HeartFlow FFRct for the computation of fractional flow reserve from coronary CT angiography

Chest pain of recent onset: assessment and diagnosis NICE guidelines [CG95]: Guidance update

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Declared interests of the authors

None

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http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

If there are none, please state 'none'.

Rider on responsibility for report

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Clinical evidence update for technical validity, diagnostic accuracy, and clinical outcomes

For the updated review of the clinical evidence for Heartflow, the EAC replicated the search strategies undertaken for the original assessment report (page 186, Appendix 2, MT252_Heartflow_v3.1). The databases were originally searched on 24th of February 2016. An updated search of PubMed only using the terms 'FFRCT' and Heartflow' was performed on 4th of April 2016. Six further studies under publication or presented as conference proceedings were submitted by the manufacturer. The results are listed in the PRISMA flowchart (Figure 1). The EAC selected the studies based on the criteria identified in the original scope. The relevant studies selected for inclusion in this update are listed below. Table 3 presents a summary of currently ongoing studies with Heartflow.

Technical validity

1. Tanaka et al. (2016)

Tanaka et al. (2016) investigated the association between FFR_{CT} and invasive FFR in coronary arteries with serial lesions, in a subgroup population of the NXT study. The authors investigated patients (n=18 patients and 18 vessels) with stable angina and clinically suspected coronary artery disease (CAD). There was no clinical follow-up. The primary outcome was the per-segment correlation between FFR_{CT} and invasive FFR values, expressed as trans-lesional delta (the difference between the proximal and distal FFR measurement of all sequential lesions). Values of trans-lesional delta for FFR and FFR_{CT} were 0.10 ± 0.09 and 0.09 ± 0.10 in distal segments, and 0.17 ± 0.10 and 0.22 ± 0.13 in proximal segments, respectively. The coefficient of correlation between trans-lesional delta FFR and FFR_{CT} in each segment was 0.92 ($p<0.001$). The authors concluded that trans-lesional delta FFR is highly correlated with FFR_{CT}.

Quality appraisal

This study retrospectively analysed a subgroup of patients from the prospective NXT trial, and therefore has a low risk of bias for flow and timing, and the index and

reference tests. Although the primary trial is significant in size and multicentre in nature, the sub-group analyses presented are constrained by smaller sample size, limiting power. This is the first study comparing non-invasive assessment of the haemodynamic significance of serial coronary lesions using FFR_{CT} with invasive FFR.

Diagnostic accuracy

2. Thompson et al. (2015)

Thompson et al. (2015) investigated the diagnostic performance of FFR_{CT} in relation to patients' sex and age, using invasive FFR measurements as the gold standard for a subgroup population of the DeFACTO study. The authors investigated patients (n=252 patients and 407 vessels) with stable angina and clinically suspected CAD and at least 1 coronary stenosis of 30-90%. For their analysis, the authors used a clinical rule that included all vessels of diameter ≥2 mm and assigned an FFR value of 0.90 for vessels with stenoses <30% and an FFR value of 0.50 for vessels with stenoses >90%. There was no clinical follow-up. The primary outcome was per patient and vessel diagnostic performance of FFR_{CT} using FFR as the reference standard. Using the clinical rule, the diagnostic performance improved in both sexes with no significant differences between them (AUC: 0.93 vs. 0.90, p=0.43). There were no differences in the discrimination of FFR_{CT} after application of the clinical use rule when stratified by age ≥65 or <65 years (AUC: 0.95 vs. 0.90, p=0.10). The authors concluded that FFR_{CT} had similar diagnostic accuracy and discriminatory power to FFR for ischemia detection in men and women irrespective of age using a cutoff point of 65 years.

Quality appraisal

This study retrospectively analysed a subgroup of patients from the prospective DeFACTO trial, and therefore, has a low risk of bias for flow and timing, and for the index and reference tests. Although the primary trial is significant in size and multicentre in nature, the sub-group analyses presented are constrained by smaller

sample size, limiting power. The findings were exploratory with the aim of deriving suggestions for optimising FFR_{CT} accuracy. Previous evidence from the DeFACTO trial was not considered eligible for inclusion as the study included patients with high pre-test likelihood of CAD (Min et al. 2012). The Thompson et al. (2015) study is included as it reports results based on sub-group analyses for age and gender. The baseline pre-test likelihood did not differ in statistical significance within these sub-groups, therefore, it is not expected that it can bias results.

Clinical outcomes

3. The SCOT-HEART investigators (2015)

The SCOT-HEART RCT investigated the effect of adding CCTA to the standard care on the diagnosis, management, and outcome of patients with suspected angina due to CAD. As secondary outcomes, the radiation dose and adverse reactions to the CT scanning procedure (such as contrast reaction, renal impairment or vasovagal response) were investigated. The study included 1778 patients recruited at 12 cardiology centres across Scotland. At 6 weeks, CCTA reclassified the diagnosis of CAD in 27% of the patients and the diagnosis of angina due to CAD in 23% patients (standard care=1% and 1%, respectively; $p<0.0001$). This changed planned investigations (15% vs. 1%, $p<0.0001$) and treatments (23% vs. 5%, $p<0.0001$) but did not affect 6-week symptom severity or subsequent admittances to the hospital for chest pain. The authors concluded that the addition of CCTA to standard clinical care clarifies the diagnosis of angina due to CAD, reduces the need for further stress testing, increases the use of ICA, and results in more focused treatment regimes that are associated with an apparent reduction in fatal and non-fatal myocardial infarction. This study supports the findings of Douglas et al. 2015 (PROMISE study) included in the original assessment report that demonstrates that there is no statistically significant difference in the rates of MACE events occurring between a diagnostic pathway that utilises CCTA vs. functional testing and supports a diagnostic pathway based on CCTA. Please see table 2 for a breakdown of the results.

Quality appraisal

This is a large multicentre randomised clinical trial that included a broad and large population of patients who are representative of those referred to the cardiology clinic for assessment of suspected angina due to CAD. This study has a low risk of bias for flow and timing, and the index and reference tests. The authors obtained diagnostic information for 99% of patients. Finally, the authors included both short and long-term follow-up. Sample size calculations are reported along with CIs, and p values are presented for all outcomes.

