institute for Medical Technology Assessment

Validation of health economic models and its impact on reimbursement decisions – does it make it a NICE case study?

Isaac Corro Ramos

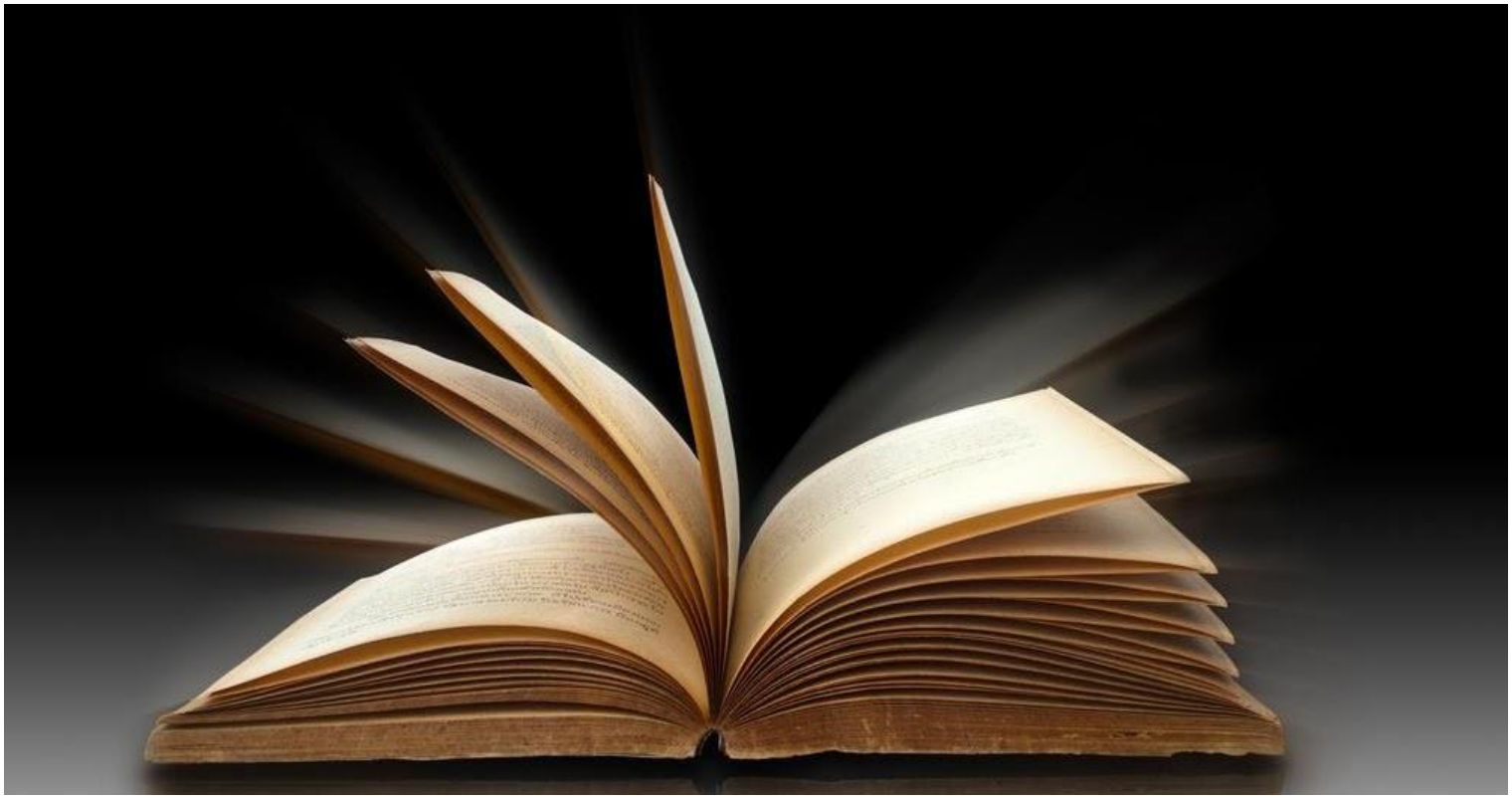
