At the end of 2011, 22 consortia started within CTMM. 17 Consortia allocated budget for medical technology assessment of the new technologies with a total budget of 7.7 million euro (both cash and in kind contributions). In total, 6 academic partners were involved in the execution of the MTA within the diagnostic translational research pipeline (UMCG, EUR, MUMC, VUMC, NKI, UMCU).

In most of the CTMM projects, the research was in the early phase of development and could therefore only be assessed with techniques and models suitable for early MTA, which were at the start of CTMM only marginally available in the Dutch MTA partners. The CTMM program provided the opportunity to establish a significant improvement of the early MTA infrastructure for translational research in the Netherlands, and to share and secure the methodology generated in the translational research projects sponsored by CTMM.

This resulted in sustainable, accessible and high-quality powerful tools to provide translational researchers the necessary decision support during the process of translational research (research, development and manufacturing phase). Ultimately, this investment is the basis of a MTA infrastructure at national level as well as in international networks.

Gimon de Graaf PhD student UMCG

"Many promising biomarkers for stratifying individuals at risk of developing a chronic disease or subsequent complications have been identified. Research into the potential cost effectiveness of applying these biomarkers in actual clinical settings has however been lacking. Investors and analysts may improve their venture decision making should they have indicative estimates of the potential costs and effects associated with a new biomarker technology already at the early stages of its development. To assist in obtaining such estimates, CTMM MTA working group has developed methods for the early health technology assessment of a novel biomarker technology."

Source: Statistics in Medicine 2012;31(23).
**Medical Technology Assessment**

Medical Technology Assessment (MTA) is the objective evaluation of a medical technology regarding its safety and performance, its (future) impact on clinical and non-clinical patient outcomes as well as its interactive effects on economical, organizational, social, juridical and ethical aspects of healthcare.

Medical technologies are assessed both in absolute terms and in comparison to other (combinations of) medical technologies, procedures, treatments or ‘doing-nothing’.

The aim of MTA is to provide objective, high-quality information that relevant stakeholders use for decision-making about for example development, pricing, market access and reimbursement of new medical technologies.

MTA is usually applied in a rather late phase of product development, often as an decision-making instrument for reimbursement (threshold value) or for value based pricing (translation into an estimate of the technology maximum sales price) (see figure 1: Classical MTA).

Currently, it becomes more and more clear that not only cost-effectiveness counts, but also other issues like medical, social, ethical and other economical issues, are increasingly important. Therefore, from either funding perspectives and investment perspectives it is noteworthy to determine if it is possible to apply MTA tools and methods to support in an early phase biomedical product development and to anticipate further development and market access (see figure 1: Early MTA).

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**Figure 1 Diagrammatic representation of the life cycle of a biomedical product**

Steps in evaluation: 1) Domain of Technology

Diagnostics testing can be applied during various disease phases ranging from “healthy” to “illness”. The described scheme described below was developed by researchers of the iMBG institute (Erasmus University Rotterdam) in order to standardize the nomenclature of the diagnostics test developed within CTMM.

Adapted from: Van Kosten tot Effecten, Chapter 8 – een handleiding voor Economische Evaluatie studies in de gezondheidszorg Prof. Dr. M van Rutten- Mölken et al.

No Disease
- Risk Factor Screening test

Disease
- Disease Screening test

Symptoms
- Diagnostic test

Diagnosis
- Prognostic test

Prognosis
- Predictive test (Companion Diagnostic test)

Therapy
- Response Monitoring test

Monitoring Therapy Response
- Relapse Monitoring test

Test Requirements
- Technical Quality
- Diagnostic Accuracy
- Diagnostic Impact
- Therapeutic Impact
- Improved Patient Outcome
- Improved Societal Outcome
In early stages of technology development health economic modelling is a powerful tool to assess the (potential) impact of the new health technology on future costs and health outcomes. It enables the use of different sources of information to answer this question. Also, it allows the exploration of the costs and outcomes of alternative options of using the new technology in clinical practice.

All CTMM technologies are still in (early) development. This means that results of the MTA will not simply be used by reimbursement authorities to decide whether or not the technology is cost-effective. Instead, the results of the MTA can help the developers make better decisions about the further development of their technology.

_STEP 1:_ The analysis plan contains a rough description of how the new technology will be applied in patient care, the target population, and the outcome measurements. Based on this information, the researcher defines the scope of the analysis by identifying the variables that need to be included in the mathematical model (APICO method)

- **Application (in patient care):** how will the test be applied in patient care
- **Population (participants):** how will the test be applied in patient care
- **Intervention:** what will CTMM-based patient care looks like
- **Comparator:** e.g. Current care, future competitors
- **Outcomes:** how will effectiveness be defined

_STEP 2:_ Description of the current care as the comparator in the MTA analysis. This consists of three phases:

- Conceptualization
- Mathematical modelling and parameter estimation
- Model validation

_STEP 3:_ The conceptual and quantitative models developed in the previous step are adapted to reflect the CTMM-based care. When dealing with a new molecular technology at the early stages of its development process, little will be known about the performance of this technology in actual clinical settings. Initial estimates of the model parameters may therefore have to be derived from surrogate data.