4. Douglas (2015)

This is the publication of the PLATFORM study results at 3 months follow up that the manufacturer submitted in confidence during the previous assessment report period. The aim of this study was to compare the impact of FFR_{CT} in selecting symptomatic patients with intermediate pre-test likelihood of CAD for invasive coronary angiography (ICA) in comparison with functional imaging testing. The study included 584 patients recruited at 11 international centres. They were prospectively assigned to receive either functional testing (n=287) or CCTA/FFR_{CT} (n=297). Each cohort was subdivided into two groups based on the evaluation plan decided before enrolment in the study: non-invasive testing (any form of stress testing or CCTA without FFR_{CT}) or ICA. The primary end-point was the percentage of those with planned ICA in whom no significant obstructive CAD (no stenosis ≥50% by core laboratory quantitative analysis or invasive FFR<0.80) was found at ICA within 90 days. Secondary endpoints including death, myocardial infarction, and unplanned revascularisation were independently and blindly assessed. The authors concluded that FFR_{CT} was a feasible and safe alternative to ICA and was associated with a significantly lower rate of ICA showing no obstructive CAD. Please see table 2 for a breakdown of the results.

Quality appraisal

This is a large prospective consecutive cohort study utilising a comparative effectiveness observational design. This study has a low risk of bias for flow and timing, the index and reference tests. All analyses were done on the prospective allocation of patients into cohorts regardless of actual care. Use of an initial roll-in group of usual care ‘control’ patients provided a detailed, real-time snapshot of

contemporaneous practice at enrolling centres, rather than using historical controls. The authors conducted sensitivity analyses of the primary endpoint, yielding similar results, thus confirming that the results were free of verification bias. However, the sample size and follow-up duration are insufficient to detect an impact of FFR_{CT} on clinical outcomes.

5. Douglas (2016)

This is the publication of the PLATFORM study results at 1 year follow up. The aim of this study was to compare the impact of FFR_{CT} in selecting symptomatic patients with intermediate pre-test likelihood of CAD for ICA in comparison with functional imaging testing. The study included 584 patients recruited at 11 international centres. They were prospectively assigned to receive either functional testing (n=287) or CCTA/FFR_{CT} (n=297). Each cohort was subdivided into 2 groups based on the evaluation plan decided before enrolment in the study: non-invasive testing (any form of stress testing or CCTA without FFR_{CT}) or ICA. The endpoints reported in this publication were the adjudicated major adverse cardiovascular events (MACE), total medical costs, and quality of life (QOL). The authors concluded that in patients with stable chest pain and planned ICA, treatment guided by CCTA and selective FFR_{CT} was associated with equivalent clinical outcomes and quality of life and lower costs. Please see table 2 for a breakdown of the results.

Quality appraisal

This is a large prospective consecutive cohort study utilising a comparative effectiveness observational design. This study has a low risk of bias for flow and timing, the index and reference tests. All analyses were done on the prospective allocation of patients into cohorts regardless of actual care. Although this study was not randomised, propensity matching analyses of all endpoints yielded similar results. Use of an initial roll-in group of usual care ‘control’ patients provided a detailed, real-time snapshot of contemporaneous practice at enrolling centres, rather than using historical controls. However, the sample size and follow-up duration may be insufficient to detect an impact of FFR_{CT} on clinical outcomes.

6. Lu (2015)

Lu (2015) investigated the added value of FFR_{CT} in comparison with CCTA as a gatekeeper to improve efficiency of referral to ICA in a subgroup analysis (n=181) of the PROMISE trial retrospectively. In the PROMISE trial, patients were randomly assigned to either undergo CCTA or functional imaging as a first line diagnostic test. End points for this subgroup analysis were rate of revascularisation and ICA that did not show obstructive CAD and MACE. Over a median follow-up period of 25 months, the addition of FFR_{CT} increased the rate of ICA with revascularisation from 49% to 61%. The rate of angiography without obstructive disease decreased from 27% to 11%. No patient with $FFR_{CT} > 0.80$ had an adverse event which ICA would have prevented. The authors concluded that FFR_{CT} has the potential to improve efficiency of referral to ICA. Please see table 2 for a breakdown of the results.

Quality appraisal

This was a retrospective analysis of the PROMISE trial, a large prospective RCT with a median follow-up of 25 months submitted as a conference presentation. The CCTA and ICA were interpreted locally leading to possible bias for the reference test. A high number (30%) of CCTA tests 1/3 was not suitable for FFR_{CT} analysis leading to potential bias of the index test. CIs and sample size calculations were not reported.

7. Norgaard (2016)

Norgaard (2016) investigated the real-world clinical utility of FFR_{CT} for decision-making in patients (n=189) with stable CAD and intermediate-range coronary lesions. Patients were followed up for a median of 12 months. The primary endpoint was the impact of FFR_{CT} on further downstream diagnostic testing. Other endpoints were the agreement between FFR_{CT} and invasive FFR, and the short-term clinical outcome after FFR_{CT} testing defined as the occurrence of MACE (death and acute myocardial infarction) or an angina episode leading to hospital admission or visit in

the outpatient clinic. The authors concluded that FFR_{CT} testing is feasible in real-world patients with intermediate-range coronary stenosis determined by CCTA, that implementation of FFR_{CT} for clinical decision-making may influence the downstream diagnostic workflow and that patients with an FFR_{CT} >0.80 who are not referred for ICA have a favorable short-term prognosis. The authors also highlight that in patients with FFR_{CT} ranging between 0.76 and 0.80, a non-negligible number of false-positive results may be expected.

Quality appraisal

This was a single-centre, retrospective observational study. The data were collected in a non-selected cohort of patients (high risk of flow and timing) and the operators were not blinded to the FFRCT results (high risk of bias for the reference test). However, it included consecutive data from a relevant study cohort in a real-world setting. CIs and sample size calculation were not reported.

