Practical Issues in Developing Economic Models for Targeted Treatments

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1 Introduction:

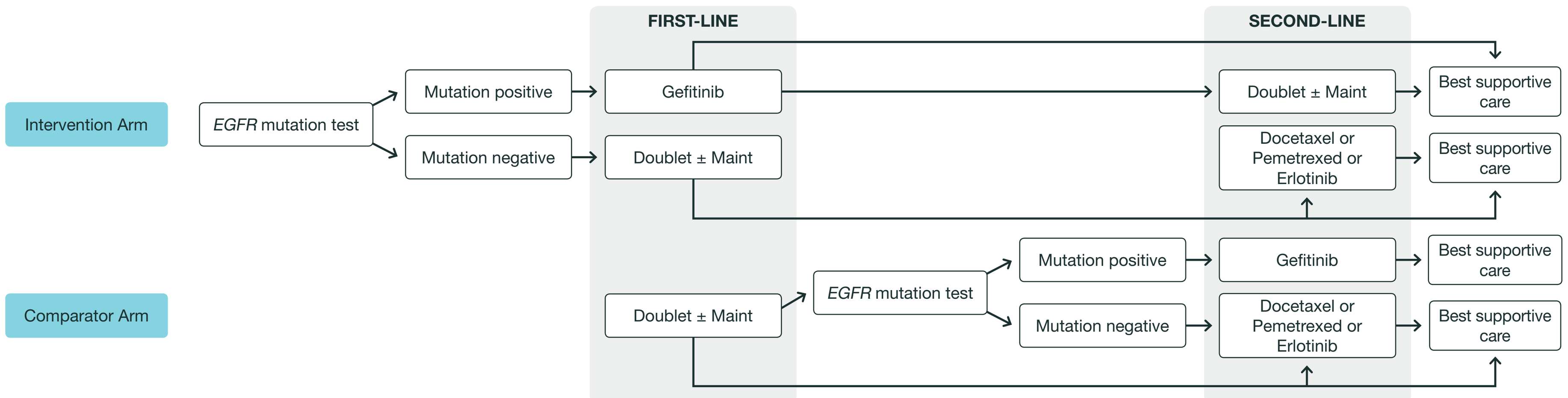
- Gefitinib (IRESSA®, AstraZeneca) has been reimbursed in Australia since 2004 for second-line treatment of patients with Epidermal Growth Factor Receptor (*EGFR*) mutation positive (M+) locally advanced or metastatic non-small cell lung cancer (aNSCLC). However, the *EGFR* mutation test was not publicly funded until much later.
- In response to this disconnect between subsidy schemes, Australian payers introduced a reimbursement process for targeted therapies in 2011 requiring joint economic assessment of the new treatment and associated diagnostic test.[1,2]
- *EGFR* mutation testing to determine eligibility to access subsidised gefitinib for first-line treatment of *EGFR* M+ aNSCLC was one of the first 'co-dependents' to navigate this new course.
- A model was constructed to enable comparison of the costs and benefits of different ways of testing for, and treating, aNSCLC.
- The IPASS study (NCT00322452[6]) presents a unique opportunity to study the impact of testing strategies on cost effectiveness because it provides information not only on patients who tested positive for *EGFR* mutation, but also patients who tested negative (*EGFR* M-).
- A number of technical issues arose during development of the model, and these have significance for the economic evaluations of future companion diagnostics and targeted therapies.