Virtual ISPOR 2021

30-11-2021

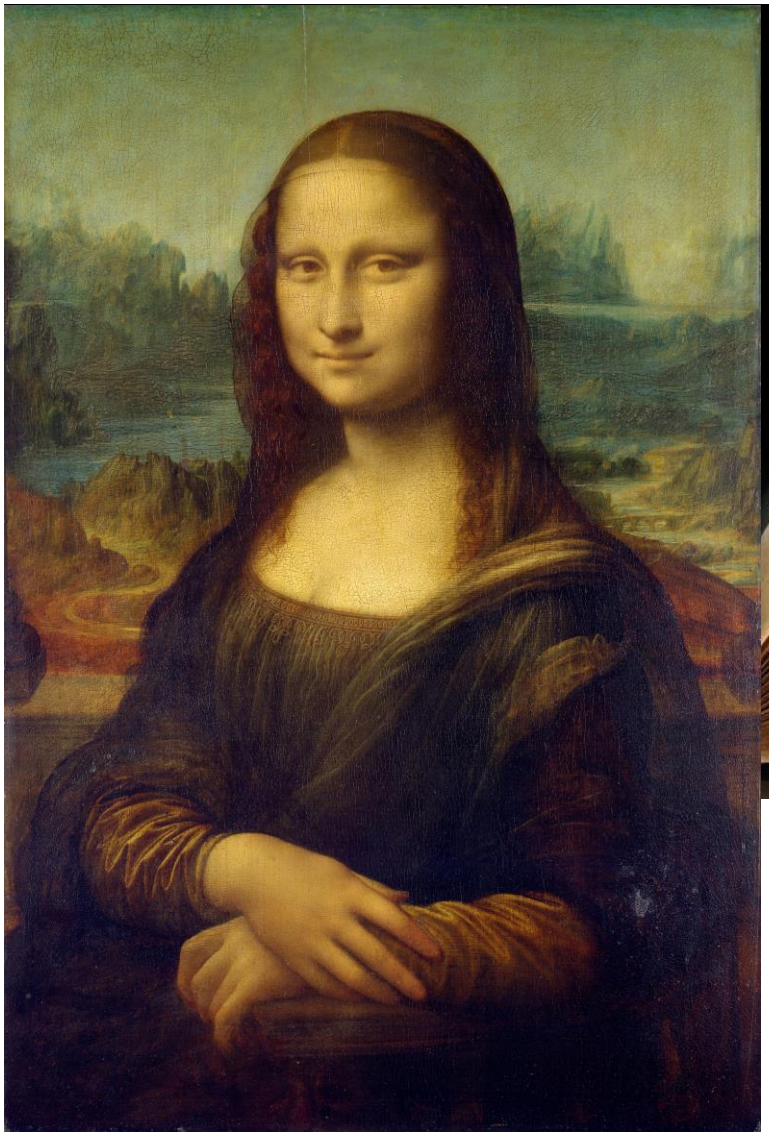
ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

What is nice vs. what NICE is?

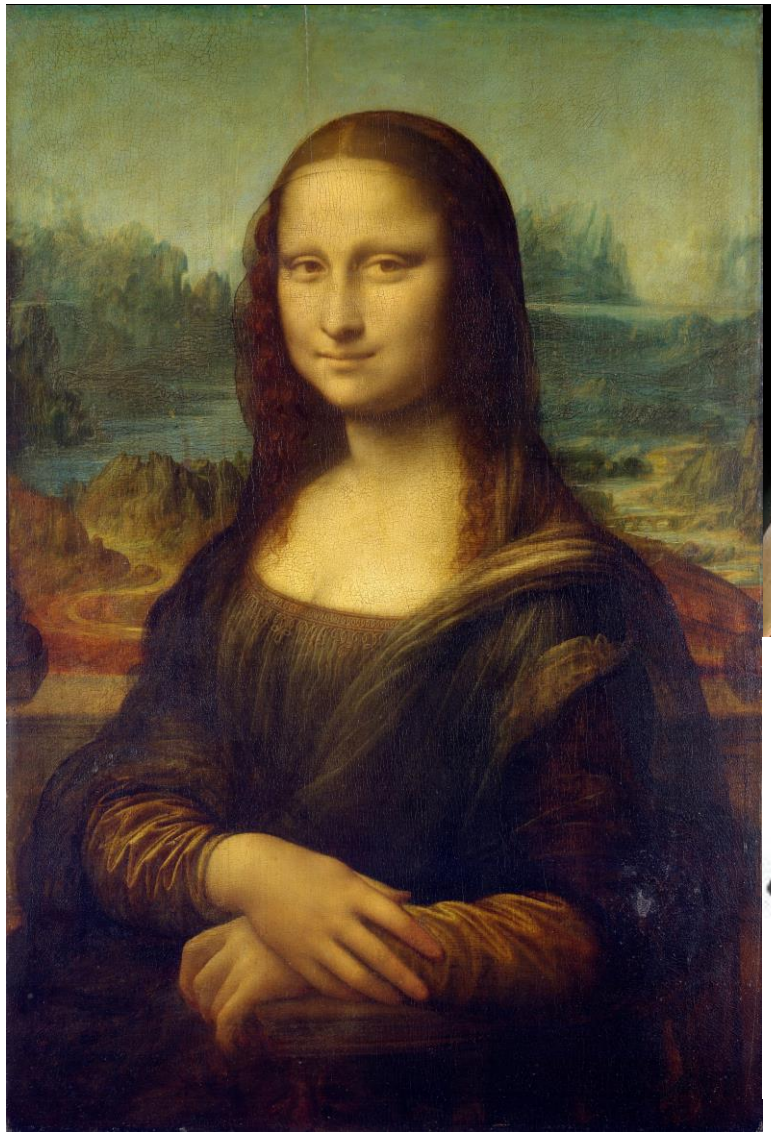
What is nice vs. what NICE is?