Table 1: Summary of key points from all included studies.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
The SCOT-HEART investigators (2015) The SCOT-HEART study NCT01149590	Prospective RCT, multi-centre, UK. Follow-up: 19 months	4146 symptomatic patients with suspected, but undiagnosed CAD Mean pre-test likelihood of CAD = unknown Patient characteristics: Age: CTA group 57.1±9.7 Functional testing group 57.0±9.7 Gender (males): CCTA group 1162 (56) Functional testing group 1163	CCTA ECHO SPECT MRI	Primary: proportion of patients diagnosed with angina pectoris secondary to CAD at 6 weeks Secondary: Resource utilisation Survival MACE Radiation dose	Medium. This study was considered to be of relevance to informing the decision problem. It confirms the results of the US-based PROMISE study with no significant differences noted in MACE events between CCTA and functional testing, while CCTA was

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		(56) BMI: CTA group 29.7±5.8 Functional testing group 29.8±6.0 Hypertension: CTA group 712 (34) Hypertension: functional testing group 683 (33) Diabetes: CTA group 223 (11) Functional testing group 221 (11)			associated with reduced ICA normalcy rates (fewer “false-positive” studies), and greater diagnostic certainty. CCTA was also associated with an increase in coronary revascularization rates (particularly of CABG), with a trend toward reduced death and myocardial infarction at 1 year.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Douglas (2015) The PLATFORM study NCT01943903	Prospective controlled comparative effectiveness observational, multi-centre, international Follow-up: 3 months	584 symptomatic patients with suspected, but undiagnosed CAD Mean pre-test likelihood of CAD = 49±17%, indicating an intermediate risk of CAD. Patient characteristics: Age: FFR_{CT} group 59.5±9.3 and 60.7±10.2 Functional testing group 57.9±10.7 and 63.4±10.9 Gender (women): FFRCT group 44 (42.3) and 74 (38.3) Functional testing group 34	CCTA/FFR_{CT} SPECT ECHO CCTA	Primary: 90-day rate of coronary angiogram showing no obstructive disease Secondary: (MACE) and MACE + vascular complications, all-cause death, non-fatal MI, resource utilization, quality of life (QOL) assessment (90 days, 180 days, 365 days), and	High This study showed that in patients with planned ICA, a diagnostic strategy based on CCTA/FFR_{CT} yielded a significantly lower rate of ICA showing no obstructive CAD. In patients with planned non-invasive testing, there was no difference between the use of CCTA/FFR_{CT} and

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		(34) and 79 (42.2) BMI: FFRCT group 27.3±3.9 and 27.1±3.9 Functional testing group 26.0±3.0 and 27.2±3.8 Hypertension: FFRCT group 57 (54.8) and 111 (57.5) Hypertension: functional testing group 38 (38) and 111 (59.4) Diabetes: FFRCT group 6 (5.8) and 30 (15.5) Functional testing group 8 (8) and 36 (19.3)		cumulative radiation exposure at 365 days.	usual care. Clinical events through 90 days were rare with either strategy. This study adds further evidence to the PROMISE and SCOT-HEART trials. Compared with PROMISE, the addition of FFRCT to CCTA prevented the reported 50% increase in ICA and revascularisations and led to a cancellation of ICA in

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
					61% of the FFR_{CT} arm and a lower rate of finding no obstructive CAD.
Douglas (2016) The PLATFORM study NCT01943903	Prospective controlled comparative effectiveness observational multi-centre, international Follow-up: 1 Year	Same population as Douglas (2015)	Same intervention and comparators as Douglas (2015)	MACE events at 1 year Cost savings at 1 year QOL at 1 year	High The study showed that in patients with planned ICA, patient care guided by CCTA/FFR_{CT} resulted in equivalent clinical outcomes, a greater increase in the EQ5D-assessed quality of life and lower costs.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
					In patients with planned ICA mean costs were 33% lower with a strategy incorporating CCTA and selective FFR_{CT}.
Lu (2015)	Retrospective observational cohort study international	181 Patients Age 61.8 ± 8.6 years Female 66 (36%) Racial/ethnic minority 18 (10%)	CCTA/FFR_{CT}	Efficiency of FFR_{CT} as gatekeeper to ICA (%ICA leading to revascularisation)	Medium Demonstrates that FFR_{CT} ≤0.80 could improve treatment efficiency by increasing the rate of ICA resulting in revascularisation from 49% to 61%.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
					Rate of ICA without obstructive disease decreased from 27% to 11%. No patient with FFR_{CT} > 0.80 had an adverse event which ICA would have prevented.
Nørgaard (2016)	Single-centre, observational Median follow up of 12 months	185 patients Patient characteristics: Age 57 ± 11 years Male 551 (47%)	CCTA/FFR_{CT}	Consequences on downstream diagnostic testing agreement between FFR_{CT} and invasive	Medium Demonstrates that FFR_{CT} testing is feasible in real-world symptomatic patients.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
		Diabetes 117 (10%) Hypertension 399 (10%) Hyperlipidaemia 340 (29%) Symptoms: Typical angina 152 (13%) Atypical angina 763 (65%) Non-anginal chest pain 176 (15%) Dyspnoea 82 (7%) Intermediate (20-80%) pre-test risk 844 (72%)		FFR Short-term clinical outcome after FFR_{CT}	No MACE events where recorded in cases with FFR_{CT}>0.8 in which ICA was deferred. A “normal” FFR_{CT} result was present in 69% of the patients, among whom ICA was successfully deferred. The coronary revascularization rate in patients with FFR_{CT} ≤0.80 was low (45%).

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Tanaka (2016)	Retrospective analysis of NXT trial sub-cohort Follow up: NA	18 patients with a total of 18 vessels Patient characteristics: Age: 60.0 ± 9 Gender (males): 17 (94) BMI: 26±4 Hypertension: 13 (72) Diabetes: 5 (28) Distal stenosis lesion: 43.6± 14.6 Proximal stenosis lesion: 50.3± 15.4	FFR_{CT} FFR	Per-segment correlation between FFR_{CT} and invasive FFR values	Low Serial coronary stenoses impact upon the hemodynamic significance of each other. This study addresses the issue of assessing sequential stenoses with FFR_{CT} that was raised in the technical evaluation report.

Study	Study design (country) Follow-up	Population (%)	Intervention and/or comparators	Outcomes considered	Usefulness to decision problem
Thompson (2015)	Retrospective analysis of DeFACTO trial sub-cohort Follow up: NA	252 patients Patient characteristics: Gender (males): 178 (70) Age: women 65.5 ± 8.6 Men: 61.9± 8.6 BMI: women 26±4.3 Men 27.0±3.5 Pre-test likelihood of CAD: women 58.5%±32 men 64.6%±34.6	FFR_{CT} FFR	Diagnostic accuracy	Medium This study provides evidence that age and sex do not impact on the diagnostic accuracy of FFR_{CT}.

