p>Costs for EGFR-TK mutation testing</p> <p>Costs associated with treatment (TKI or standard chemotherapy within current NICE recommendations</p> <p>Costs associated with the downstream events of cancer, including the management of adverse events associated with treatment</p>

Pharmacogenetics of warfarin and carbamazepine

- The antiepileptic drug carbamazepine can cause serious and potentially lethal hypersensitivity reactions in a small number of patients
- Association between several genes within the major histocompatibility complex on Chromosome 6 and hypersensitivity reactions
- BNF under cautions: test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin
- not mentioned in NICE guideline on epilepsy, Jan 2012
- The widely used anticoagulant warfarin is difficult to use because of the wide variation in dose required to achieve a therapeutic effect, and the risk of serious bleeding. The most important genes affecting the pharmacokinetic and pharmacodynamic parameters of warfarin are CYP2C9 (cytochrome P(450) 2C9) and VKORC1 (vitamin K epoxide reductase complex subunit 1)
- Implementation of pre-prescription genotyping and individualized warfarin therapy represents an opportunity to minimize the risk of haemorrhage without compromising effectiveness
- Not assessed by NICE

Pharmacoeconomics of pharmacogenetics

- Use of pharmacogenetic testing in clinical practice is limited so far
- Often insufficient robust evidence on whether testing provides good value
- Analytical validity, clinical validity, clinical utility, cost effectiveness
- 2008 Systematic review from: 20 papers identified, methodological issues with most of them, important limitation of several studies related to the failure to provide a sufficient evidence-based rationale for an association between genotype and phenotype
- 2010 systematic review: 34 articles, most showed clinical validity, only 2 clinical utility
- 2010 US-based evaluation of warfarin: suggests that warfarin pharmacogenomic testing may provide a small clinical benefit with significant uncertainty in economic value.

Summary and next steps

- Companion diagnostics can be, and have been included in NICE technology appraisals of new drugs and in NICE diagnostics assessments
- Challenges in the assessments can be overcome and pragmatic approaches taken
- Data and evidence requirements will increase
- Methods Guide update
- Need to involve NICE Implementation teams
- Merlin et al 2012 Framework

Links to information

- Diagnostics programme:
 - <http://www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictchnologiesguidance/developingnicediagnostictchnologiesguidance.jsp>
- Technology Appraisals Method Guide (2012 consultation)
 - <http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalsprocessguides/GuideToMethodsTA201112.jsp>
- Merlin T, Farah C, Schubert C, Mitchell A, Hiller JE, Ryan P. Assessing personalized medicines in Australia: A national framework for reviewing codependent technologies. Medical Decision Making, August 15, 2012.
 - <http://mdm.sagepub.com/content/early/2012/08/20/0272989X12452341>
- Vegter S, Boersma C, Rozenbaum M *et al*: Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. *Pharmacoeconomics* 26(7), 569-87 (2008).
- Meckley LM, Gudgeon JM, Anderson JL *et al*: A policy model to evaluate the benefits, risks and costs of warfarin pharmacogenomic testing. *Pharmacoeconomics* 28(1), 61-74 (2010).
- Wong et al. Cost Effectiveness of Pharmacogenomics: A Critical and Systematic Review. *Pharmacoeconomics*: 2010 Volume 28 - Issue 11 - pp 1001-1013