UNIVERSITY OF TWENTE.

Early assessment of the health economic impact of CTCTrap: a liquid biopsy in cancer

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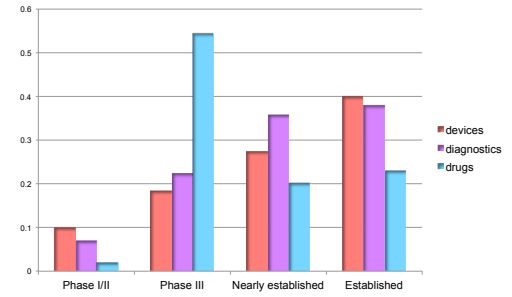


Source:
Euroscan database / N=1085 cases
14 HTA agencies

Ibargoyen *et al*, Int. J. TA Healthcare 2009

What is early modeling?

- Emphasis on efficient use of resources in medical product development and market access
  - Determine health economic value (for society) early on to either continue or discontinue further development
- But also different meanings:
  - Early modeling/horizon scanning for (research) priority setting
    - From a societal perspective – i.e. allocative efficiency
  - Early stage modeling for R&D and commercial decisions
    - From an industry perspective – i.e. business opportunities

Early modeling for R&D decisions

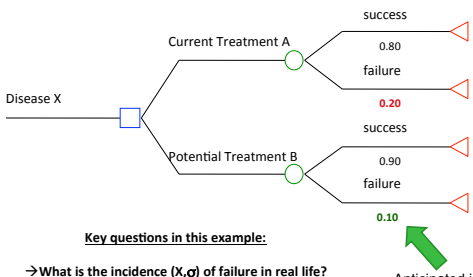
Table 1. Similarities and Differences between Classical HTA and Early HTA

	Classical HTA	Early HTA
Aim	Assess safety, effectiveness, and cost-effectiveness profiles of a new technology	Assess (likely) safety, effectiveness, and cost-effectiveness profiles of a new technology
Decision support	Decision support for **regulators, payers, and patients** about *market clearance, payment, and usage of a technology*	Decision-support for **manufacturers and investors** about *design and management of a technology, as well as regulatory and reimbursement strategy*
Available evidence	Usually evidence from clinical studies performed with the new technology	Evidence from early bench and animal testing, early clinical experience, and from previous generations of the technology
Influence on technology performance	Limited or no influence on clinical performance of a new technology	Potentially significant influence on (future) clinical performance of a new technology

INTL. J. OF TECHNOLOGY ASSESSMENT IN HEALTH CARE 24:1, 2008 37

Pietzsch & Paté-Cornell, Int. J. Techn. Assessm. Healthcare, 2008

Early Health Economic Modeling: A simple starting point



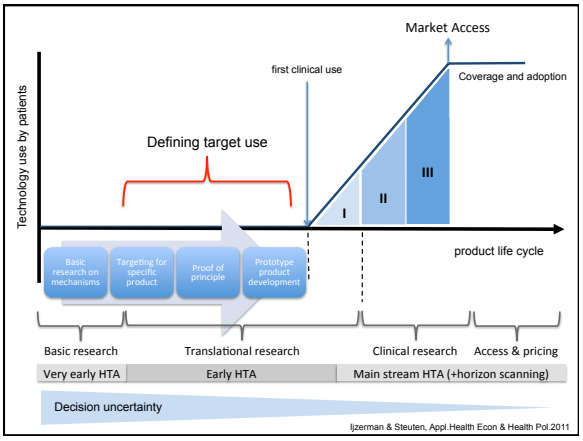
Key questions in this example:

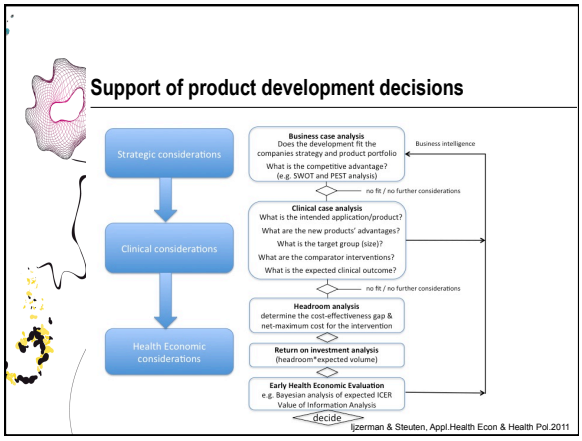
→What is the incidence (X,σ) of failure in real life?
→What is the QALY loss (X,σ) of failure/disease?
→How is failure managed in real life
→what is the cost (X,σ) of failure?

