EUnetHTA CRC screening full Core Model pilot: reflections on why and how

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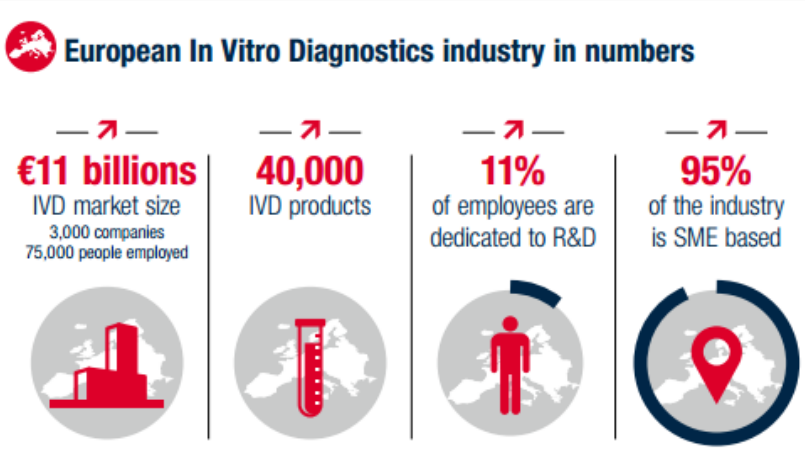
Agenda

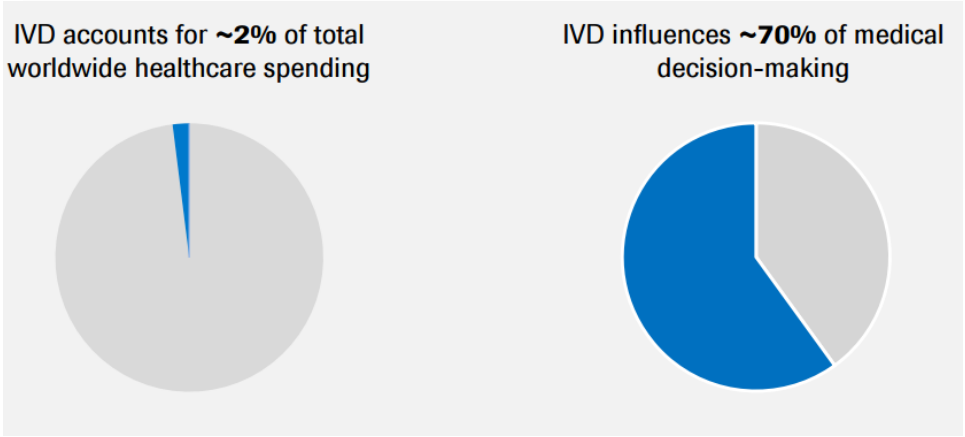
Background on IVD market access

The EUnetHTA Full Core Model CRC screening pilot- reflection from IVD industry stakeholder advisor

Conclusion

In vitro diagnostics (IVD) are non-invasive tests based on samples (blood, urine, salvia, sweat, stool)

