Mid-Term Review Netherlands Metabolomics Centre 2008-2010

FINAL REPORT

Mid-Term Review Committee Netherlands Metabolomics Centre
- 29 April 2011 -

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Introduction

Scope of the review

The Mid-Term Review Committee of the Netherlands Metabolomics Centre is an independent body that has been approved as such by the Netherlands Genomics Initiative (NGI) to evaluate the activities and research of the Netherlands Metabolomics Centre. This assessment covers the activities and the research in the years 2008-2010. The Standard Evaluation Protocol (SEP) 2009-2015 was used as a guideline.

On the basis of the business plan, progress reports, output tables, other relevant information and interviews with representatives from the Centre, the Committee's tasks were to:

- Assess the overall quality of the Centre and its constituent research programmes;
- Make recommendations.

Structure of this report

Chapter 1 describes the activities of the Committee, its composition and its working methods. Chapter 2 contains the assessment of the Centre as an organisation. Chapter 3 contains the assessment of individual Themes of the NMC. Chapter 4 provides general conclusions and final recommendations. The appendices include Curricula Vitae of the Committee Members, a statement of independence, an overview of the scores, and the Committee meeting schedule.

Chapter 1 The Mid-Term Review Committee and the review procedure

Composition of the Committee
Composition of the Committee was as follows:

- Dr. Nico Overbeeke (chairman), The Netherlands
- Dr. Mike Gibney, University College Dublin, Ireland
- Dr. Roy Goodacre, University of Manchester, United Kingdom
- Dr. Rima Kaddurah–Daouk, Duke University, United States of America
- Dr. Lloyd Sumner, Noble Foundation, United States of America

Dr. Pieter Stolk was appointed secretary to the Committee.

The Committee Members possessed substantial expertise in the field of scientific research and had an affinity with or experience in valorisation. A short curriculum vitae of the Committee Members is included in Appendix 1.

Independence
All Members of the Committee signed a statement of independence (Appendix 2). This provides the safeguard that their review was unbiased and independent. Any existing professional relationships between Committee Members and research groups were reported and discussed in the Committee Meeting. The Committee concluded that all Committee Members could fulfil their task fully independently and perceived no risk in terms of bias or undue influence.

Data provided to the Committee
The Committee received the following documentation:

- Netherlands Metabolomics Centre Business Plan;
- Overall Progress Report 2008-2010;
- Individual Progress Reports for the Research Themes, Technology Platforms, Associate Projects and Valorisation Supporting Activities;
- Output table 2008-2010;
- The guidelines for evaluation (NGI Reporting Format, Standard Evaluation Protocol [SEP] 2009-2015 and a guide to evaluate societal relevance of research [ERiC)]).

Procedures followed by the Committee
NGI provided a protocol for the review of the Centre. The review was based on the documentation provided by the Centre and the interviews with representatives of the Centre.

After the selection of the Mid-Term Review Committee Members, the formal evaluation activities started after receiving the extensive self-evaluation document of the NMC in February 2011.

Committee Members were asked in advance of the meeting to prepare specific questions to be posed during the interviews and also to award individual scores for each of the review criteria. A preliminary advice form was provided for this purpose. These scores served as the basis for the Committee discussions.

The review responsibilities were divided between the Committee Members by assigning each of them the 'lead' for 2-3 of the themes/clusters based on the research portfolio of the NMC. The Committee Members individually prepared a preliminary assessment per Theme, scores, key questions and points for discussion. These items were discussed in 1:1 telephone conferences in the week prior to the meeting with the Chairman and the Secretary in order to prepare a package with preliminary views ahead of the meeting.

These views were briefly discussed on the afternoon of the 20th of March 2011 before the start of the meetings.
During the site visit from 21 – 22 March the nine Themes were reviewed through a +/- 45-minute interview for each Theme, led by the assigned 'lead' Committee Member with additions from the full Committee. Without exception, the Committee appreciated the open and constructive atmosphere of all interviews. The Committee felt that in many interviews there was a strong tendency and wish by the Committee and interviewees to go into more scientific depth. Unfortunately, the time restrictions of the Review did not allow room for that.

The Committee reviewed the input for a further 15 minutes after each interview and arrived at consensus scores and various key points to capture for comments and recommendations.

On 21 March 2011 the Committee commenced with an introduction of the NGI by the NGI representative Dr. Colja Laane (Director of NGI) and a discussion of the review procedure, followed by a discussion of the activities and results of the Centre. Eight interviews were held this day. The next day, the Committee visited the Unilever Research Laboratory in Vlaardingen and conducted four additional interviews. Finally, the Committee retired to reach a unanimous decision concerning the overall review scores and concluded with recommendations.

Scores, commentary and recommendations were drawn up during the meetings by the Secretary of the Committee. Comments were processed in a draft text, which was sent to the Committee for factual corrections, comments and approval after the site visit. The final version, approved by all Committee Members, was available on 29 April 2011 and sent to the Netherlands Genomics Initiative before 1 May 2011.