2 Methods:

Model Structure

- An individual patient simulation (Excel[3] with @RISK[4]) was used to develop the model for an aNSCLC population.
- **Figure 1** shows the model structure where the comparator arm represents the standard of care (SOC), no *EGFR* mutation test and treatment of all patients with first-line platinum-based doublet chemotherapy versus the proposed intervention, *EGFR* mutation test and gefitinib treatment for patients with *EGFR* M+ aNSCLC and SOC for patients with *EGFR* M- and *EGFR* status unknown.
- In the comparator arm, progressed patients could be mutation tested to determine suitability for second-line gefitinib. However, this rarely happened in clinical practice. The model assumes that after second-line therapy all patients receive a mixture of subsequent therapies and/or best supportive care (BSC) until death. Third-line and fourth-line treatment for aNSCLC are not modelled explicitly.
- A five-year time horizon was adopted based on Australian data that indicated the survival rate for NSCLC at this time point was approximately 12%.[5]
- A cycle length of 21-days was used to correspond to the cycle length of platinum-based doublet chemotherapy administration. A half-cycle correction was applied.
- The model assumed a societal perspective, as recommended by the PBAC Guidelines.[2]
- Australian dollars (AUD) were used with discounting at the rate of 5% for both costs and benefits.
- The model calculated the outcomes of life years gained, quality-adjusted life years and costs.
- The model was based on the IPASS Study patient population. Data from subgroup analyses in patients with known *EGFR* mutation status confirmed the benefit of tyrosine kinase inhibitors (TKIs) in patients with *EGFR* M+, but also the potential harm to patients with *EGFR* M- in the first-line setting.[7-9] Data were thus available for patients with *EGFR* M+ and *EGFR* M- status treated with both gefitinib and SOC. This information was critical to development of a screening module and survival curves.
- The base case uses Weibull regression models. The model assumed no difference in overall survival between the treatment arms.
- The AZ-sponsored INTEREST Study (NCT00076388), of gefitinib versus docetaxel in second-line aNSCLC was utilised for patients continuing active treatment.[10,11] Additional parameters were estimated using a clinician survey, local data sources and searches of the published literature.
- Drug, monitoring and administration costs were derived for Australian clinical practice and as suggested by Guidelines.[2]
- Costs of adverse events (AE) were based on hospitalisation rates observed in IPASS and INTEREST in conjunction with Australian Refined Diagnosis Related Group (AR-DRG) costs.[12] Hospital and non-hospital costs were added to obtain an average cost of AEs for each treatment.

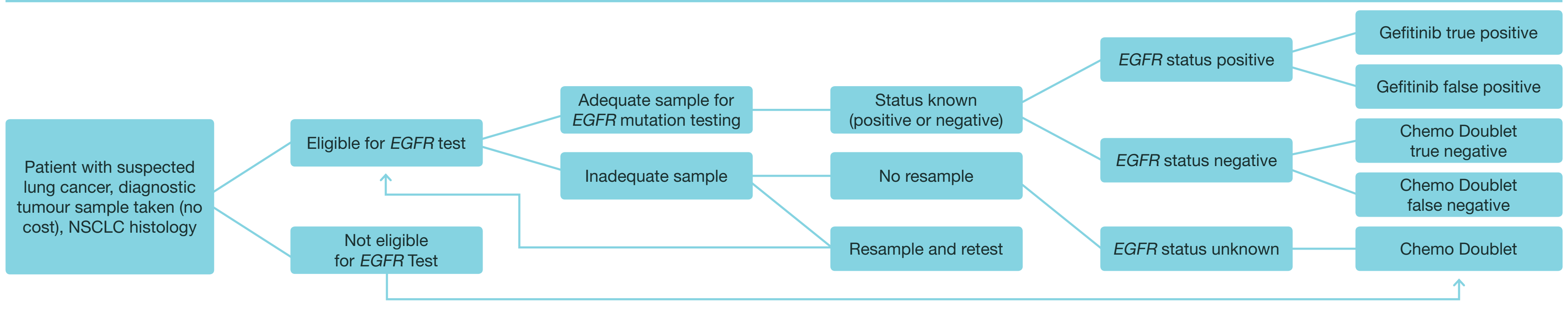
Figure 1 *- Model structure*


FIRST-LINE
SECOND-LINE
Intervention Arm
EGFR mutation test
Mutation positive
Mutation negative
Gefitinib
Doublet ± Maint
Doublet ± Maint
Docetaxel or Pemetrexed or Erlotinib
Best supportive care
Best supportive care
Comparator Arm
Doublet ± Maint
EGFR mutation test
Mutation positive
Mutation negative
Gefitinib
Docetaxel or Pemetrexed or Erlotinib
Best supportive care
Best supportive care