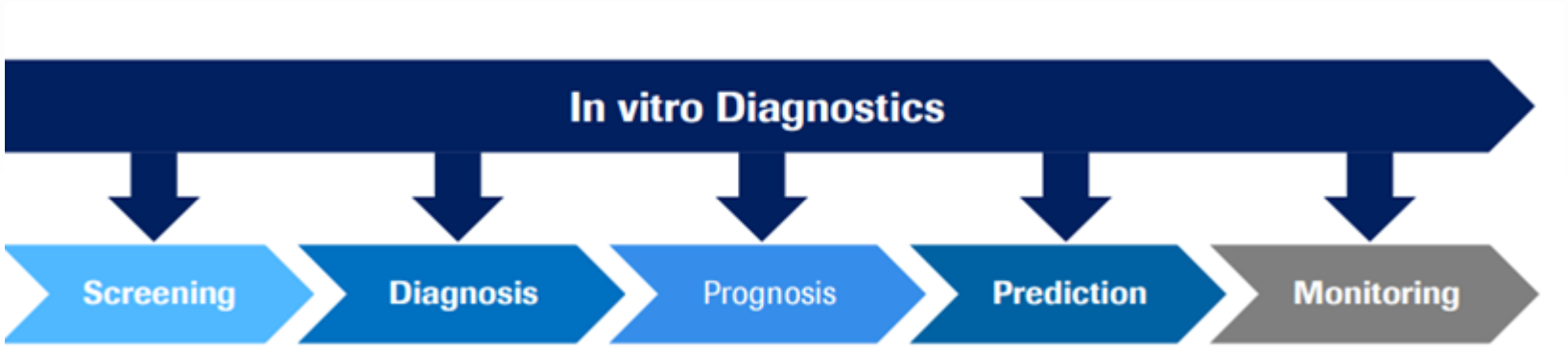




Source: EDMA

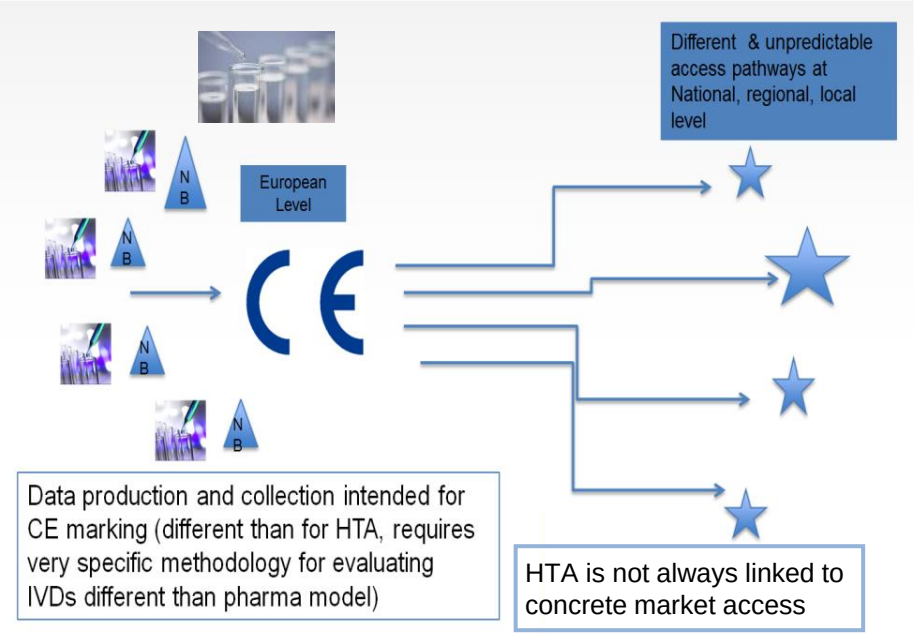
European Diagnostic Manufacturers Association (EDMA) is an international, non-profit organisation representing the medical in vitro diagnostics (IVD) industry in Europe.

IVD comprise a wide range of products.



Source: EDMA

Where does HTA fit in market access pathways for IVDs?



Source: EDMA

Diagnostics Application	France	Germany		UK
		Outpatient	Inpatient	
Diagnosis	No formal HTA HAS in review *(unless cancer INCa)*	AG Labor review *(unless existing EBM/ GÖA code)*	No formal HTA required, depending on care setting	No formal HTA required
Screening	HTA type assess HAS review *(unless cancer, then INCa involvement)*	AG Labor review in all cases for reimbursement	AG Labor review in all cases	No formal HTA required
Predictive / Treatment Selection	HAS review *(unless cancer, then INCa involvement)/ HTA will be conducted in parallel with companion drug*	AG Labor review *(unless existing EBM/ GÖA code/ HTA may be conducted in parallel with companion drug*	No formal HTA required, depending on care setting/ *HTA may be conducted in parallel with companion drug*	Formal HTA occurs in context of NICE drug review – requires RCT
Prognosis	No formal HTA required	AG Labor review *(unless existing EBM/ GÖA code)*	No formal HTA required	No formal HTA required
Monitoring	In function application	AG Labor review *(unless existing EBM/ GÖA code)*	No formal HTA required	No formal HTA required

- Inter- and intra-national heterogeneity in pathway of IVD Market access and reimbursement in Europe
- Mainly lack of associated funding
- Inconsistent and local decision-making criteria

Health Technology Assessment Network (HTAN=strategic level)

HTAN drives synergies between HTA and regulatory issues

But, who needs HTA type of information at launch of an IVD?
Who has requested such type of information?
Is HTA needed when there is functioning price competition?