Anticipated in TPP (target product profile)

Early health economic models

- Deterministic sensitivity analysis
  - What effect size would be needed to demonstrate value
  - What range of prices is acceptable
  - What model parameters drive value
  - What priorities for evidence generation
- Uncertainty in early models
  - Parameter uncertainty, possible to quantify using VOI
  - Decision maker uncertainty
    - What criteria are used for decision making ?
    - ICER, impact, burden of disease, prevalence
- Some uncertainty can be solved if comparator is known, yet this is difficult to determine early stage



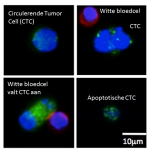


Approaches to identify potential use and impact

- Qualitative interviews and expert consultations about expected benefits, including delphi methods
- Belief elicitation experiments to identify most promising use and to elicit priors
- Multi-criteria decision methods to support decision making in a more transparent way
- Preference elicitation methods to quantify willingness to pay or utility of an incremental improvement
- Health economic or disease models to identify room for improvement
  - Cost-effectiveness gap analysis
  - (Early) health economic modeling

Circulating Tumor Cells TheRapeutic Apheresis

- CTCTrap is EU funded (7th framework program)
  - Lead partner is the University of Twente (Leon Terstappen)
  - Several partners from industry, universities and cancer centers:
  - IGR Paris, ICR London, LMU Munchen, IOV Padua
- Workpackage on health economics

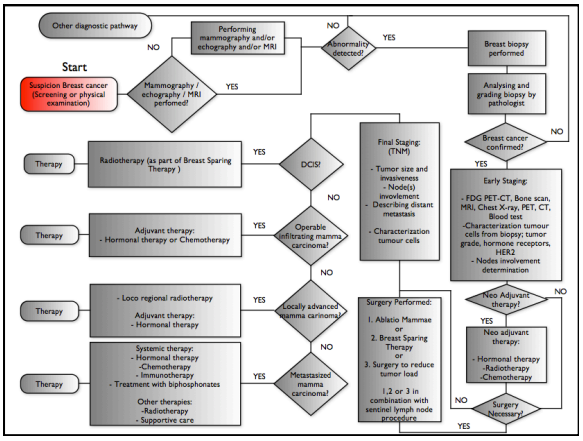


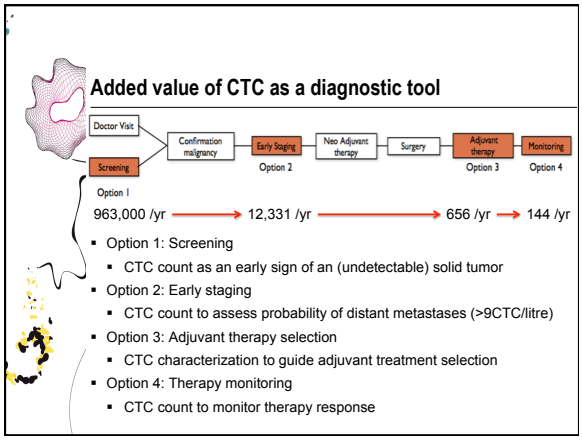
Circulating Tumor Cells TheRapeutic Apheresis