Screening Test Module

A 'screening module' was developed to explore the effect of restricting use of gefitinib as first-line treatment to patients with *EGFR* M+ status **(refer Figure 2)**. The model allowed exploration of various screening and treatment comparisons such as reflex testing at diagnosis, irrespective of stage of disease. The model also allowed for the evaluation of the cost effectiveness of the mutation test. This was done by using gefitinib as first-line treatment in both regimens but only having the *EGFR* mutation tests in one regimen. Operating characteristics of the *EGFR* test that were able to be altered were: percentage of patients eligible for mutation testing; percentage of patients with a useable biopsy (impact of sample and testing issues); percentage of patients *EGFR* M+ (prevalence); and performance of mutation test methods. The IPASS study results were used as a default gold standard (known as an 'evidentiary' standard) and assumed to reflect the results for true *EGFR* status. The screening module needed to allow flexibility in assessing the impact of changing the sensitivity and specificity of the *EGFR* mutation test method. This enabled assessment of the impact of false positive and false negative test results.

Figure 2 *- Structure of screening test module*


Patient with suspected lung cancer, diagnostic tumour sample taken (no cost), NSCLC histology
Eligible for EGFR test
Not eligible for EGFR Test
Adequate sample for EGFR mutation testing
Inadequate sample
Status known (positive or negative)
No resample
Resample and retest
EGFR status positive
EGFR status negative
EGFR status unknown
Gefitinib true positive
Gefitinib false positive
Chemo Doublet true negative
Chemo Doublet false negative
Chemo Doublet

3 Results:

Base Case and Sensitivity Analyses

The base case of the model **(refer Table 1)** assumes patients are left untreated in the period between the end of active doublet cycles and progression. However, switch maintenance therapy (Maint) is commonly used in Australia and the costs of maintenance offset the costs of gefitinib (which is used throughout the period to progression) reducing the Incremental Cost Effectiveness Ratio (ICER). Even when maintenance patients are assumed to respond similarly to gefitinib patients (same PFS benefit), the ICER is improved. When maintenance therapy is used, patients still suffer the adverse events and quality of life impact associated with IV doublet.

Table 1 *- Model results using differing 'base case' assumptions for prevalence, switch maintenance and gefitinib efficacy*

ASSUMPTIONS	5 YEAR QALY			5 YEAR TOTAL COSTS (AU $)			5 YEAR ICER
	Gefitinib	Doublet	Diff (G - D)	Gefitinib	Doublet	Diff (G - D)	
100% M+, No Maintenance	1.3393	1.2401	0.0992	$33,517	$36,643	-$3,126	-$31,513
15% M+, No Maintenance	0.9015	0.8863	0.0152	$22,258	$22,345	-$87	-$5,718
15% M+, 100% Maintenance	0.9015	0.8863	0.0152	$39,825	$41,422	-$1,596	-$105,186
15% M+, 30% Maintenance	0.9015	0.8863	0.0152	$27,528	$28,068	-$540	-$35,558
15% M+, 10% Maintenance	0.9015	0.8863	0.0152	$24,015	$24,253	-$238	-$15,664
15% M+, 30% Maint, EQUAL PFS	0.9015	0.8899	0.0116	$27,528	$28,586	-$1,058	-$91,004
15% M+, 10% Maint, EQUAL PFS	0.9015	0.8875	0.0140	$24,015	$24,425	-$411	-$29,341

EGFR testing regimens to target TKI treatment at various points in the patient's life from diagnosis through to palliative care were compared in sensitivity analyses **(refer Table 2)**. The results were most sensitive to choice of comparator such as: inclusion of switch maintenance following doublet chemotherapy; proportion of patients receiving second-line therapies including targeted TKI; and use of subsequent untargeted TKI. *EGFR* testing + gefitinib was a dominant economic strategy when compared to commonly used treatment alternatives. Assuming the most conservative comparator strategies, *EGFR* test + gefitinib remained cost-effective. Decreasing the specificity of *EGFR* testing (false positive rate) or including a mortality benefit to EGFR TKI worsened the ICER.