⇒ Information involves cost of producing it
⇒ Information should be needed
⇒ Cost of producing information should be balanced with importance of question to be answered
⇒ More clarity on decision maker‘s and HTA‘s needs can help the IVD industry produce further fit-for-purpose evidence and incentivize innovation to fill unmet needs (e.g. informing treatment decisions)

The EUnetHTA Full Core Model CRC screening pilot- reflection from IVD industry stakeholder advisor

EUnetHTA Core Model domains

Scope

RAPID

FULL

1. Health problem and current use of technology
2. Description and technical characteristics
3. Safety
4. Clinical effectiveness
5. Costs and economic evaluation
6. Ethical analysis
7. Organisational aspects
8. Social aspects
9. Legal aspects

Souce: EUnetHTA

EUnetHTA colorectal cancer screening full Core Model pilot

- Very comprehensive HTA covering all EUnetHTA Core Model domains answering about 130 questions for a very important health problem: http://www.eunethta.eu/outputs/core-hta-colorectal-cancers-crcs-screening-tests [1]
- No manufacturer of guaiac fecal occult blood tests (gFOBT) and fecal immunochemical testing (FIT) is member of EDMA HTA Task Force
- EDMA has commented on
  - HTA protocol
  - Draft report incl. search strategies
  - Public consultation
  - Final public report

[1] Jefferson T, Cerbo M, Vicari N [eds.]. Fecal Immunochemical Test (FIT) versus guaiac-based fecal occult blood test (FOBT) for colorectal cancer screening [Core HTA], Agenas - Agenzia nazionale per i servizi sanitari regionali; 2014. [cited 22 June 2015]. Available from: http://meka.thl.fi/ViewCover.aspx?id=206

Relevant HTA process aspects/learnings

- Relevance of EUnetHTA pilots can be increased by more active participation of decision makers and local HTA agencies during scoping.
- The final HTA protocol should always be made available for reasons of transparency and reproducibility.
- In principle, the EUnetHTA Core Model allows a broader value perspective- for which technologies is it needed?
- Safety and effectiveness domains should be done by one team and within one literature search (within this pilot: two teams performing two searches=> unbalanced assessment of benefit and harm)
- If harms of some kind are included, benefits of the equivalent kind need to be assessed as well (e.g. psychological harms & benefits).
- Very lengthy process/ local uptake slow

How to synchronize health needs, payers‘ WTP and manufacturers‘ resources to invest?

- Facing diverging market access / HTA requirements manufacturers need clarity on what is valued and how early on in their product / evidence development.
- Decision makers value additional information (EUnetHTA Core Model assessment elements) less, whilst opportunity cost for manufacturer increase with each information to be produced.
- Depending on information needs and product (class) characteristics, a more flexible and pragmatic approach to evidence requirements elicitation / HTA scoping (disease specific guidelines) than just „rapid“ or „full“ Core Model should be considered.

Conclusion

Conclusion

- Evidence generation should be focused on the needs of the users of the information (e.g. decision makers).
- Relevance of EUnetHTA pilots especially depends on active participation of decision makers and local HTAs during scoping.
- Applying the **full** EUnetHTA Core Model is a lengthy process and uptake has been slow.
- More clarity on decision maker‘s and HTA‘s needs can help the IVD industry produce further fit-for-purpose evidence and incentivize to contribute to solve major health issues, if known early.
- Applying the EUnetHTA Core Model in a flexible way in this respect should be considered.
- A more flexible and pragmatic approach to evidence requirements elicitation / HTA scoping than just „rapid“ or „full“ Core Model should be considered used.
- Disease specific guidelines may play a broader role in the future for guiding evidence generation besides early dialogues.

Back-up: EDMA HTA position paper (http://www.edma-ivd.be/index.php?page=HTA)

Taking into account general aspects of HTA at EU Member States and EU level, EDMA is certain that:

- If an HTA on IVDs is requested, the HTA should be performed in order to inform a decision point through a "fit-for-purpose" approach. Such an approach should be:

HTA should be performed with the aim of informing a decision point in a "fit-for-purpose" approach.

- Linked to a decision about coverage, reimbursement, funding and/or use.
- Adapted to the specifics of in vitro diagnostics (IVD) technologies.
- Using appropriate and specific methodologies to demonstrate the value of IVDs.
- Developed in cooperation with other relevant stakeholders including industry.