Table 2: Clinical outcomes results of included studies.

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
The SCOT-HEART investigators (2015) The SCOT-HEART study NCT01149590	ECHO SPECT CCTA MRI	The use of CCTA was associated with the cancellation of 121 functional stress tests and 29 invasive coronary angiograms. Conversely, CCTA was associated with 94 further ICAs. The changes in diagnoses and investigations	After 1.7 years, CCTA was associated with a 38% reduction in fatal and non-fatal myocardial infarction (26 vs. 42, HR=0.62, 95% CI 0.38–1.01; p=0.0527), but this was not significant. Of those 1778	CCTA was not associated with an increase in the proportion of coronary revascularisation (11.2 vs. 9.7%; p=0.0611)	The median radiation dose was 4.1 (IQR 3·0–5·6) mSv, (dose-length product 291 [216–397] mGy.cm); more than a third (37%) of the dose was attributable to the measurement of the coronary artery calcium score.	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		were associated with changes in the subsequent recommendations for preventive (18% vs. 4% respectively; p<0.0001) and antianginal (9% vs. 1% respectively; p<0.0001) treatments	participants who underwent CCTA, 31 (2%) had an adverse event related to the CCTA (13 contrast reactions, 7 contrast extravasations, 4 vasovagal reactions, 4 headaches, and 3 other reactions). All adverse events were mild and self-limiting			

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
			with no cases of anaphylaxis or renal failure.			
Douglas (2015) The PLATFORM study NCT01943903	MRI SPECT ECHO CCTA	Among those with intended ICA (FFR_{CT}-guided=193; standard of care= 187), no obstructive CAD was found at ICA in 24 (12%) in the CCTA/FFR_{CT} arm and 137 (73%) in the standard of care arm (risk	Clinical event rates within 90 days were low between the standard of care and CCTA/FFR_{CT} arms.	NA	Among those intended for ICA, the mean cumulative radiation exposure (9.9 vs. 9.4 mSv, p=0.20) was similar between the 2 groups.	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		difference 61%, 95% CI= 53–69, p<0.0001) Among those intended for non-invasive testing, the rates of finding no obstructive CAD at ICA were 13% (CCTA/FFR_{CT}) and 6% (standard of care), p=0.95 Invasive coronary angiography was cancelled in 61% of the cases after				

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
		receiving CCTA/FFR_{CT} results.				
Douglas (2016) The PLATFORM study NCT01943903	MRI SPECT ECHO CCTA	NA	2 MACE events in each arm of the planned invasive group (risk difference -0.03 [CI -8.6 to +8.5]) and 1 in the planned noninvasive cohort (risk difference -1.00 [CI -12.7	NA	Cumulative 1-year radiation exposure in patients with an intended invasive evaluation was similar in the usual care cohort (mean: 10.4 ± 6.7 mSv) and FFR_{CT} cohort	Functional status and QOL improved from baseline to 1-year of follow-up in the planned noninvasive group ($p<0.001$ for all measures), with greater

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
			to +10.7]).		(mean: 10.7 ± 9.6 mSv), p=0.21. Cumulative 1-year radiation exposure in patients with an FFR_{CT}-guided evaluation was higher than in the usual care cohort (mean: 9.6 ± 10.6 mSv vs. 6.4 ± 7.6 mSv, p<0.001)	improvements in patients in the FFR_{CT} strategy group than the usual care group on the EQ-5D (mean change of 0.12 for FFR_{CT} vs. 0.07 for usual care, p=0.02)

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
Lu (2015)	CCTA FFR_{CT}	NA	NA	FFR_{CT} ≤0.80 resulted in better prediction of revascularisation and MACE than CCTA stenosis ≥70%. FFR_{CT} ≤0.80 as gatekeeper to ICA increased the % of ICA leading to PCI from 49%	NA	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
				to 61% Rate of angiography without obstructive disease decreased from 27% to 11% No patient with FFR_{CT} > 0.80 had an adverse event which ICA would have prevented		

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
Nørgaard (2016)	CCTA/FFR_{CT}	NA	Patients with an FFR_{CT} value >0.80 being deferred from invasive coronary angiography have a favourable short-term prognosis. There were no adverse cardiac events where FFR_{CT}>0.8 and ICA deferred. Median follow-	In patients with FFR_{CT} ≤0.80 being referred to ICA, 45% (22 of 49) underwent coronary revascularization	Cumulative radiation exposure, mSv ICA=8.8±6.6 FFR_{CT}=3.2±1.1	NA

Study	Index test(s)	Resource utilisation	MACE/Adverse events	Revascularisation rates	Radiation dose	QOL
			up time of 12 months.			