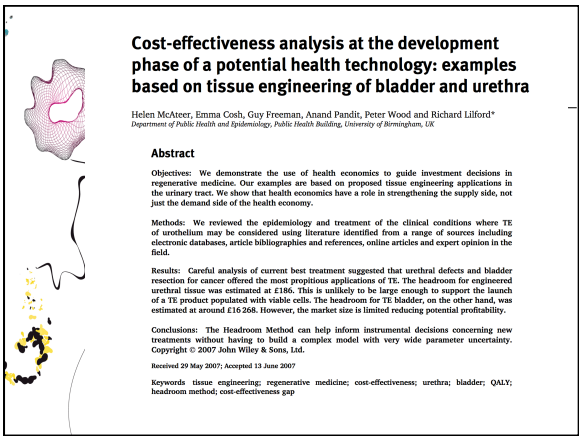
- CTC refers to cells that detach from a primary tumor or metastatic site, circulate and may form metastasis
- CTC represent a liquid biopsy and are useful for tailoring treatment and prognosis of survival
- Yet, the presence of CTC in peripheral blood is relative low 1 per 10^{5-7} cells
- Current methods, like Cellsearch®, only isolate 7.5 ml which allows detection of CTCs in about half of the patients
- Next step to increase sensitivity is to detect CTC by sampling at least 1 liter fresh blood (or alternatives like detection of tumor particles) and to develop methods for automated CTC expression profiling

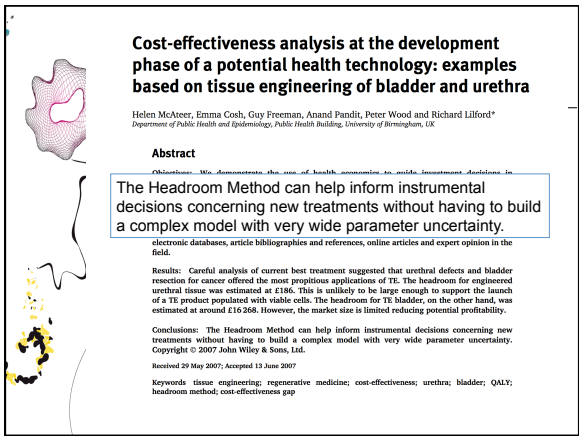
Potential clinical utility of CTCTrap

- Increased sensitivity for detecting CTC, and hence improved prognosis and therapy decisions
  - Earlier detection of a primary tumor (screening)
  - Better detection of the probability of metastatic disease in patients diagnosed with breast cancer
- Better characterization of tumor expression profiles
  - Analysis of discordance primary tumor, CTC and distant metastasis ptentially causing lack of treatment response
- Better monitoring of therapy response
  - Potential to stop expensive drug treatment


Other diagnostic pathway
Performing mammography and/or echography and/or MRI
Abnormality detected?
Start
Suspicion Breast cancer (Screening or physical examination)
Mammography / echography / MRI performed?
Breast biopsy performed
Analysing and grading biopsy by pathologist
Breast cancer confirmed?
Therapy
Radiotherapy (as part of Breast Sparing Therapy)
DCIS!
Final Staging: (TNM)
- Tumor size and invasiveness
- Node(s) involvement
- Describing distant metastasis
- Characterization tumour cells
Early Staging:
- FDG PET-CT, Bone scan, MRI, Chest X-ray, PET, CT, Blood test
-Characterization tumour cells from biopsy; tumor grade, hormone receptors, HER2
- Nodes involvement determination
Therapy
Adjuvant therapy:
- Hormonal therapy or Chemotherapy
Operable infiltrating mamma carcinoma!
Therapy
- Loco regional radiotherapy
Adjuvant therapy:
- Hormonal therapy
Locally advanced mamma carinoma!
Surgery Performed:
1. Ablatio Mammae
or
2. Breast Sparing Therapy
or
3. Surgery to reduce tumor load
1,2 or 3 in combination with sentinel lymph node procedure
Neo Adjuvant therapy?
Neo adjuvant therapy:
- Hormonal therapy
-Radiotherapy
-Chemotherapy
Therapy
Systemic therapy:
- Hormonal therapy
-Chemotherapy
- Immunotherapy
- Treatment with biphosphonates
Other therapies:
-Radiotherapy
- Supportive care
Metastasized mamma carcinoma!
Surgery Necessary?
YES
NO


Added value of CTC as a diagnostic tool
Doctor Visit
Screening
Confirmation malignancy
Early Staging
Option 2
Neo Adjuvant therapy
Surgery
Adjuvant therapy
Option 3
Monitoring
Option 4
Option 1
963,000 /yr
12,331 /yr
656 /yr
144 /yr
Option 1: Screening
CTC count as an early sign of an (undetectable) solid tumor
Option 2: Early staging
CTC count to assess probability of distant metastases (>9CTC/litre)
Option 3: Adjuvant therapy selection
CTC characterization to guide adjuvant treatment selection
Option 4: Therapy monitoring
CTC count to monitor therapy response