- ✓ **Value of Diagnostic Information**
- ✓ **Broad Clinical Utility**
- ✓ **Payers values**
- ✓ **Pragmatic evidence requirements**

- A timely dialogue involving manufacturers should be an integral part of the HTA process.

Joint Assessments/tools **Used at National Level** ***To inform decision making***

EUnetHTA CRC screening pilot: Background

Colorectal cancers (CRCs) arise mostly from previously begin adenomas and have effective treatment if diagnosed early in their evolution. It is for these reasons that they are amenable to screening. Screening can be done via three approaches: imaging, endoscopy and stool-based identification. Two of the techniques used in stool-based based identification are the object of this core HTA, collectively knows as Fecal occult blood tests (FOBT): (guaiac, so-called gFOBT and immunochemical testing, so called FIT, also known as Immunochemical Faecal Occult Blood Test (iFOBTs).

EUnetHTA CRC screening pilot: Background

CRC is the 3rd most common cancer worldwide, and the second most frequent in developed countries with an estimated 1,234,000 cases worldwide in 2008. There are large variations between regions. Incidence rates are higher in Australia/New Zealand (39.0 per 100,000), Western Europe (33.1 per 100,000) and Southern Europe (31.1 per 100,000) and lower in Western Africa (4.9 per 100,000), South-Central Asia (4.5 per 100,000) and Middle Africa (3.7 per 100,000) {6}. In 2008 an estimated 8% of total cancer-related deaths was caused by CRC. Incidence and mortality from CRC are higher in men that in women.

EUnetHTA CRC screening pilot: Background

Currently screening practices vary considerably across Europe (see assessment element CUR14), several different types and brands of FOB tests are available, with different performance characteristics. gFOBT is the longest established of the two basic techniques, guaiac and immune based. There are several potential advantages and disavantages of gFOBT use. The advantages are mainly due to the cheapness, acceptability and long standing nature of the procedure. The disadvantages of gFOBT are its lack of automation, laboriousness and lack of specificity for human Haemoglobin, requiring a period of dietary preparation before testing.

EUnetHTA CRC screening pilot: Background

FITs are a newer class of Faecal Occult Blood tests compared to gFOBTs and reputedly have improved test characteristics compared to gFOBT. iFOBTs have been used for population CRC screening in Japan since 1992. In the US, the first iFOBT (OC-Sensor) was approved by the FDA (Food and Drug Administration) since 2001. The aim of population-based screening for CRC is to reduce morbidity and mortality from CRC through both, prevention (by the removal of adenomas before they had a chance to become malignant, so CRC incidence is reduced) and earlier diagnosis of CRC (at early, curable stage).

EUnetHTA CRC screening pilot: Background

A wide range of qualitative and quantitative FITs is presently available, with varying levels of sensitivity and specificity. They all use antibodies raised against human haemoglobin (Hb) to detect human blood present in faeces.

The aim of this core HTA was to compare the diagnostic and clinical performance of FITs with gFOBT for detection of CRC.

EUnetHTA CRC screening pilot: Results-Safety of the technology (SAF)

As FIT and gFOBT are non-invasive tests no direct harms are likely. Indirect harms can be caused by a wrong or delayed diagnosis or by harms related to subsequent colonoscopy (such as local trauma). The psychological impact of screening (including consequences of any false-positive and false-negative test results) and patient discomfort related to the procedures are the potential harms to be assessed as the overall number of adverse events depends on sensitivity and specificity of the screening tests. False-positive results may cause anxiety and distress, overdiagnosis and overtreatment. The false-negative test results may delay the detection of illness and the start of treatment. Organisational factors affecting harms include false-positive test results from gFOBT with a lax dietary preparation and FIT samples should be kept in refrigerated. Personnel experience and dexterity is also a factor.

EUnetHTA CRC screening pilot: Results- Safety of the technology (SAF)

Harms colonoscopy are estimated at 5% of procedures whereas 68% of people who received a false positive experienced stress and 46% of those who received an invitation to screening were worried and 15% very worried.

Effectiveness of the technology (EFF)

Our searches were unable to identify a direct comparison of the two techniques with meaningful cancer-specific outcomes such as CRC mortality within screening programmes.