_STEP 4:_ After all parameters have been specified, an initial cost-effectiveness analysis can be conducted in a traditional way (i.e., by applying Monte Carlo simulation). By performing sensitivity analysis on the new technology's cost and performance parameters (e.g., sensitivity and specificity in case of a new diagnostic test), the HTA researcher can provide a benchmark for the minimum performance that the technology would have to show to make it a viable alternative for actual clinical practise.

Source: Dr. K. Redekop & Dr. D. Postmus, CTMM
Steps in evaluation: 3) Key elements of (early) MTA

**Head Room Analysis**
A headroom analysis determines the societal value and commercial viability of innovations in health care by using a threshold approach. It looks at the potential value of the use of a new health technology in a specific clinical setting and population. It asks the question whether the new health technology would be cost-effective if it would work as well as one would hope. It gives the maximum potential cost of the new technology factoring in any health service savings. If this cost [the headroom] is too low - then investments are not worthwhile.

**Multi Criteria Decision Analysis**
Multi-criteria decision analysis (MCDA) refers to a family of methods for assessing the relative desirability of alternative courses of action whose possible consequences have been expressed in terms of multiple criteria. Early during the translational research process, such methods can be used to determine at what stage of the clinical disease process the introduction of a new technology is likely to have the biggest clinical and economic impact. Later on in this process, MCDA could be applied to assist in tailoring the design of the developed products to the needs of health care professionals and patients.

**Risk Prediction & Patient stratification**
Risk prediction refers to the use of information about a patient to estimate the risk that something (e.g., disease, clinical event, death) will occur in the future. This information can be collected in various ways, including not only diagnostic tests but also via a physical examination or patient anamnesis. Patient stratification involves the separation of patients into different subcategories, each of which will be treated in a different way. The two terms are related since predicted risks may be used to stratify patients. For example, patients at a high risk of an event may be put into one stratum or subcategory, patients at a medium risk may be put in a second stratum and patients at low risk may be put in a third stratum. Significant improvement of existing prediction models is a first step towards appropriate patient stratification and possibly improved treatment.

**Cost-effectiveness analysis**
Cost-effectiveness analysis is the comparative analysis of alternative courses of action, taking into account all relevant costs and health consequences. It tells us the extra cost per extra unit of benefit achieved when comparing one health technology against another. The extra unit of benefit is often expressed in Quality Adjusted Life Years (QALYs): one life year in perfect health. Decisions are made by comparing the additional costs for an additional QALY to a threshold. This threshold puts a limit on society’s willingness to pay for a QALY. Cost-effectiveness analysis informs the adoption in health care technologies by assessing the value for money.
<table>
<thead>
<tr>
<th>Consortium</th>
<th>MTA Model</th>
<th>Applied (early) MTA analyses</th>
<th>MTA leader</th>
</tr>
</thead>
</table>
| DeCoDe     | MISCAN model  
Decision model for treatment of Colorectal Cancer  
ASCCA screening model | Early economic evaluation to determine the impact of several screenings options  
Early economic evaluation to assess the impact of several prognostic tests on costs and outcomes of treatment strategies  
Patient preferences for different screening options | Prof.dr. C.A. Uyl-de Groot (EUR) |
| BioCHIP    | Decision model for treatment of acute myeloid leukemia  
Decision model for treatment of multiple myeloma | Early economic evaluation of impact of several prognostic tests on costs and outcomes of treatments | Prof.dr. C.A. Uyl-de Groot  
Dr. K. Redekop (EUR) |
| AIRFORCE   | Micro simulation model for a treatment response test in patients with non-small cell lung cancer  
Markov model for treatment of patients with head & neck cancer | Early economic evaluation to assess the impact of several prognostic tests on costs and outcomes of several treatment strategies in both lung cancer and head& neck cancer. | Prof.dr. C.A. Uyl-de Groot (EUR) |
| BREASTCARE | Markov models for predictors of response to high dose alkylating chemotherapy in triple negative breast cancer  
Markov models for response-guided neo-adjuvant chemotherapy in breast cancer with 1) ultrasound and clinical examination, and 2) magnetic resonance imaging | Early economic evaluation to determine the minimum prevalence and performance of the biomarkers  
Value of information analysis to determine research priorities and efficient research designs | Prof.dr. W. van Harten (NKI) |
| MAMMOTH    | Multi-state Monte Carlo simulation is used to assess the potential impact of adding tumor markers to the diagnostic work-up of metastatic breast cancer in order to enable clinicians to 'personalize' treatment. | Early economic evaluation and quasi headroom analyses. | Prof.dr. E. Buskens and Prof G.H. de Bock (UMCG) |
| PCMM       | Mathematical analyses;  
MISCAN micro simulation model for screening of prostate cancer | Relations between statistical performance measures, such as the Net Reclassification Index, and cost-effectiveness.  
Head room analysis for new screening markers. | Prof.dr. E. Steyerberg  
(EMC);  
Dr. D. Postmus (UMCG) |
| VOLTA      | The breast cancer models developed within the MAMMOTH consortium will be applied within VOLTA. For metastatic colon cancer a similar approach will be used should HIFU appear clinically feasible in this patient group. | | Prof.dr. E. Buskens  
and Prof.dr. G.H. de Bock (UMCG) |
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</thead>
</table>
| CIRCULATING CELLS | Markov model for persons with intermediate risk to develop cardiovascular events  
Markov model for patients with coronary artery disease | Risk prediction & Patient stratification, Headroom Analysis        | Dr. K. Redekop (EUR)     |
| TRIUMPH        | Advanced disease multistate model for 1) early diagnosis of pre-clinical Heart Failure (HF) as well as 2) predicting survival and hospitalization in patients that are discharged from the hospital after acute HF. | Risk Prediction & Patient stratification, Headroom Analysis       | Prof.dr. E. Buskens Dr. D. Postmus (UMCG) |
| PREDICCT       | Advanced disease multistate model for 1) early diagnosis Diabetes Mellitus type 2 as well as 2) macro and micro-vascular complications in Diabetic patients | Risk prediction & Patient stratification, Multi-criteria decision analysis | Prof.dr. E. Buskens Dr. D. Postmus (UMCG) |
| INCOAG         | Markov model for Peripheral Arterial Disease                              | Headroom Analysis & Cost-effectiveness analysis of risk assessment and tailored treatment | Dr. M. Joore (MUMC+)     |
| PARISK         | Markov model for TIA/minor stroke patients with carotid stenosis of 30-69% | Risk prediction & Patient stratification, Headroom Analysis       | Dr. K. Redekop (EUR)     |
| COHFAR         | Markov Model for 1) biomarker-guided patient selection for Cardiac Resynchronization Therapy (CRT) in patients with Cardiac Arrhythmias 2) short term variability (STV) in heart rate to guide ICD-implantation for the primary prevention of ventricular tachycardia (VT) | Headroom analysis                                                | Dr. T. van Asselt (MUMC+, UMCG) |
| EMINENCE       | Markov Model for the cost-effectiveness of using new imaging modalities in the treatment of 1) chronic total occlusion (CTO) 2) Aortic valve stenosis (AS) | Headroom analysis                                                | Dr. C. Dirksen (MUMC+)   |
Other CTMM Disease areas: MTA models & analysis