Table 2 *- Sensitivity Analysis for EGFR M+ prevalence 15%*

Univariate Sensitivity Analyses	5 YEAR QALY			5 YEAR TOTAL COSTS (AU $)			5 YEAR ICER	% Change From Base-Line
	Gefitinib	Doublet	Diff (G - D)	Gefitinib	Doublet	Diff (G - D)		
Base Case	0.9015	0.8863	0.0152	$22,258	$22,345	-$87	-$5,718	0.00%
Proportion of alive patients going onto 2nd-Line Treatment (Base Case uses 60% Both Arms)								
44% Doublet => Gefitinib / 44% Gefitinib => Doublet	0.9020	0.8857	0.0163	$21,249	$20,634	$615	$37,760	760.41%
80% Doublet => Gefitinib / 80% Gefitinib => Doublet	0.9009	0.8871	0.0138	$23,523	$24,494	-$970	-$70,454	-1132.24%
Survival Benefit								
Survival Benefit (≈3 mth M+)	0.9191	0.8863	0.0328	$22,570	$22,345	$225	$6,858	219.94%
Survival Benefit (≈6 mth M+)	0.9391	0.8863	0.0527	$22,922	$22,345	$577	$10,945	291.43%
Percentage of Patients True M+ (Base Case uses 15% M+)								
10%	0.8748	0.8647	0.0101	$21,566	$21,479	$87	$8,639	251.09%
20%	0.9267	0.9067	0.0200	$22,907	$23,171	-$264	-$13,190	-130.70%
Sensitivity/Specificity (Base Case assumes errors built into IPASS results)								
98% Sensitivity	0.9010	0.8862	0.0148	$22,235	$22,312	-$76	-$5,153	9.87%
94% Sensitivity	0.9003	0.8861	0.0142	$22,199	$22,255	-$57	-$3,976	30.47%
90% Sensitivity	0.8996	0.8859	0.0136	$22,164	$22,204	-$40	-$2,945	48.50%
98% Specificity	0.8996	0.8863	0.0132	$22,227	$22,407	-$180	-$13,571	-137.35%
94% Specificity	0.8956	0.8863	0.0093	$22,150	$22,534	-$384	-$41,467	-625.25%
90% Specificity	0.8912	0.8863	0.0050	$22,076	$22,668	-$592	-$119,535	-1990.66%
Cost of BSC (Base Case uses $500)								
$250	0.9015	0.8863	0.0152	$19,268	$19,238	$30	$1,977	134.58%
$750	0.9015	0.8863	0.0152	$25,248	$25,452	-$204	-$13,412	-134.58%
***EGFR* Test Cost (Base Case uses $414.12)**								
$200	0.9015	0.8863	0.0152	$21,963	$22,228	-$265	-$17,482	-205.77%
$600	0.9015	0.8863	0.0152	$22,514	$22,446	$68	$4,496	178.63%
Cost of Re-Biopsy Not including Complications (Base Case uses $1128.19)								
$600	0.9015	0.8863	0.0152	$22,195	$22,311	-$116	-$7,621	-33.30%
$1,600	0.9015	0.8863	0.0152	$22,314	$22,375	-$61	-$4,017	29.74%
Cost of Re-Biopsy Complications Requiring Hospitalisation (Base Case uses $10,657)								
$5,000	0.9015	0.8863	0.0152	$22,211	$22,319	-$108	-$7,145	-24.96%
$23,371	0.9015	0.8863	0.0152	$22,364	$22,402	-$38	-$2,510	56.11%
Cost of Re-Biopsy Complications Not Requiring Hospitalisation (Base Case uses $151.00)								
$500	0.9015	0.8863	0.0152	$22,261	$22,346	-$85	-$5,630	1.54%
Doublet AE Costs (Base Case uses $1741)								
$1,241	0.9015	0.8863	0.0152	$21,801	$21,847	-$46	-$3,029	47.02%
$2,241	0.9015	0.8863	0.0152	$22,716	$22,843	-$128	-$8,410	-47.09%
Overall Chemotherapy Monitoring Costs (Base Case uses $663.46)								
$300	0.9015	0.8863	0.0152	$18,881	$18,762	$119	$7,838	237.08%
$500	0.9015	0.8863	0.0152	$20,739	$20,734	$6	$379	106.62%

4 Discussion:

This cost-utility analysis demonstrated that, even without a survival benefit (per clinical data confounded by treatment switch), testing non-squamous / NOS NSCLC patients at diagnosis for *EGFR* mutation status, and treating patients with known *EGFR* mutation positive locally advanced or metastatic NSCLC with first-line gefitinib was cost-effective. A crucial factor in the assessment was the comparator to be replaced. The model found that if platinum-based doublet chemotherapy was followed by switch maintenance therapy, in even a low proportion of patients, then the overall costs of therapy in the intervention arm were lower than current standard of care.