What is nice vs. what NICE is?



What is nice vs. what NICE is?



What is nice vs. what NICE is?

What NICE is?

institute for Medical Technology Assessment

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Read about our approach to COVID-19

Guidance

Evidence-based recommendations developed by independent committees, including professionals and lay members, and consulted on by stakeholders.

View all guidance

Get involved

We want you to be involved in our work. Tell us what matters to you, your organisation or your community.

There are many ways you can get involved as a healthcare professional or a member of the public.

About us

Find out more about

- who we are
- what we do

and how we support

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

What NICE is?

institute for Medical Technology Assessment

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Read about our approach to COVID-19

Guidance

Evidence-based recommendations developed by independent committees, including professionals and lay members, and consulted on by stakeholders.

View all guidance

Get involved

We want you to be involved in our work. Tell us what matters to you, your organisation or your community.

There are many ways you can get involved as a healthcare professional or a member of the public.

About us

Find out more about

- who we are
- what we do

and how we support

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

What NICE is?

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Technology appraisal guidance

Technology appraisals are recommendations on the use of new and existing medicines and treatments within the NHS.

institute for Medical Technology Assessment

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

What NICE is?

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Technology appraisals take one of 3 forms:

- A single technology appraisal (STA) which covers a single technology for a single indication.
- A fast track appraisal (FTA) which also covers a single technology for a single indication but with a shorter process time to speed up access to the most cost-effective new treatments.
- A multiple technology appraisal (MTA) which normally covers more than one technology, or one technology for more than one indication.

What NICE is?

institute for Medical Technology Assessment

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Technology appraisals take one of 3 forms:

- A single technology appraisal (STA) which covers a single technology for a single indication.
- A fast track appraisal (FTA) which also covers a single technology for a single indication but with a shorter process time to speed up access to the most cost-effective new treatments.
- A multiple technology appraisal (MTA) which normally covers more than one technology, or one technology for more than one indication.

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Objectives

- Review on validation efforts reported within NICE technology appraisals
- Determine whether validation efforts might have had any influence on NICE recommendations

Validation efforts in NICE TAs

institute for Medical Technology Assessment

NICE National Institute for Health and Care Excellence

Search NICE...

Sign in

NICE Pathways | NICE guidance | Life sciences | Standards and indicators | Evidence search | BNF | BNFC | CKS | Journals and databases

Read about our approach to COVID-19

Home > About > What we do > Our programmes > NICE guidance > Technology appraisal guidance > Technology appraisal processes

Single technology appraisal (STA) timeline

These are the main stages in the single technology appraisal (STA) process.

Timings are approximate. For a full description of the appraisal process, please see our process guide and methods guide.

Topics are referred to us by ministers following the topic selection process.

We started using this process in April 2018.

- View the STA process we used before April 2018
- View the timeline for multiple technology appraisals

Timeline

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Validation efforts in NICE TAs

institute for Medical Technology Assessment

Timeline

wk0

Development starts

We invite relevant stakeholders to take part in the appraisal.

All non-company consultees have 8 weeks to submit a statement on the potential clinical and cost effectiveness of a treatment.

› Find out more about consultee submissions

Organisations can apply to become a consultee or commentator at any point of the process.

wk0

Request for evidence

We ask the intervention technology company to produce a submission of all relevant evidence - published and unpublished - for the appraisal.

They have 8 weeks to produce the company submission.