Cost-effectiveness analysis at the development phase of a potential health technology: examples based on tissue engineering of bladder and urethra
Helen McAteer, Emma Cosh, Guy Freeman, Anand Pandit, Peter Wood and Richard Lilford*
Department of Public Health and Epidemiology, Public Health Building, University of Birmingham, UK
Abstract
Objectives: We demonstrate the use of health economics to guide investment decisions in regenerative medicine. Our examples are based on proposed tissue engineering applications in the urinary tract. We show that health economics have a role in strengthening the supply side, not just the demand side of the health economy.
Methods: We reviewed the epidemiology and treatment of the clinical conditions where TE of urothelium may be considered using literature identified from a range of sources including electronic databases, article bibliographies and references, online articles and expert opinion in the field.
Results: Careful analysis of current best treatment suggested that urethral defects and bladder resection for cancer offered the most propitious applications of TE. The headroom for engineered urethral tissue was estimated at £186. This is unlikely to be large enough to support the launch of a TE product populated with viable cells. The headroom for TE bladder, on the other hand, was estimated at around £16 268. However, the market size is limited reducing potential profitability.
Conclusions: The Headroom Method can help inform instrumental decisions concerning new treatments without having to build a complex model with very wide parameter uncertainty.
Copyright © 2007 John Wiley & Sons, Ltd.
Received 29 May 2007; Accepted 13 June 2007
Keywords tissue engineering; regenerative medicine; cost-effectiveness; urethra; bladder; QALY; headroom method; cost-effectiveness gap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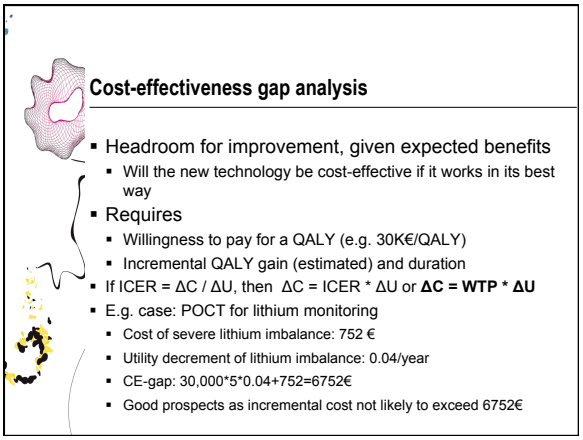
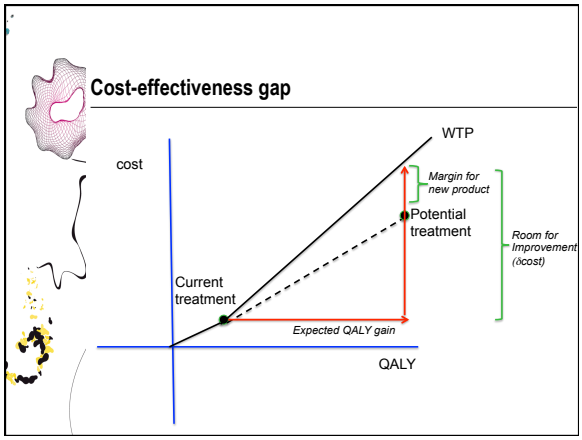
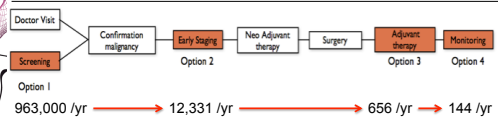

Cost-effectiveness gap analysis
Headroom for improvement, given expected benefits
Will the new technology be cost-effective if it works in its best way
Requires
Willingness to pay for a QALY (e.g. 30K€/QALY)
Incremental QALY gain (estimated) and duration
If ICER = ΔC / ΔU, then ΔC = ICER * ΔU or ΔC = WTP * ΔU
E.g. case: POCT for lithium monitoring
Cost of severe lithium imbalance: 752 €
Utility decrement of lithium imbalance: 0.04/year
CE-gap: 30,000*5*0.04+752=6752€
Good prospects as incremental cost not likely to exceed 6752€


