Epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer: a systematic review and cost-effectiveness analysis

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Kleijnen Systematic Reviews Ltd in collaboration with Erasmus University Rotterdam and Maastricht University

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Contributions of authors

Marie Westwood and Penny Whiting planned and performed the systematic review and interpretation of evidence. Manuela Joore, Thea van Asselt and Bram Ramaekers planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong contributed to planning and interpretation of cost-effectiveness analyses and acquisition of input data for modelling. Kate Misso devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

Errata

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Original text:

Marie Westwood and Penny Whiting planned and performed the systematic review and interpretation of evidence. Manuela Joore, Thea van Asselt and Bram Ramaekers planned and performed the cost-effectiveness analyses and interpreted results. Nigel Armstrong and Kelly Lee contributed to planning and interpretation of cost-effectiveness analyses and acquisition of input data for modelling. Kate Misso devised and performed the literature searches and provided information support to the project. Jos Kleijnen and Johan Severens provided senior advice and support to the systematic review and cost-effectiveness analyses, respectively. All parties were involved in drafting and/or commenting on the report.

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Section 3.2 Results of the assessment of clinical effectiveness

Section 3.2.1 What are the technical performance characteristics of the different EGFR mutation tests?

<u>EGFR mutation test methods (Figure 2, Table 3)</u>

p. 38

Original text: “A combination of fragment length analysis and pyrosequencing was used in three laboratories and Sanger sequencing in two; other tests were each used in single laboratories.”

Revised text: “A combination of fragment length analysis and pyrosequencing was used in two laboratories and Sanger sequencing in two; other tests were each used in single laboratories.”

p.39

Original text: “The third use Sanger sequencing, TaqMan/Real Time PCR/Entrogen and Fragment Length Analysis and also cite verification of mutations and insufficient tumour cell as their reason for using multiple tests.”

Revised text: “The third use Sanger sequencing, TaqMan/Real Time PCR/Entrogen and Fragment Length Analysis and also cite verification of mutations and insufficient tumour cell as their reason for using multiple tests. Personal communication from this laboratory during stakeholder consultation clarified that TaqMan/Real Time PCR/Entrogen and Fragment Length Analysis are used where sequence analysis has failed, due to poor quality DNA (fragmented/degraded) and are not used to compensate for low tumour load.”

Section 3.2.2 What is the accuracy of EGFR mutation testing, using any test, for predicting response to treatment with tyrosine kinase inhibitors?

EGFR mutation test accuracy p 48

Original text: “Four of the five studies, which used direct sequencing methods to identify EGFR mutations reported high estimates of specificity (>80%) for OR and specificities ranged from 60 to 80%.”

Revised text: “Four of the five studies, which used direct sequencing methods to identify EGFR mutations reported high estimates of specificity (>80%) for OR and sensitivities ranged from 60 to 80%.”

Section 4.2 Model structure and methodology

Section 4.2.1 EGFR-TK mutation tests considered in the model p. 73, final bullet point

Original text: “Therascreen® and Pyrosequencing Kit”

Revised text: “Therascreen® EGFR Pyro Kit”

Figure 10, p.75

Original text: “Anti-EGFR TKI”

Revised text: “EGFR-TKI”

Figure 13, p.83

Original heading text: “Progression free survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-20 mutations[5]”

Revised heading text: "Progression free survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-21 mutations[5]"

Figure 14, p.84

Original heading text: "Overall survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-20 mutations[5]"

Revised heading text: "Overall survival for patients tested with the Therascreen® EGFR PCR Kit[50] and with direct sequencing of all exon 19-21 mutations[5]"

Table 22: EGFR Mutation test costs based results online survey in reference laboratories in England and Wales p 88, final row, first column

Original text: "Therascreen® and Pyrosequencing Kit"

Revised text: "Therascreen® EGFR Pyro Kit"

Table 23: Explanation of calculation of proportion of patients with unknown mutations status due to a technical failure in the laboratory per test p 90, final row, first column

Original text: "Therascreen® and Pyrosequencing Kit"