› Find out more about evidence submissions

institute for Medical Technology Assessment

Validation efforts in NICE TAs

Timeline

wk0

Development starts

We invite relevant stakeholders to take part in the appraisal.

All non-company consultees have 8 weeks to submit a statement on the potential clinical and cost effectiveness of a treatment.

› Find out more about consultee submissions

Organisations can apply to become a consultee or commentator at any point of the process.

wk0

Request for evidence

We ask the intervention technology company to produce a submission of all relevant evidence - published and unpublished - for the appraisal.

They have 8 weeks to produce the company submission.

› Find out more about evidence submissions

Validation efforts in NICE TAs

institute for Medical Technology Assessment

wk8

Deadline for evidence submissions

wk9

Evidence review begins

An independent academic centre (called the Evidence Review Group) critiques the company's evidence submission and prepares a report on the clinical- and cost-effectiveness of the technology. This is called the ERG report.

wk10

Request for clarification sent to company

If the evidence submission is incomplete, we consult with the Evidence Review Group and send a letter of clarification to the company.

The company has 10 working days to respond.

wk12

Deadline for receipt of the expert statements

wk16

Evidence report (ERG) received by NICE

Validation efforts in NICE TAs

institute for Medical Technology Assessment

wk8

Deadline for evidence submissions

wk9

Evidence review begins

An independent academic centre (called the Evidence Review Group) critiques the company's evidence submission and prepares a report on the clinical- and cost-effectiveness of the technology. This is called the ERG report.

wk10

Request for clarification sent to company

If the evidence submission is incomplete, we consult with the Evidence Review Group and send a letter of clarification to the company.

The company has 10 working days to respond.

wk12

Deadline for receipt of the expert statements

wk16

Evidence report (ERG) received by NICE

Validation efforts in NICE TAs

institute for Medical Technology Assessment

wk8

Deadline for evidence submissions

wk9

Evidence review begins

An independent academic centre (called the Evidence Review Group) critiques the company's evidence submission and prepares a report on the clinical- and cost-effectiveness of the technology. This is called the ERG report.

wk10

Request for clarification sent to company

If the evidence submission is incomplete, we consult with the Evidence Review Group and send a letter of clarification to the company.

The company has 10 working days to respond.

wk12

Deadline for receipt of the expert statements

wk16

Evidence report (ERG) received by NICE

institute for Medical Technology Assessment

wk28

Documents sent to the appraisal committee

The appraisal committee is an independent advisory committee that makes the recommendations.

We send attendees:

- the ERG report and any comments
- the company submission
- written submissions from non-company consultees
- personal statements from patient, clinical and commissioning experts
- the final scope of the appraisal and the list of stakeholders
- technical report
- comments received during technical engagement.

We don't send the papers to any members of the public who have registered to attend the meeting.

› Find out more about the committee and how you can attend a meeting.

institute for Medical Technology Assessment

wk28

Documents sent to the appraisal committee

The appraisal committee is an independent advisory committee that makes the recommendations.

We send attendees:

- the ERG report and any comments
- the company submission
- written submissions from non-company consultees
- personal statements from patient, clinical and commissioning experts
- the final scope of the appraisal and the list of stakeholders
- technical report
- comments received during technical engagement.

We don't send the papers to any members of the public who have registered to attend the meeting.

› Find out more about the committee and how you can attend a meeting.

institute for Medical Technology Assessment

wk28

Documents sent to the appraisal committee

The appraisal committee is an independent advisory committee that makes the recommendations.

We send attendees:

- the ERG report and any comments
- the company submission
- written submissions from non-company consultees
- personal statements from patient, clinical and commissioning experts
- the final scope of the appraisal and the list of stakeholders
- technical report
- comments received during technical engagement.

We don't send the papers to any members of the public who have registered to attend the meeting.

› Find out more about the committee and how you can attend a meeting.

institute for Medical Technology Assessment

wk30

Appraisal committee meet to consider the evidence

We hold an appraisal committee meeting to consider the committee papers and hear from nominated clinical, patient and NHS commissioning experts.

The committee decides whether to produce final recommendations, known as a final appraisal document (FAD) or draft recommendations known as an appraisal consultation document (ACD).

The FAD is the final draft of the guidance and not open to comment (see week 35).

If an ACD is needed we send the document out for comment (see week 33).

We only produce an ACD when the recommendations from the appraisal committee don't recommend use of the technology, or limit the use of the technology beyond the specifications in the marketing authorisation.

Part 1 of this meeting is open to members of the public and press.