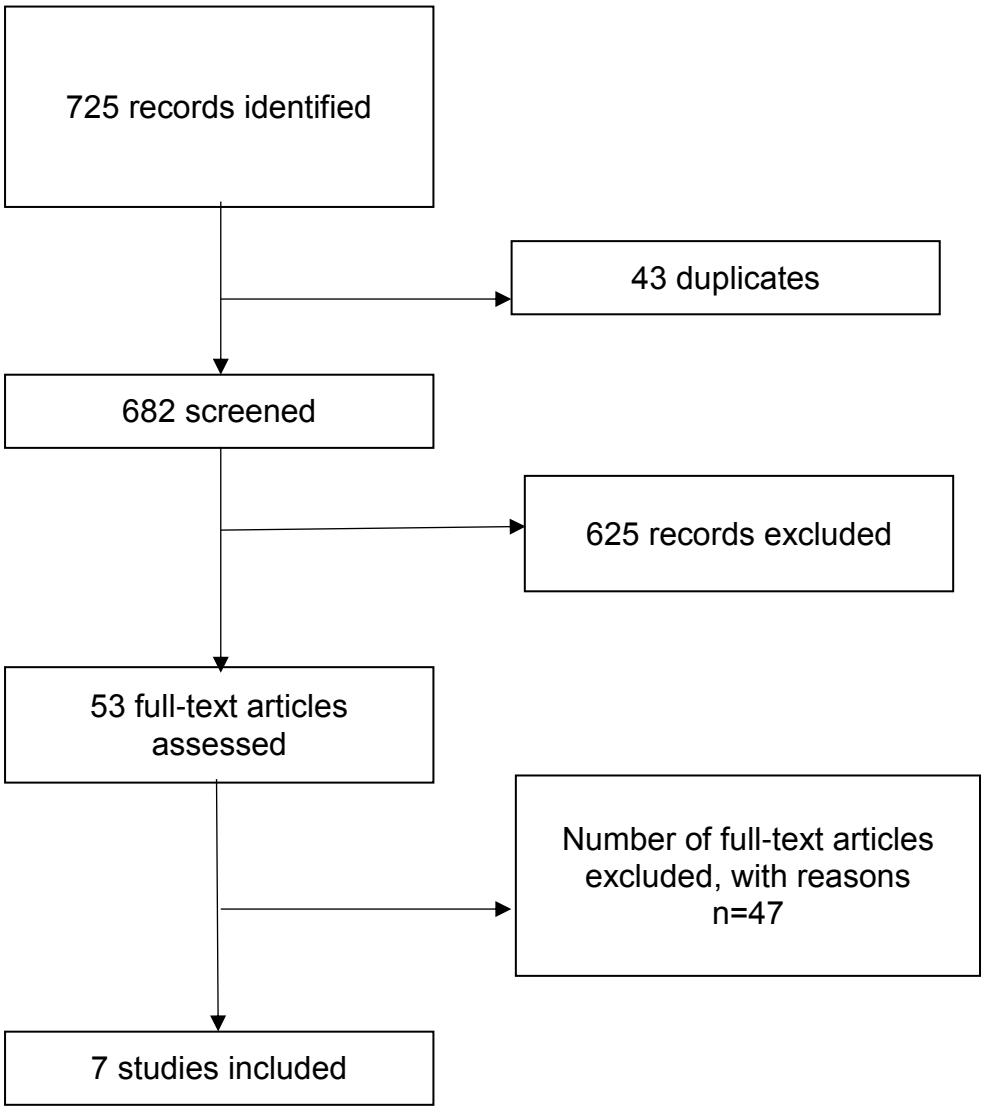
Conclusion of the clinical evidence

The External Assessment Centre considered that the new evidence submitted from the 1-year follow-up of the PLATFORM study supported the company's claims regarding resource use, rates of ICA and PCI, and quality of life in comparison with the standard of care cohort. Additionally, the 1-year follow-up evidence from the PLATFORM and PROMISE studies supports the company's claim that major adverse cardiac events are equivalent between a diagnostic pathway that utilises CCTA and FFRCT vs. functional-testing, and CCTA vs. functional imaging respectively. It also considered that the evidence from the PLATFORM study shows similar cumulative 1-year radiation exposure in patients intended for invasive evaluation but higher in the FFRCT cohort in patients intended for non-invasive evaluation. This finding is to be expected as many patients in the non-invasive evaluation received a noninvasive test which did not require the use of radiation. As a conclusion the submitted evidence on clinical outcomes supports the 'value proposition' of an FFRCT-guided strategy vs. standard of care, mainly in patients with planned invasive investigation, with equivalent results between FFRCT and functional imaging in the non-invasive cohort.

Table 3: Ongoing clinical studies with Heartflow.

Trial name	NCT number	Number of patients	Study Objectives
CREDENCE	NCT02173275	618	Direct head-to-head comparison of coronary CTA plus FFR_{CT} versus myocardial perfusion imaging by SPECT or PET
DECIDE-Gold	NCT02178904	156	Comparison of FFR_{CT} versus dual-energy CT rest/stress perfusion imaging
CONSERVE	NCT01810198	1500	Evaluation of FFR_{CT} as a "gatekeeper" to invasive coronary angiography (secondary aim)
ADVANCE	NCT02499679	ND	Prospective longitudinal registry to evaluate prognostic implications of FFR_{CT}

Figure 1: PRISMA flow diagram showing the EAC's search results for diagnostic accuracy and clinical outcomes.



Economic evidence update

Published economic evidence

In total, 273 publications were identified for title and abstract review in the updated search performed on 18 April 2016 (some of which were obtained in the original search). Based on inclusion and exclusion criteria, 22 studies were retrieved for further full text review. Four were excluded as they had been captured in the original search, 3 were excluded because they did not meet the population specified in the scope, 6 did not include FFR_{CT}, and 8 were not economic analysis studies (Figure 2). One study in the updated search (Hlatky et al. 2015) met the inclusion criteria for this literature review (Table 4).

Hlatky et al. (2015) investigated the quality of life (QoL) and economic outcomes of FFR_{CT} in the PLATFORM study (described in the Douglas et al. 2016 study summary). Hlatky et al. (2015) aimed to compare the costs and QoL of FFR_{CT} versus standard care to evaluate patients with suspected coronary artery disease. The study assessed QoL at baseline and 90 days using the 7-item Seattle Angina Questionnaire and the 5-item EuroQOL scale (EQ-5D) as well as a visual analogue scale. Cumulative medical costs were measured over 90 days for each patient by multiplying a standardised cost weight for each medical resource by the number of resources used by the individual patient. Medicare reimbursement rates (the national average of technical and professional fees in the US) from 2015 were applied as cost weights and online pharmacy costs were used for drugs. Patients were prospectively assigned to receive either standard of care testing (n=287) or CCTA/ FFR_{CT} (n=297). Mean costs were $7,343 (£4,993) among the FFR_{CT} patients and $10,734 (£7,299) among standard testing patients ($p<0.0001$). In the non-invasive stratum, mean costs were not significantly different ($p=0.26$) between the FFR_{CT} patients ($2,679; £1,822) and the standard care patients ($2,137; £1,453). Overall, each QoL score improved in the study population ($p<0.0001$) and QoL scores improved more in FFR_{CT} patients than in standard care patients. In the invasive cohort, the improvements in QoL were similar in the FFR_{CT} and standard care patients.