Revised text: "Therascreen® EGFR Pyro Kit"

Section 4.3 Model analyses

Table 26: Probabilistic results for 'Evidence on comparative effectiveness available' analysis: base case and sensitivity analyses, p 95

Original table:

Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 19-21**		
			Cost	**QALY**	**Cost/QALY**
Base case					
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,660	-0.207	£32,167
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.109*			
Sensitivity analysis: updated costs					
Therascreen® EGFR PCR Kit	[redacted]	0.874	-£9,194	-0.286	£32,196
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.160*			
Sensitivity analysis: unknowns from survey					

Therascreen® EGFR PCR Kit	[redacted]	0.905	-£7,130	-0.206	£34,555
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.111*			

[a]Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Revised table:

Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 19-21)**		
			Incremental Cost	**Incremental QALY**	**Incremental Cost/QALY**
Base case					
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,660	-0.207	£32,167[a]
Direct sequencing of all exon 19-21 mutations[b]	[redacted]	*1.109*			
Sensitivity analysis: updated costs					
Therascreen® EGFR PCR Kit	[redacted]	0.874	-£9,194	-0.286	£32,196[a]
Direct sequencing of all exon 19-21 mutations[b]	[redacted]	*1.160*			
Sensitivity analysis: unknowns from survey					
Therascreen® EGFR PCR Kit	[redacted]	0.905	-£7,130	-0.206	£34,555[a]
Direct sequencing of all exon 19-21 mutations[b]	[redacted]	*1.111*			

[a] Cost saved / QALY lost

[b] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Table 27: Probabilistic results for 'linked evidence' analysis, base case, p.97

Original table:

Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 18-21)**		
			Incremental Cost	**Incremental QALY**	**Incremental Cost/QALY**
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,040	-0.190	£31,849
Direct sequencing of all exon 18-21 mutations	[redacted]	1.092			
Direct sequencing of all exon 19-21 mutations[a]	[redacted]	*1.109*	*£619*	*0.017*	*£35,634*
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)[a]	[redacted]	*1.109*	*£658*	*0.017*	*£38,251*

[a] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Revised table:

Strategy	**Cost**	**QALY**	**Compared to Direct sequencing (exon 18-21)**		
			Incremental Cost	**Incremental QALY**	**Incremental Cost/QALY**
Therascreen® EGFR PCR Kit	[redacted]	0.902	-£6,040	-0.190	£31,849[a]
Direct sequencing of all exon 18-21 mutations	[redacted]	1.092			
Direct sequencing of all exon 19-21 mutations[b]	[redacted]	*1.109*	*£619*	*0.017*	*£35,634*
Direct sequencing or WAVE-HS for inadequate samples (<50% tumour cells)[b]	[redacted]	*1.109*	*£658*	*0.017*	*£38,251*

[a] Cost saved / QALY lost

[b] Although this test was not listed in the scope, it was included in the analyses as discussed in section 4.2.1.

Table 29: Probabilistic results for 'assumption of equal prognostic value' analysis, sensitivity analyses: unknown based on survey, p.100-101

Original table:

Strategy			Compared to Direct sequencing of all exon 18-21mutations			Compared to next best strategy			
	Costs	QALYs	Incremental cost	Incremental QALYs	Incremental cost / QALY	Comparator	Incremental cost	Incremental QALYs	Incremental cost / QALY
Sanger sequencing and Fragment length analysis / PCR of negative samples	[redacted]	0.871	-£226	-0.007	£33,437				
High Resolution Melt analysis	[redacted]	0.871	-£211	-0.007	£31,848	Sanger sequencing and Fragment length analysis / PCR of negative samples	£14	0.000	Extended dominance
Sanger sequencing or Therascreen® EGFR PCR Kit for samples with insufficient tumour cells	[redacted]	0.877	-£40	-0.001	£45,629	Sanger sequencing and Fragment length analysis / PCR of negative samples	£186	0.006	Extended dominance
Therascreen® EGFR PCR Kit	[redacted]	0.877	-£26	-0.001	£24,977	Sanger sequencing and Fragment length analysis / PCR of negative samples	£200	0.006	Extended dominance
Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	[redacted]	0.878	-£18	0.000	Dominated	Sanger sequencing and Fragment length analysis / PCR of negative samples	£207	0.007	£30,602
Direct Sequencing or WAVE-HS[a]	[redacted]	*0.878*	*£0*	*0.000*	*Dominated*	*Sanger Sequencing or Roche Cobas for samples with*	*£18*	*0.000*	*Dominated*