› Register to attend a meeting

For non-cancer topics, the committee meeting cannot go ahead until the Committee for Medicinal Products for Human Use (CHMP) opinion is published.

institute for Medical Technology Assessment

wk30

Appraisal committee meet to consider the evidence

We hold an appraisal committee meeting to consider the committee papers and hear from nominated clinical, patient and NHS commissioning experts.

The committee decides whether to produce final recommendations, known as a final appraisal document (FAD) or draft recommendations known as an appraisal consultation document (ACD).

The FAD is the final draft of the guidance and not open to comment (see week 35).

If an ACD is needed we send the document out for comment (see week 33).

We only produce an ACD when the recommendations from the appraisal committee don't recommend use of the technology, or limit the use of the technology beyond the specifications in the marketing authorisation.

Part 1 of this meeting is open to members of the public and press.

› Register to attend a meeting

For non-cancer topics, the committee meeting cannot go ahead until the Committee for Medicinal Products for Human Use (CHMP) opinion is published.

Let's take a (small) break…

Poll question 1, Multiple choice

- What is the chance that a cancer submission to NICE gets a *positive recommendation at the first appraisal committee meeting (ACD)*?
  - Less than 5%
  - More than 5% but less than 30%
  - More than 30% but less than 50%
  - More than 50%

Poll question 2, Multiple choice

- What is the chance that a cancer submission to NICE gets a *positive recommendation at the first appraisal committee meeting (ACD) if some validation issues have been identified*?
  - Less than 5%
  - More than 5% but less than 30%
  - More than 30% but less than 50%
  - More than 50%

Poll question 3, Multiple choice

- What is the chance that a cancer submission to NICE, for which some validation issues were identified at the first appraisal committee meeting (ACD), *reports an ICER within the acceptable range of thresholds*?
  - Less than 5%
  - More than 5% but less than 30%
  - More than 30% but less than 50%
  - More than 50%

Role of validation in NICE TAs

institute for Medical Technology Assessment

Guide to the methods of technology appraisal 2013

Process and methods [PMG9] Published: 04 April 2013

Process and methods

5 The reference case

Role of validation in NICE TAs

institute for Medical Technology Assessment

Guide to the methods of technology appraisal 2013

Process and methods [PMG9] Published: 04 April 2013

Foreword

5.7.4 The methods of quality assurance used in the development of the model should be detailed and the methods and results of model validation should be provided. In addition, the results from the analysis should be presented in a disaggregated format and should include a tabular presentation of information on estimates of life-years gained, mortality rates (at separate time points if appropriate) and the frequency of selected clinical events predicted by the model.

Review of NICE TAs

institute for Medical Technology Assessment

Published

Guidance, NICE advice and quality standards

Published | In consultation | In development | Proposed

Filter by title or keyword: cancer [Filter]

Filter (3 active)

Last updated date

From date: dd / mm / yyyy

To date: dd / mm / yyyy

Apply date filters

Showing 1 to 10 of 218

Date | Title

cancer ✖ Type: Guidance ✖ Type: Quality standard ✖

Title	Reference number	Published	Last updated
Selpercatinib for treating advanced thyroid **cancer** with RET alterations	TA742	3 November 2021	3 November 2021
Apalutamide with androgen deprivation therapy for treating high-risk hormone-relapsed non-metastatic prostate **cancer**	TA740	28 October 2021	28 October 2021
Apalutamide with androgen deprivation therapy for treating hormone-sensitive metastatic prostate **cancer**	TA741	28 October 2021	28 October 2021

ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Review of NICE TAs

Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small-cell lung cancer

Technology appraisal guidance [TA724] Published: 08 September 2021

Guidance | Tools and resources | Information for the public | Evidence | History

History

A list of downloadable documents created during development.

Expected publication

- Equality Impact Assessment (Guidance development) PDF 139 KB
  08 September 2021

Invitation to participate

- Final scope PDF 232 KB
  07 July 2020

Final appraisal document

- Final appraisal document
- Final appraisal document PDF 332 KB
  06 August 2021
- Committee papers PDF 1.68 MB
  06 August 2021

Appraisal consultation

- Appraisal consultation
- Committee papers PDF 10.52 MB
  08 April 2021
- Public committee slides PDF 708 KB
  08 April 2021

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Review of NICE TAs

- March 2020: 489 published TAs
- Unfeasible to review all. Focused on cancer appraisals: 114 in total
- Terminated (by the company) appraisals excluded.
- TAs not provided sufficient information about validation, also excluded
- Final: 79 TAs included