<table>
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<tr>
<th>Consortium</th>
<th>MTA Model</th>
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<td>LeARN</td>
<td>Probabilistic patient level model (decision tree + time to event model)</td>
<td>Headroom analysis &amp; Cost-effectiveness of use of biomarkers for hypothetical disease-modifying treatment decision in mild cognitive impairment</td>
<td>Dr. M. Joore (MUMC+)</td>
</tr>
</tbody>
</table>
| TRACER     | A decision tree model for diagnosis in the first year, followed by an individual patient Markov model for treatment of rheumatoid arthritis (RA) in the remaining years. | 1) Early economic evaluation and headroom analysis of several tests to diagnose and start treatment in very early RA (arthralgia patients).  
2) Early economic evaluation and headroom analysis of several tests to diagnose and start treatment in early RA (unclassified arthritis patients).  
3) Early economic evaluation of several predictive tools (serum drug levels and antibody development MRP 8/14) and monitoring tools RA (Handscan) for decision making regarding (biological) treatment in established RA | Prof.dr. M Rutten (EUR) & Dr. P. Welsing (UMCU) |
## eMTA - Theses

<table>
<thead>
<tr>
<th>Thesis</th>
<th>Consortium</th>
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<td>Luuk Goede</td>
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<td><em>BMC Neurol.</em></td>
<td>Optimizing the use of expert panel reference diagnoses in diagnostic studies of multidimensional syndromes. BMC Neurol. 2014 Oct 4;14:190</td>
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<tr>
<td><em>Neurobiol Aging.</em></td>
<td>Test sequence of CSF and MRI biomarkers for prediction of AD in subjects with MCI. 2012 Oct;33(10):2272-81</td>
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**List of MTA Publications**
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CIRCULATING CELLS

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TRIUMPH

TRIUMPH

TRIUMPH

TRIUMPH

TRIUMPH

PREDICCI

PREDICCI

PREDICCI

PARISk

PARISk

INCOAG

INCOAG

INCOAG

Other Sources
• IJzerman MJ & Steuten LM. Early assessment of medical technologies to inform product development and market access: a review of methods and applications. Appl Health Econ Health Policy. 2011 Sep 1;9(5):331-47.
• Prof. Dr. M van Rutten- Mülken et al Van Kosten tot Effecten, Chapter 8 – Een handleiding voor economische evaluatie studies in de gezondheidszorg
<table>
<thead>
<tr>
<th>eMTA Partners</th>
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<tr>
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<tr>
<td>Maastricht University Medical Center (MUMC+)</td>
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<td>Netherlands Cancer Institute (NKI)</td>
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<td>University Medical Center Groningen (UMCG)</td>
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