Quality Appraisal

The quality of the PLATFORM study is appraised under the Douglas et al. (2015) study in the 'Evidence update for technical validity, diagnostic accuracy and clinical outcomes' section. The economics portion of the study by Hlatky et al. (2015) examined the effect of the technology on both costs and QoL and appropriately compared it to the standard of care. The study was conducted in 11 European centres, however the practice patterns at these centres may have differed and the costs used US Medicare weights. The use of these costs may limit their generalisability to the UK. Costs were not discounted due to their short follow-up time frame (of 90 days). Sensitivity analyses increasing the cost of FFR_{CT} showed that the group consistently had lower costs when compared with the standard of care group in the invasive testing stratum.

Figure 2: PRISMA flow diagram showing the updated search results

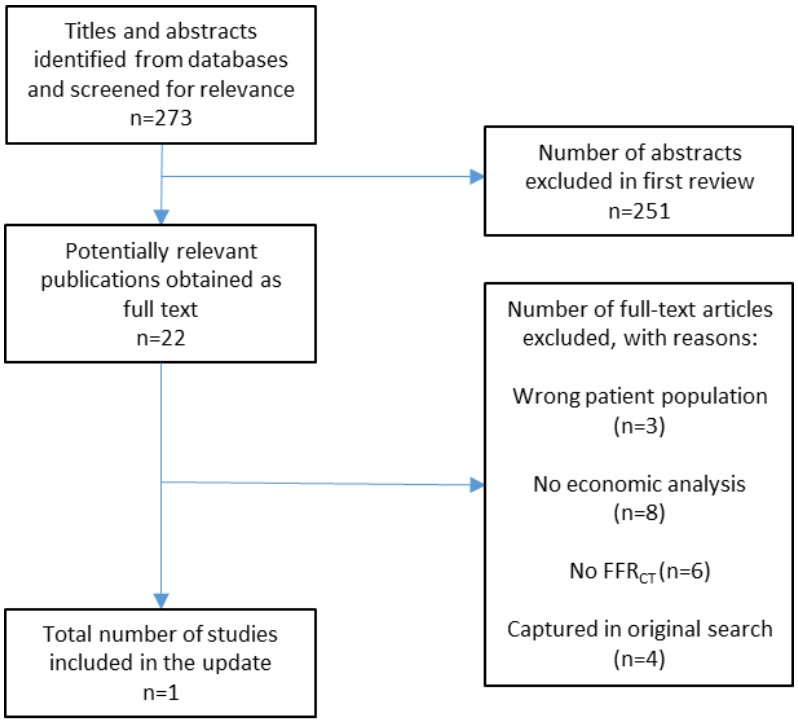


Table 4: Economic evaluation results of included study

Study	Study design (country)	Outcomes	Results	Sensitivity Analysis
Hlatky et al. (2015) The PLATFORM study	Prospective observational, multi-centre, international	Costs: enumerated the use of key medical resources from the time of enrolment through to the 90-day follow-up visit, and multiplied the cumulative costs for each patient by a standardised cost weight for each medical resource (using 2015 US Medicare reimbursement rates) Effects: Assessed quality of life at baseline and 90 days using the 7-item Seattle Angina Questionnaire and the 5-	Mean costs were $7,343 (£4,993) among FFR_{CT} patients and $10,734 (£7,299) among standard care patients ($p<0.0001$). In the non-invasive stratum, mean costs were not significantly different ($p=0.26$) between the FFR_{CT} patients ($2,679; £1,822) and the standard care patients ($2,137; £1,453). Overall, each QoL score improved in the study population ($p<0.0001$) and QoL scores improved more in FFR_{CT}	The cost weight for FFR_{CT} was set to 7 times the cost weight of CTA: $8,619 (£5,861) vs. $10,734 (£7,299) $p < 0.0001$) in the FFR_{CT} versus standard of care strategies. The costs equalised when the cost weight for FFR_{CT} was set to 20 times the

Study	Study design (country)	Outcomes	Results	Sensitivity Analysis
		item EuroQOL scale (EQ-5D) and a visual analogue scale.	patients than in standard care patients. In the invasive cohort, the improvements in QoL were similar in the FFR_{CT} and standard care patients.	cost weight for CTA.

MT252 –Cost Model Update

The NICE guideline on chest pain (NICE clinical guideline CG95) was reviewed in December 2014 and new evidence was identified relating to the use of non-invasive tests for the diagnosis of CAD in people with stable chest pain of suspected cardiac origin. The review also identified new evidence on clinical prediction models which may impact the assessment of the pre-test likelihood of CAD in this population. Based on the evidence and economics analysis, changes have been made to the clinical guideline. The most important recommendation was offering 64-slice (or above) coronary CT angiograph (CCTA) to patients with features of typical or atypical angina based on clinical assessment, irrespective of pre-test likelihood scoring (10-90%). This was based on economic analysis undertaken as part of the clinical guidance review which showed that CCTA had the lowest cost per correct diagnosis for all pre-test likelihood groups (10-29%, 30-60% & 61-90%) for both 50% and 70% stenosis thresholds. The use of non-invasive functional imaging for myocardial ischaemia was recommended if 64-slice (or above) CCTA indicates CAD of uncertain functional significance or is non-diagnostic. The updated guideline also recommends offering invasive coronary angiography (ICA) as a second-line investigation when the results of non-invasive functional imaging are inconclusive.

Implications for the Heartflow model

Based on the new recommendations in the revised chest pain guideline, the Heartflow cost model submitted by the sponsor and subsequently revised by the EAC has been updated. The key changes to the model are as follows.

1. Different pathways (from CG95) for the three likelihood groups have now been replaced with a single pathway (Figure 2). All the patients with pre-test likelihood of 10-90% are now offered 64-slice (or above) CCTA as the first line investigation. Functional imaging is offered following uncertain CCTA results and ICA is offered if the results of functional imaging are also uncertain.
2. The updated pathway is similar to the 10-29% pathway in CG95, except that calcium scoring is not included. CT calcium scoring has been excluded because topic experts who contributed to the chest pain economic model

advised that this would rarely be carried out in isolation from a full CCTA in practice. The Heartflow model also excludes isolated calcium scoring.