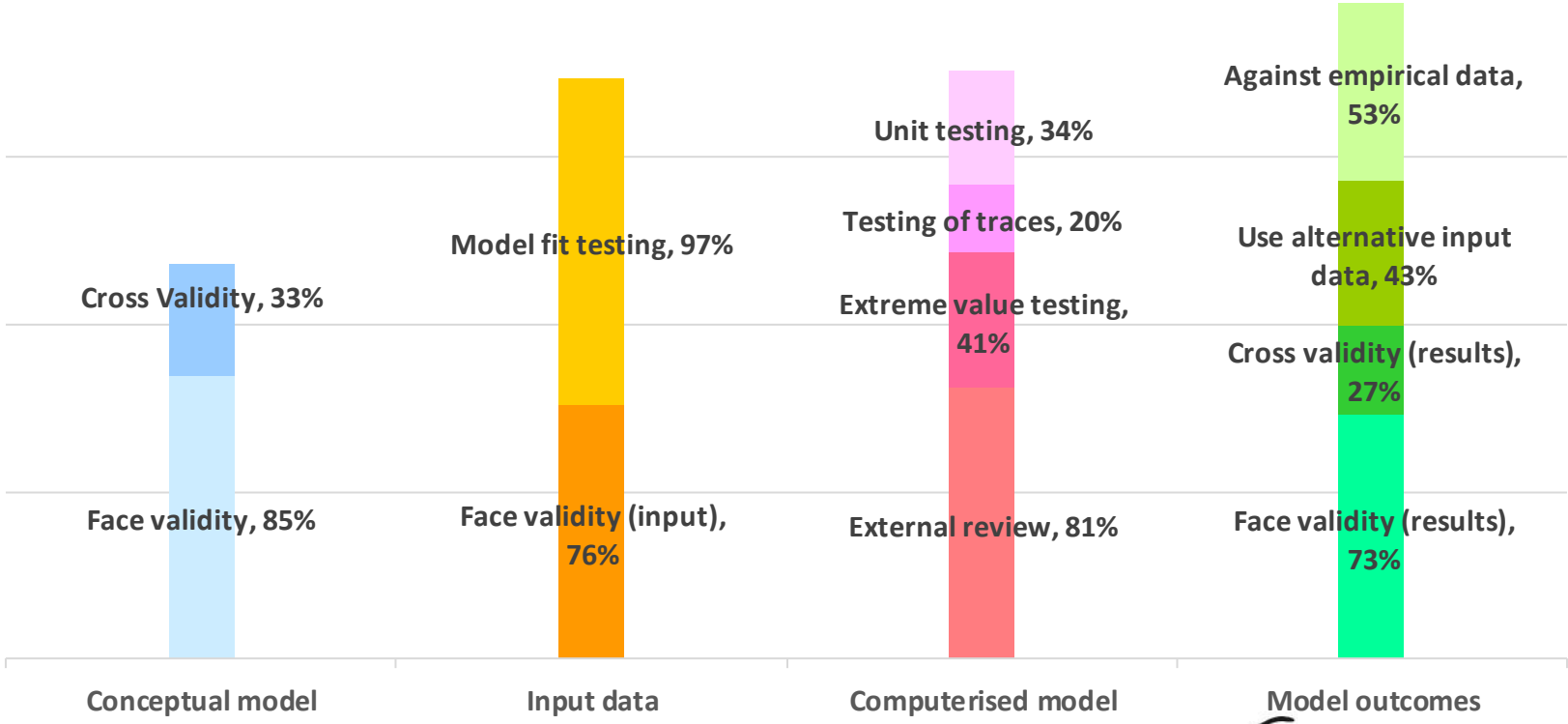
Important documents

- Validation efforts
  - Company submission (including a cost-effectiveness model)
  - ERG report
- Validation issues
  - ACD
  - FAD

Results - Validation efforts in NICE TAs

institute for Medical Technology Assessment

AdViSHE



ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Results – Validation and recommendations

		Recommended at ACD		Recommended at FAD		
		No	Yes	No	Yes	Total
Validation perceived as issue	No	26 (32.9%)	21 (26.6%)	0 (0%)	26 (32.9%)	47 (59.5%)
	Yes	32 (40.5%)	0 (0%)	9 (11.4%)	23 (29.1%)	32 (40.5%)
	Total	58 (73.4%)	21 (26.6%)	9 (11.4%)	49 (62%)	79 (100%)