However on the basis of several single studies and systematic review FIT have higher detection rates than gFOBT for adenomas, at the expense of a drop in specificity. We concluded that Overall, FIT performance is superior to the standard gFOBT for the detection of CRC and advanced adenomas in a population based screening setting.

EUnetHTA CRC screening pilot: Results- Costs, economic evaluation of the technology (ECO)

FIT lacks evidence of its effect on mortality when used in a screening programme, but both tests are more cost-effective than no screening. Cost-effectiveness models tend to suggest FIT has more favourable ICERs than gFOBT but its higher sensitivity means that there is a need for higher capacity in undertaking diagnostic colonoscopies with an increased up-front resource use and cost associated with the increased number of colonoscopies.

EUnetHTA CRC screening pilot: Results- Ethical aspects of the technology (ETH)

The tests are very similar, making ethical problems around choice less important. Overall there appears to be dominance of FIT over gFOBT and both dominate no screening. However in the absence of a direct clinical comparison the evidence base is unstable as shown by the different ICERs in ECO5. A full assessment should be carried out in context to define the costs and opportunity costs as well as the benefits of choice between the two types of test.

EUnetHTA CRC screening pilot: Results- Organisational aspects of the technology (ORG)

CRC screening is carried out with significant variation across the EU in terms of organization and type of screening test. There partial or complete screening programmes in 19 of the 27 EU countries. Organised screening is considered better than opportunistic screening. In 2007, gFOBT was used as the only screening method in twelve countries: Bulgaria, Czech Republic, Finland, France, Hungary, Latvia, Portugal, Romania, Slovenia, Spain, Sweden, and United Kingdom. In six countries, two types of tests were used: FIT and FS in Italy, and gFOBT and colonoscopy in Austria, Cyprus, Germany, Greece, and Slovak Republic. FIT is being used in 6 European countries: Russia, Lithuania, Italy, Scotland, Spain and Slovenia.

EUnetHTA CRC screening pilot: Results- Organisational aspects of the technology (ORG)

National screening programmes use risk-based criteria to define who should receive screening invitations. The target population for a CRC screening programme includes all people eligible to attend screening on the basis of age and geographical area of residence. Altough there are variations, people who are between 50 and 75 are invited to be screened. Screening programmes with FIT carry an investment penalty including equipment for screening, premises, office material for posting invitations and re-invitations, IT equipment and other office devices such as printers, and human resources including administrative and health personnel, investment in education of personnel and their training. Every country needs to assess their costs independently using cost-effectiveness analyses or other economic evaluation method. Investments that are needed for implementation of FIT are therefore country specific.

EUnetHTA CRC screening pilot: Results- Social aspects of the technology (SOC)

We found good evidence that FIT has better compliance than gFOBT in screening. The reasons for this finding are unclear and under researched but may include socio-cultural factors and the need for dietary prepration for gFOBT.

Legal aspects of the technology (LEG)

Legals implications of detecting colorectal cancer include the necessity to provide Sufficient information and informed consent, the right of access to (best) health care once a presumptive diagnosis is made, freedom in taking part, protection of personal data, equal right of access according to need and in the case of regional inequalities, access abroad and the right to charge contributions to the cost of the programme.

EUnetHTA CRC screening pilot: Closing Remarks

The Core Model is not intended to provide a cookbook solution to all problems but to suggest a way in which information can be assembled and structured, and to facilitate its local adaptation. The information is assembled around the nine domains, each with several result cards in which questions and possible answers are reported.

The reasons for having a standardised but flexible content and layout are rooted in the way HTA is conducted in the EU and in the philosophy of the first EUnetHTA Joint Action (JA1) production experiment.

EUnetHTA CRC screening pilot: Closing Remarks

HTA is a complex multidisciplinary activity addressing a very complex reality – that of healthcare. Uniformly standardised evidence-based methods of conducting assessments for each domain do not exist (Corio M, Paone S, Ferroni E, Meier H, Jefferson TO, Cerbo M. Agenas – Systematic review of the methodological instruments used in Health Technology Assessment. Rome, July 2011.)).

There are sometimes variations across and within Member States in how things are done and which aspects of the evaluation are privileged. This is especially so for the "softer" domains such as the ethical and social domains.