3. Two strategies are compared in the updated model 1) using CCTA to inform treatment of stable angina and 2) using FFR_{CT} (Heartflow) after a positive CCTA result to inform treatment. The square box in the model structure denotes a decision node, circles denote chance nodes and triangles denote terminal nodes which indicate treatment for stable angina with either percutaneous coronary intervention (PCI) or optimal medical therapy. The time horizon for the model is 1 year to capture the impact of diagnosis on initial treatment.
4. The diagnostic accuracy for CCTA, ICA and functional imaging are estimates from the EAC meta-analysis of per-patient based diagnostic accuracy. The EAC did not use the estimates from the clinical guideline because the EAC meta-analysis is based on studies relevant to the Heartflow technology. However, the updated cost model has been subjected to sensitivity analysis using values taken from the economic model in the revised clinical guideline.
5. In the chest pain economic model in the revised guideline, test costs are taken from the most recent NHS reference costs (Table 5). These costs have also been updated in the Heartflow model. It should be noted that the cost of cardiac magnetic resonance imaging (CMR) is taken from the Payment by Results tariff rather than the reference cost, since the chest paint guideline committee determined that the reference cost for CMR was not representative of its true cost. The tariff is believed to better represent the cost of CMR.

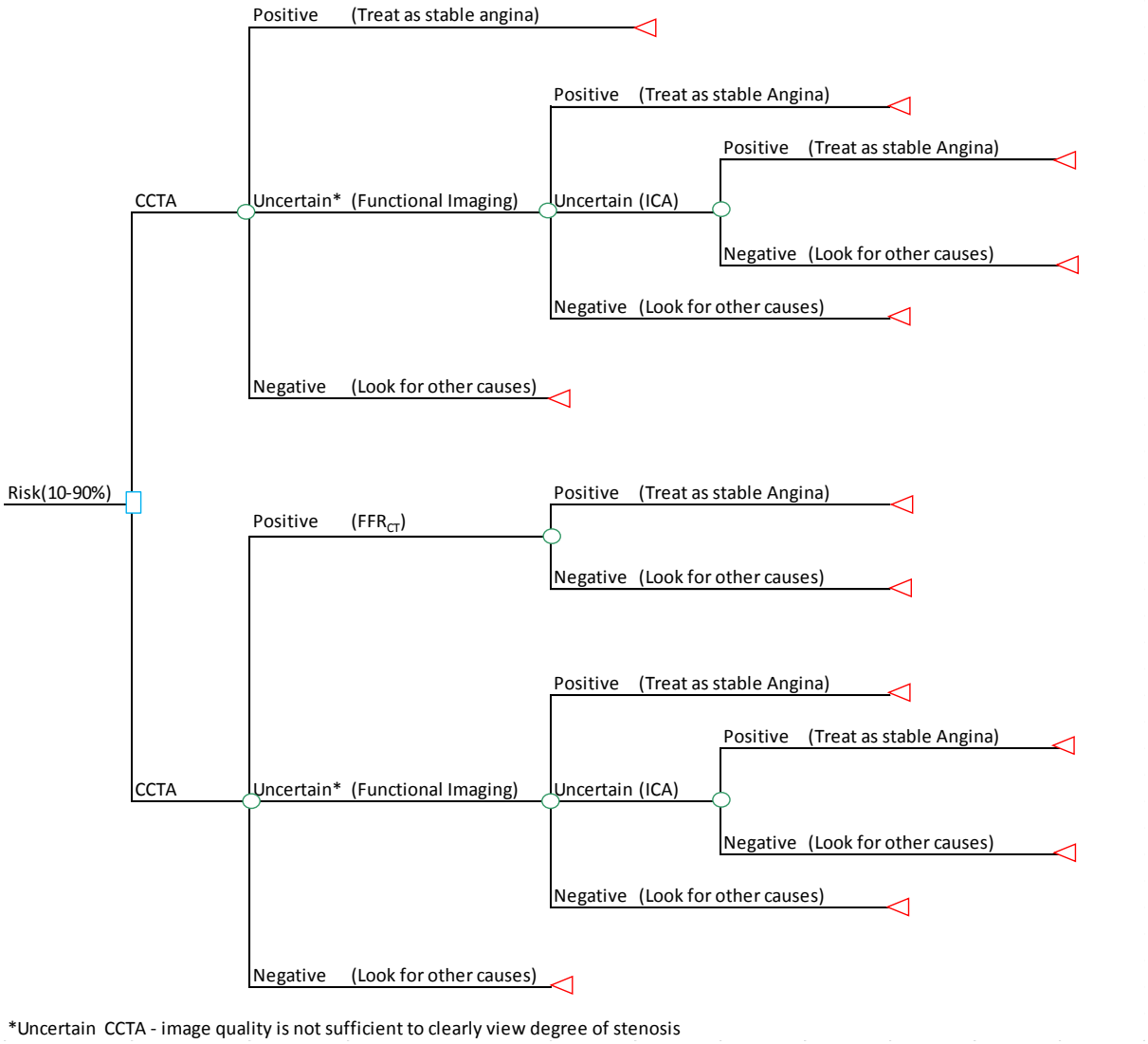


Figure 3: Updated chest pain model structure

Table 5: Cost of tests used in the updated chest pain economic model

Test	Code, description	Source	Amount
ICA	EY43A to EY43F, Standard cardiac catheterisation	NHS Reference Costs 2014-15, weighted average	£1685
CCTA	RD28Z, Complex computerised tomography scan	NHS Reference Costs 2014-15	£122
SPECT	RN21Z, Myocardial perfusion scan, stress only	NHS Reference Costs 2014-15	£367
ECHO	EY50Z, Complex echocardiogram	NHS Reference Costs 2014-15	£271
CMR	RA67Z, Cardiac magnetic resonance imaging scan, pre and post contrast	Enhanced Tariff Option 2015-16	£515

Results

Base case

The average total cost per patient tested following the updated NICE guideline adapted to incorporate FFR_{CT} compared to the updated NICE guideline alone is presented in Table 6. Three separate model results using different functional imaging techniques (SPECT, MRI and ECHO) have been estimated by the EAC. The results show that the adapted pathway using FFR_{CT} has a cost saving of £214, irrespective of the functional imaging test used. This is because functional imaging is applied downstream from the identification of CT positive patients who might benefit from FFR_{CT} to the group of patients with uncertain CT results not eligible for FFR_{CT} and hence the impact on costs is independent of the decision to undertake FFR_{CT}. The cost savings from FFR_{CT} occur as a result of ICA and PCI avoided (46-48%) by the

use of Heartflow technology. The main drivers of the cost are the diagnostic accuracy of CCTA, ICA and FFR_{CT} and the price of the technology.