Results – Validation and recommendations

		Recommended at ACD		Recommended at FAD		
		No	Yes	No	Yes	Total
Validation perceived as issue	No	26 (32.9%)	21 (26.6%)	0 (0%)	26 (32.9%)	47 (59.5%)
	Yes	32 (40.5%)	0 (0%)	9 (11.4%)	23 (29.1%)	32 (40.5%)
	Total	58 (73.4%)	21 (26.6%)	9 (11.4%)	49 (62%)	79 (100%)

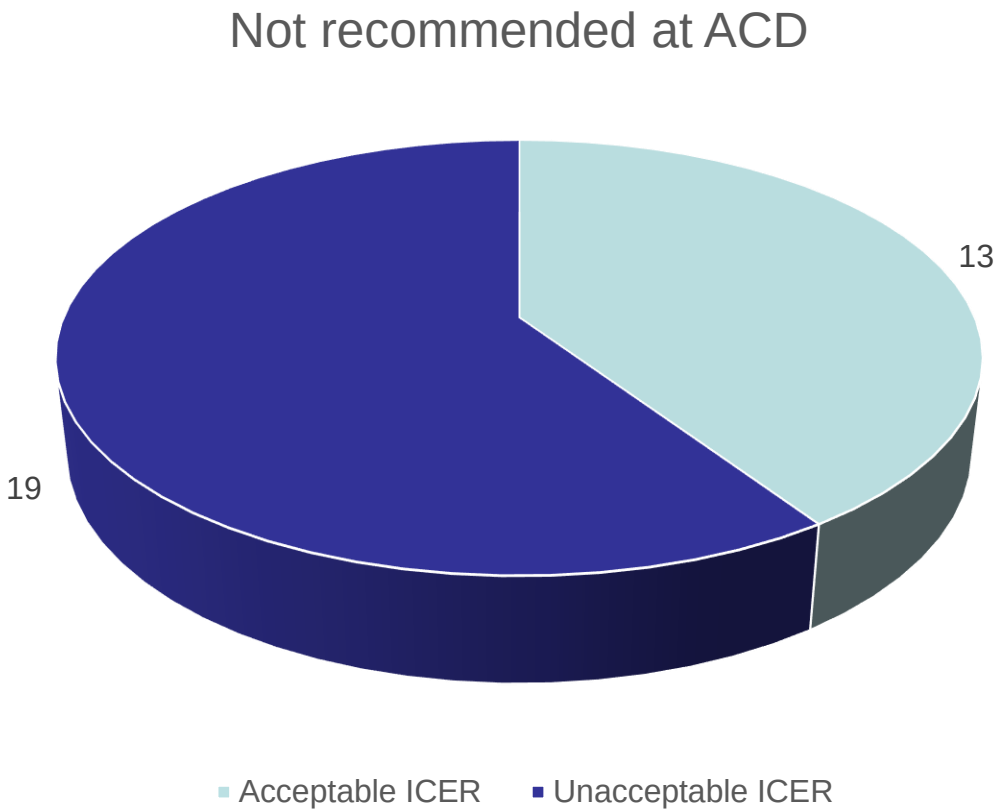
Results – Validation and recommendations

institute for Medical Technology Assessment

		Recommended at ACD		Recommended at FAD		
		No	Yes	No	Yes	Total
Validation perceived as issue	No	26 (32.9%)	21 (26.6%)	0 (0%)	26 (32.9%)	47 (59.5%)
	Yes	32 (40.5%)	0 (0%)	9 (11.4%)	23 (29.1%)	32 (40.5%)
	Total	58 (73.4%)	21 (26.6%)	9 (11.4%)	49 (62%)	79 (100%)

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Results - Validation and recommendations



Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

Enzalutamide for hormone-relapsed non-metastatic prostate cancer

1 Recommendations

1.1 Enzalutamide is not recommended, within its marketing authorisation, for treating high-risk hormone-relapsed non-metastatic prostate cancer in adults.

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

The company's definition of high risk does not closely match what is considered high risk in clinical practice

3.4 The company's decision problem focused on the subset of people with hormone-relapsed non-metastatic prostate cancer whose disease is at 'high risk' of metastasis, defined as:

- an absolute prostate-specific antigen (PSA) level of 2 ng/millilitre or more
- a PSA doubling time of 10 months or less.