Strategy			Compared to Direct sequencing of all exon 18-21mutations			Compared to next best strategy			
	Costs	QALYs	Incremental cost	Incremental QALYs	Incremental cost / QALY	Comparator	Incremental cost	Incremental QALYs	Incremental cost / QALY
						insufficient tumour cells			
Direct Sequencing of exon 18-21	[redacted]	0.878				Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£18	0.000	Dominated
Direct Sequencing of exon 19-21[a]	[redacted]	*0.878*	*£0*	*0.000*	*£615,549*	*Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells*	*£19*	*0.000*	*Dominated*
Roche Cobas	[redacted]	0.879	£15	0.001	£19,501	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£33	0.001	Extended dominance
Fragment Length analysis combined with Pyrosequencing	[redacted]	0.879	£62	0.001	£79,807	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£81	0.001	Extended dominance
Single strand conformation analysis	[redacted]	0.886	£264	0.008	£31,080	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£283	0.008	£33,338

Revised table:

Strategy			**Compared to Direct sequencing of all exon 18-21mutations**			**Compared to next best strategy**			
	Costs	**QALYs**	**Incremental cost**	**Incremental QALYs**	**Incremental cost / QALY**	**Comparator**	**Incremental cost**	**Incremental QALYs**	**Incremental cost / QALY**
Sanger sequencing and Fragment length analysis / PCR of negative samples	[redacted]	0.871	-£226	-0.007	£33,437 [a]				
High Resolution Melt analysis	[redacted]	0.871	-£211	-0.007	£31,848 [a]	Sanger sequencing and Fragment length analysis / PCR of negative samples	£14	0.000	Extended dominance
Sanger sequencing or Therascreen® EGFR PCR Kit for samples with insufficient tumour cells	[redacted]	0.877	-£40	-0.001	£45,629 [a]	Sanger sequencing and Fragment length analysis / PCR of negative samples	£186	0.006	Extended dominance
Therascreen® EGFR PCR Kit	[redacted]	0.877	-£26	-0.001	£24,977 [a]	Sanger sequencing and Fragment length analysis / PCR of negative samples	£200	0.006	Extended dominance
Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	[redacted]	0.878	-£18	0.000	Dominated	Sanger sequencing and Fragment length analysis / PCR of negative samples	£207	0.007	£30,602
Direct Sequencing or WAVE-HS[a]	[redacted]	*0.878*	*£0*	*0.000*	*Dominated*	*Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells*	*£18*	*0.000*	*Dominated*

Strategy			Compared to Direct sequencing of all exon 18-21mutations			Compared to next best strategy			
	Costs	QALYs	Incremental cost	Incremental QALYs	Incremental cost / QALY	Comparator	Incremental cost	Incremental QALYs	Incremental cost / QALY
Direct Sequencing of exon 18-21	[redacted]	0.878				Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£18	0.000	Dominated
Direct Sequencing of exon 19-21[a]	[redacted]	*0.878*	*£0*	*0.000*	*£615,549*	*Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells*	*£19*	*0.000*	*Dominated*
Roche Cobas	[redacted]	0.879	£15	0.001	£19,501	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£33	0.001	Extended dominance
Fragment Length analysis combined with Pyrosequencing	[redacted]	0.879	£62	0.001	£79,807	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£81	0.001	Extended dominance
Single strand conformation analysis	[redacted]	0.886	£264	0.008	£31,080	Sanger Sequencing or Roche Cobas for samples with insufficient tumour cells	£283	0.008	£33,338

[a] Cost saved / QALY lost