Table 6: Base case results (patient based)

	Average total cost per patient (patient based)		
	(Functional Imaging: SPECT) Model	**(Functional Imaging: MRI) Model**	**(Functional Imaging: ECHO) Model**
NICE Updated Guideline	£1,321	£1,301	£1,259
Adapted NICE Guideline using FFR_{CT}	£1,107	£1,087	£1,045
Difference (cost saving)	£214	£214	£214

Sensitivity analysis

Table 7 reports the impact of sensitivity analysis on the results for a number of variables. None of the analyses change the conclusion that Heartflow technology saves costs. Of interest is the price of the technology. The sponsor reduced the price of the technology to £700 from its original listing of £888 during assessment. Even at the original list price, the technology is cost saving (£139). The EAC also used estimates of diagnostic accuracy of CCTA and ICA used in the revised chest pain guideline economic model (highlighted in yellow) in the sensitivity analysis. The meta-analysis estimates from the chest pain guideline for functional imaging were not used in the sensitivity analysis, since diagnostic accuracy of functional imaging did not affect the cost savings at all. Using the meta-analysis estimates from the chest pain economic model did not change the cost savings conclusion of the technology. Heartflow remains cost saving in all scenarios.

Table 7: Sensitivity Analysis

Cost Savings by Price of FFR_{CT}

Price HeartFlow		SPECT	MRI	ECHO
£ 500		-£293	-£293	-£293
£ 600		-£253	-£253	-£253
£ 700		-£214	-£214	-£214
£ 800		-£174	-£174	-£174
£ 888		-£139	-£139	-£139
£ 1,000		-£94	-£94	-£94
£ 1,200		-£15	-£15	-£15

Cost Savings by Dx Sensitvity of FFR_{CT}

Dx Sensitivity FFR_{CT}	SPECT	MRI	ECHO
76%	-£255	-£255	-£255
78%	-£247	-£247	-£247
80%	-£239	-£239	-£239
84%	-£222	-£222	-£222
86%	-£214	-£214	-£214
88%	-£206	-£206	-£206
90%	-£198	-£198	-£198
92%	-£189	-£189	-£189
93%	-£185	-£185	-£185

Cost Savings by Dx Specificity of FFR_{CT}

Dx Specificity FFR_{CT}	SPECT	MRI	ECHO
72%	-£176	-£176	-£176
73%	-£181	-£181	-£181
74%	-£187	-£187	-£187
77%	-£203	-£203	-£203
79%	-£214	-£214	-£214
81%	-£225	-£225	-£225
83%	-£236	-£236	-£236
85%	-£247	-£247	-£247

Cost Savings by Dx Sensitivity of Functional Imaging

Dx Sensitivity	SPECT		MRI		ECHO	
63%	-£214	81%	-£214	33%	-£214
65%	-£214	84%	-£214	35%	-£214
68%	-£214	87%	-£214	40%	-£214
71%	-£214	89%	-£214	43%	-£214
73%	-£214	91%	-£214	45%	-£214
76%	-£214	93%	-£214	47%	-£214
79%	-£214	95%	-£214	54%	-£214
81%	-£214	97%	-£214	57%	-£214

Cost Savings by Dx Specificity of Functional Imaging

Dx Specificity	SPECT		MRI		ECHO	
60%	-£214	81%	-£214	85%	-£214
61%	-£214	84%	-£214	86%	-£214
63%	-£214	87%	-£214	87%	-£214
65%	-£214	89%	-£214	89%	-£214
67%	-£214	91%	-£214	90%	-£214
69%	-£214	93%	-£214	91%	-£214
71%	-£214	95%	-£214	92%	-£214
73%	-£214	97%	-£214	93%	-£214
74%	-£214			94%	-£214

Cost Savings by Dx Sensitivity of CCTA

Dx Sensitivity of CCTA	SPECT	MRI	ECHO
92%	-£215	-£215	-£215
93%	-£215	-£215	-£215
94%	-£214	-£214	-£214
95%	-£214	-£214	-£214
96%	-£213	-£213	-£213
97%	-£212	-£212	-£212

Cost Savings by Dx Specificity of CCTA

Dx Specificity CCTA	SPECT	MRI	ECHO
65%	-£243	-£243	-£243
66%	-£235	-£235	-£235
67%	-£226	-£226	-£226
68%	-£214	-£214	-£214
69%	-£208	-£208	-£208
70%	-£200	-£200	-£200
71%	-£191	-£191	-£191
72%	-£182	-£182	-£182
78%	-£130	-£130	-£130

Cost Savings by Dx Sensitivity of ICA

Dx Sensitivity of ICA	SPECT	MRI	ECHO
52%	-£200	-£200	-£200
54%	-£203	-£203	-£203
58%	-£207	-£207	-£207
62%	-£212	-£212	-£212
64%	-£214	-£214	-£214
66%	-£216	-£216	-£216
70%	-£221	-£221	-£221
72%	-£223	-£223	-£223
74%	-£225	-£225	-£225
100%	-£255	-£255	-£255

Cost Savings by Dx Specificity of ICA

Dx Specificity ICA	SPECT	MRI	ECHO
76%	-£244	-£244	-£244
77%	-£240	-£240	-£240
79%	-£231	-£231	-£231
81%	-£222	-£222	-£222
83%	-£214	-£214	-£214
85%	-£204	-£204	-£204
86%	-£199	-£199	-£199
87%	-£195	-£195	-£195
88%	-£190	-£190	-£190
100%	-£136	-£136	-£136

Cost Savings by Functional Test Uncertain proportion

Functional uncertain	SPECT	MRI	ECHO
1%	-£214	-£214	-£214
5%	-£214	-£214	-£214
7%	-£214	-£214	-£214
10%	-£214	-£214	-£214
12%	-£214	-£214	-£214
15%	-£214	-£214	-£214
20%	-£214	-£214	-£214

Cost Savings by CCTA Uncertain proportion

CCTA uncertain	SPECT	MRI	ECHO
1%	-£235	-£235	-£235
5%	-£225	-£225	-£225
7%	-£221	-£221	-£221
10%	-£214	-£214	-£214
12%	-£209	-£209	-£209
15%	-£202	-£202	-£202
20%	-£190	-£190	-£190

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