The prevalence of *EGFR* mutations in the target population is an important variable to the cost effectiveness of a screening/treatment regimen. Where the true prevalence is rare, the average cost associated with identifying each patient for treatment begins to increase, and become more important than the cost of drug. In this case, when the expected prevalence of *EGFR* mutations in the Australian NSCLC population was reduced to 10%, the proposed strategy was no longer dominant. Atherly and Camidge demonstrated similar impacts on cost-effectiveness of differences in test and drug costs and enrichment of the population eligible for screening, using testing for ALK rearrangements to access crizotinib (XALKORI®, Pfizer) in NSCLC.[13]

Low prevalence may also have other implications. Across all patients screened in our model the incremental health gain, in terms of QALY gains, may appear to be very small (0.018). In fact, the 15% of patients who tested *EGFR* M+ and were treated with gefitinib, received an approximate 0.1 QALY gain (from PFS advantage and better utility with a less toxic oral agent). Standard techniques to evaluate 'all comers' medicines are not directly applicable to targeted therapies and do not fully elucidate the value accrued to the 'targeted' population. This is demonstrated in the cost-effectiveness analysis of EML4-ALK fusing testing and targeted first-line crizotinib treatment conducted by Djalalov and colleagues.[14]

Similarly, the ICERs generated when there is a small denominator (benefit difference over the model population) can be unstable. Even relatively small changes in the numerator (cost difference) may be dramatically amplified, and lead to large changes in the ICER. Given the additional variables and diversity of information integrated into a test + drug economic model, the ICER might be poorly suited to use as a decision tool in personalized medicine. A further flow on with altering the test (population tested, test performance) not only changes the initial treatment options but also changes treatment regimens in second, third and fourth line. If expensive combination treatments are used in later stages then the clear clinical benefit of keeping patients alive longer might lead to a worse ICER. Again caution should be used when evaluating an ICER in this context.

Work towards the development of agreed economic evaluation techniques to use in assessment of test and treat strategies, includes the output of the ISPOR Personalised Medicine Special Interest Group (Faulkner et al. 2012[15]) who have published a comprehensive summary of the reimbursement challenges for personalised medicine. Annemans et al. 2013,[16] identify specific methodological issues, with reference to current guidelines for economic evaluations, and provide suggestions on application within assessments. Doble and colleagues[17] present a checklist of test characteristics to include in a model-based economic evaluation. Buchanan, Wordsworth and Schuh (2013) note that, thus far, no consensus on whether existing economic evaluation methods are sufficient to evaluate test and treat strategies has been made by the health economics community. They suggest that the key methodological challenges fall into five categories: analytical approach, costs and resource use, measuring outcomes, measuring effectiveness and other.[18]

In response to increasing numbers of new pharmaceuticals requiring the use of companion diagnostics, in 2011 the United Kingdom National Institute for Health and Care Excellence (NICE) established a Diagnostics Assessment Programme (DAP), in addition to the existing Technology Appraisal Programme, with the expectation that there will be evolution of both programmes as the field develops.[19] The French National Authority of Health (HAS) released a Methodological paper in 2014[20] regarding assessment of 'companion' diagnostic tests. They state that as evaluation of companion diagnostics must take into account the impact on individual health (clinical utility), i.e. the health outcomes from drug treatments received based on test results, then standard HTA methods will continue to apply, albeit with updates to specific elements. HAS says that the demonstration of clinical utility of the diagnostic test is a prerequisite to the joint assessment of the companion test and an associated targeted therapy. This is similar to the Australian approach where the biomarker, test and drug are considered separately before the costs and benefits of using together.[1]

5 Conclusion:

EGFR mutation testing and access to EGFR TKIs for first-line treatment of aNSCLC were reimbursed nationally from 1 January 2014. The challenges associated with integrated economic evaluation of targeted therapies are becoming more clearly understood, however further work is required to ensure that the value individuals gain, especially in oncology, are not lost in the complexity and confounding by treatment switch. We believe this is an ethical imperative for all involved in ensuring access to personalised medicines.

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