Cost-effectiveness gap
cost
WTP
Margin for new product
Potential treatment
Room for Improvement (↓cost)
Current treatment
Expected QALY gain
QALY

Added value of CTC as a diagnostic

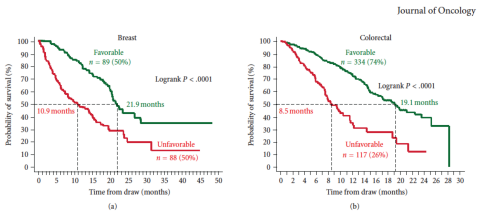


Option 1

963,000 /yr → 12,331 /yr → 656 /yr → 144 /yr

- Option 1: Screening
  - CTC count as an early sign of an (undetectable) solid tumor
- Option 2: Early staging
  - CTC count to assess probability of distant metastases (>9CTC/litre)
- Option 3: Adjuvant therapy selection
  - CTC characterization to guide adjuvant treatment selection
- Option 4: Therapy monitoring
  - CTC count to monitor therapy response

Early staging: CTC count for prognosis (option 2)



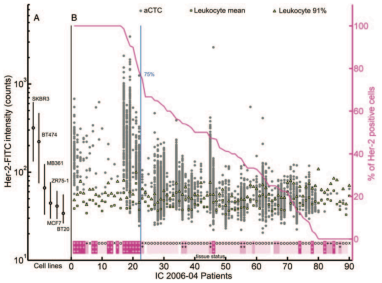
Threshold is 5 CTC/7.5ml blood, which may be too late to prevent metastases

Miller MC, Doyle GV, Terstappen LWMM. Significance of Circulating Tumor Cells Detected by the CellSearch System in Patients with Metastatic Breast Colorectal and Prostate Cancer. J Oncol. 2010;2010:617421.

Potential health economic benefit (option 2)

- Based on CTC count, two groups can be identified:
  - <= 9+/-6 CTC per liter and >9 +/- 6 CTC per liter
  - Threshold determines the probability of distant metastases, which can not yet be detected using standard imaging
- It is estimated that 33% of patients in stage I-III develop into stage IV in 10 years.
  - Some of them may be protected from distant metastases if surgery was performed earlier (incremental gain in QALY's)
- CTC profiling may impact treatment decisions:
  - Currently, expensive neo-adjuvant treatment only used in aggressive breast cancer or if suspicion of metastasis
  - Additional staging with CTC may lead to more efficient prescription of neo-adjuvant therapy

HER2 disconcordance primary tumor / CTC (option 3)



Ligthart ST *et al* Unbiased quantitative assessment of Her-2 expression of circulating tumor cells in patients with metastatic and non-metastatic breast cancer. Annals Oncology 2012

Potential health economic benefit (option 3)

- Progression-free survival may be increased if treatment provided according to receptor status of primary and distant metastasis
- This also implies an increase in costs:

		Disconcordance rates			Estimated gain in PFS			Estimated extra cost
Primary tumor	%	CTC receptor	% disconcordance	% patients	Initial therapy	Switch to	Incremental PFS (months)	Per patient (€)
HR+,HER+		*Not considered as downgrading therapy based on CTC receptor status not very likely.*						
HR-,HER-	13.4	HR-, HER+	6.69	0.9	Chemo	Trastuzumab+ chemo	2.8	36,298
HR-,HER-	13.4	HR+, HER+	2.5	0.34	Chemo	Trastuzumab+ hormone	9.3	30,585
HR+,HER-	68.9	HR+, HER+	1.9	1.31	Hormone	Trastuzumab+ Hormone	9.0	36,298
HR-,HER+	7.5	HR+, HER+	22	1.65	Trastuzumab+ chemo	Trastuzumab+ hormone	4.3	-5,712
Weighted averages:				4.2%			5.83	19,457

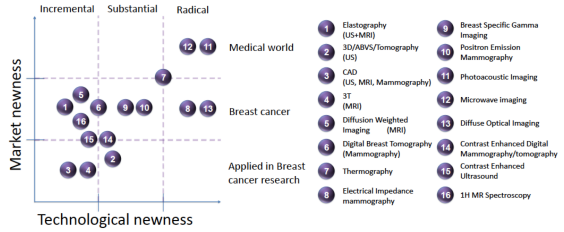
Cost-effectiveness gap results & assumptions