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

The overall survival data are immature

3.8 The company presented 2 of 3 planned interim analyses of overall survival: the first after 135 deaths (coinciding with the final analysis for metastasis-free survival; see section 3.7), and the second after 285 deaths (about 1 year later). The company stated that it intends to do another interim analysis and a final analysis. The committee appreciated that, in its amended statistical plan, the company planned the final analysis for when 596 deaths had occurred. It agreed that the overall survival data from PROSPER presented by the company were immature

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Example – TA580

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

Subsequent treatments in PROSPER confound overall survival

3.11 The company presented information on the treatments used after metastasis for each treatment arm in PROSPER. The committee noted that:

- Some patients in the enzalutamide plus ADT arm had further treatment with abiraterone and enzalutamide, which would not be available in NHS clinical practice and for which there may be a survival benefit.

Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

The relationship between enzalutamide and quality of life is not appropriately modelled

3.12 The patient experts explained that they had no problems with any aspect of their quality of life while having enzalutamide over several years. The company presented health-related quality-of-life data from PROSPER measured after 22 months of follow up using various quality-of-life instruments. These included the Brief Pain Inventory, the European

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

The company's model structure introduces additional uncertainty by splitting overall survival

3.14 The company chose a model structure in which overall survival needed breaking down into death before or after metastasis to align the data with the model states. However, this increased uncertainty in the model. The company stated that it chose this model structure to reflect clinical practice. The committee considered that the company did not sufficiently justify using a model structure that increased uncertainty. The company

ERASMUS UNIVERSITEIT ROTTERDAM
iMTA

Example – TA580

institute for Medical Technology Assessment

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final Appraisal Document

Post-progression survival is biased

3.16 The committee noted that the company's extrapolation of post-metastasis survival did not preserve randomisation in PROSPER because most patients in the ADT arm, but only half of those in the enzalutamide arm, developed metastasis. This introduced selection bias because the extrapolation of the enzalutamide arm was based only on patients whose disease metastasised early (relative to the median time to metastasis), whereas the extrapolation of the ADT was based on almost all patients whose disease metastasised. It also meant that the extrapolation was

Example – TA258

institute for Medical Technology Assessment

5.4 Conclusions of the cost-effectiveness section

It is the view of the ERG that the model submitted by the manufacturer does not conform sufficiently with the requirements of the NICE scope[7] to provide reliable evidence of the likely clinical effectiveness and cost effectiveness of erlotinib in first-line treatment of EGFR M+ NSCLC patients. Moreover, the current model structure is not easily modifiable by the ERG within the resources available to be able to provide such evidence for the Committee to consider.

Example – TA258

In order to be suitable to inform the appraisal committee the ERG considers the current model would need to be substantially modified to include additional comparators, the results of an extended PFS mixed treatments comparison using a more comprehensive and robust evidence network, and the costs and health outcomes of second-line systemic therapies. In addition, the logic of the model should be modified to include meta-analysis results from available OS results for EGFR TKIs, without assuming that PFS gains automatically convert to OS gains, and a wider range of scenario analyses should be explored covering the assumptions and uncertainties identified here.

6 IMPACT ON THE ICER OF ERG ADDITIONAL ANALYSES

Not applicable.

Example – TA258

In order to be suitable to inform the appraisal committee the ERG considers the current model would need to be substantially modified to include additional comparators, the results of an extended PFS mixed treatments comparison using a more comprehensive and robust evidence network, and the costs and health outcomes of second-line systemic therapies. In addition, the logic of the model should be modified to include meta-analysis results from available OS results for EGFR TKIs, without assuming that PFS gains automatically convert to OS gains, and a wider range of scenario analyses should be explored covering the assumptions and uncertainties identified here.

6 IMPACT ON THE ICER OF ERG ADDITIONAL ANALYSES

Not applicable.

1 Appraisal Committee's preliminary recommendations

1.1 The Committee is minded not to recommend erlotinib for the first-line treatment of locally advanced or metastatic EFGR mutation-positive non-small-cell lung cancer (NSCLC).

1.2 The Committee recommends that NICE requests the manufacturer to provide an updated economic model and analyses to determine the cost-effectiveness of erlotinib in comparison with gefitinib when the progression-free survival and the utilities for the progression-free survival health state are assumed to be equal for the two treatments.

Example – TA258

Final appraisal determination

Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**
- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).

Conclusion

- Validation efforts
  - Most frequently reported: face validity (conceptual model and results).
  - Less frequently reported: cross validity (conceptual model and results)
- Validation issues
  - Validation issues at ACD always “implied” a negative recommendation
- Validation plays a role in NICE recommendations