		CE - gap analysis			Extrapolated to society	
Option	Total population & fraction to benefit	Estimated QALY gain	Estimated saving (€)	Headroom (€)	Resources available to implement CTC (€)	Health impact (QALY gain)
1. Screening	963,000 13,008 (4,86%)	0,01	€ 159.-	€ 459	€ 2,068,271.-	130
2. Early staging to decide optimal therapy	12,331 4,069 (33%)	1	€ 12,351.-	€ 42,351.-	€ 50,256,219.-	4,069
3. Late staging to decide about adjuvant therapy	656 28 (4,20%)	0,17	€ -19,457.-	€ -14,356.-	€ -544,796.-	4,8
4. Therapy monitoring	144 32 (22%)	0	€ 2,214.-	-	€ 70,848.-	0

Assumptions

- The estimate of the population to benefit from CTCTrap is based on the Netherlands Cancer Registry. NL has close to 17 million inhabitants
- CE-gap analysis assumes a societal WTP of 30,000€/QALY
- Resources available to implement CTCTrap at no extra societal cost.
- Estimates of QALY gain and savings are based on literature and available data registries
- Analysis based on current guidelines and costs of e.g. trastuzumab

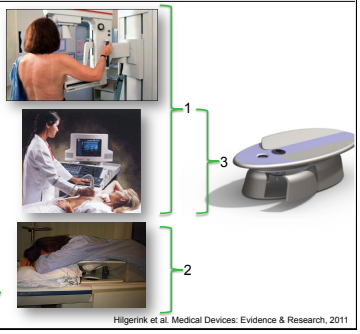
Developments in medical imaging for breast cancer



Ten Tije, NVTTG 2012

Photoacoustic imaging in breast cancer

- Mammography
  - Screening
  - **Diagnostic**
- **US**
- **MRI**
- Biopsy



Hilgerink et al. Medical Devices: Evidence & Research, 2011

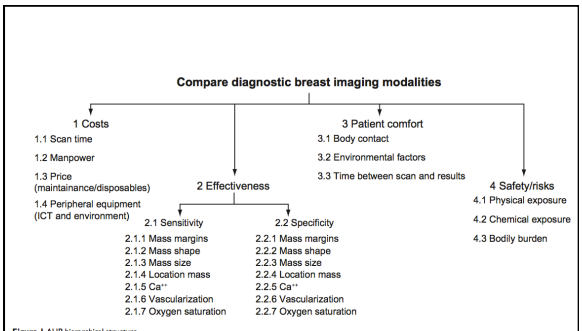


Figure 1 AHP hierarchical structure.
Abbreviation: AHP, analytic hierarchy process.

Medical Devices: Evidence and Research 2011:4

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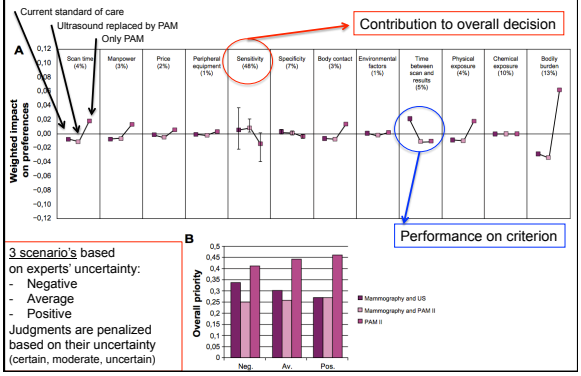
Comparison with ultrasound and mammography



3 scenario's based on experts' uncertainty:
- Negative
- Average
- Positive

Judgments are penalized based on their uncertainty (certain, moderate, uncertain)

Future outlook of early modeling

- Early health economic models add value, but the incremental CE ratio is a rather implicit decision criterion
  - ICER only one factor considered for reimbursement
  - A wider perspective is necessary
- In HEE the target product and comparator are known, in early R&D such options usually not
- Disease modeling and CE-gap analysis are easy to use methods to determine room for improvement but rely on many assumptions
- These methods can therefore at best support the decision and development process