In the overall evaluation a differentiated view and weighing was applied to do justice to the differences in how much of the research in the various Themes had been carried out already.

It should be stipulated at this point that this process does lead to a fairly good judgment on the top-line performance of the NMC and its individual Themes. However, in view of the limited time available, most of our recommendations should not be seen as final with strong underpinning verdicts but as suggestions for further development by the NMC management. Nevertheless, there are some points where the Committee feels sufficient evidence for strong recommendations. These are mentioned in Chapter 2.

Chapter 2: Review on the level of the Centre as an organisation

Brief description of the Centre
The mission of the Netherlands Metabolomics Centre is the creation of a world-class metabolomics knowledge infrastructure to improve personal health and quality of life.

The Netherlands Metabolomics Centre is a public-private partnership between the following organisations: Unilever, DSM, MSD, TNO, Plant Research International / Wageningen University, University Medical Centre Utrecht, University of Amsterdam and Leiden University / Leiden University Medical Centre.

NMC is one of the four technology centres of the Netherlands Genomics Initiative, and one of the in 16 Genomics Centres in the Netherlands. In 2006, NMC received a start-up grant of € 1 million from the Netherlands Genomics Initiative, followed in 2008 by a grant of € 25 million for research and, in addition, € 1.5 million for valorisation. All partners together invest another € 26.5 million in matching activities. The NMC-program started in the summer of 2008.

Overall evaluation of the Centre as organisation:

Quality:	5
Productivity:	4
Relevance:	5
Valorisation:	4
Vitality and feasibility (viability):	4

Summary
The overall judgment of the Committee on the NMC is that the approach within the NGI is very unique; this has led to a world class Centre where the various relevant technologies, disciplines and application expertise's for metabolomics research come together in a unique manner at a world class level. This organizational structure has led the Committee to believe that the institute currently has a lead over international competition, but this lead of approximately two years has to be sustained in the near future and this will require, among others, some future actions as described below.

Presently, the NMC is still in an early phase of development (it started in 2008) fully in line with expectations for such a break-through technology area. To reap the full benefits the management should do everything it takes to create a situation where the programs can be continued for at least a further 5-7 years; this is required to sustain the world-class level and to maximise the potential of the invested capital. The Committee believes that the additional investment will have the potential for the NMC to further perform on a world-class level, which will lead to the attraction of international R&D and concomitant international research grants, will contribute to the critical mass of the Dutch life sciences community and will help create a highly educated workforce in The Netherlands.

The scoring of the NMC as a whole is based on the observations within the various Themes as well as discussions with the management and the advisory board. They should also be seen in the context of the recommendations the committee has made (Chapter 4) and which the committee trusts will be implemented to strengthen the NMC to deliver the ambitions. Specific attention should be given to valorisation. The NMC is performing well compared to the average of the NGI achievements in patent production and attracting companies (the main scoring parameters of the NGI). However, much more attention could be given to attracting (foreign) research grants, a parameter not on the NGI scoring list (see also Chapter 4).

Chapter 3: Assessment of the NMC Research Program

The Committee assessed the following nine Themes that constitute the NMC Research Program:

Research Themes
- Quantitative profiling Research Theme
- Metabolite Identification Research Theme
- Biostatistics Research Theme

Technology Platforms
- Data Support Platform Initiative
- Demonstration and Competence Lab

Associate Projects
- Nutrition and Health Associate Project
- Plant Associate Project
- Microbial driven Associate Project
- Biomedical Associate Project

The assessment of the Committee, both quantitative and qualitative, is described in this chapter of the report.

- **Quantitative Profiling Research Theme**

Theme Leader:	Hans-Gerd Janssen (Unilever)
Research years (NGI Grant):	38
NGI Grant:	€ 4.471.992
Matching:	€ 3.800.000
% of total grant used by Dec 2010:	55%

Assessment

Quality:	4
Productivity:	4
Relevance:	4
Valorisation:	4
Vitality and feasibility:	4

Qualitative assessment and recommendations
The aim of the NMC Quantitative Profiling Theme is to develop a new generation of metabolomics platforms inspired by biology and driven by technological opportunities. Two groups of projects can be distinguished within this Theme:

1. Projects that focus on specific regions of the full metabolome with region selection being driven by biological needs;
2. Projects that aim to develop innovative analytical technologies for future generation metabolomics platforms.

A total of 11 interdependent projects have been defined. The projects started approximately 1 and 2.5 years ago.

The Quantitative Profiling projects are currently addressing key fundamental issues encountered in metabolomics including limited chemical annotations/biological context, depth-of-coverage, dynamic range, spatially & temporally resolved sampling, and knowledge extraction. Thus, the projects define a sound trajectory and there is great enthusiasm for these efforts. This team is critical for the future success of NMC. This future success will depend on linking the technology push with a biological/clinical pull. The ingredients seem to be in place.

The team has apparently developed a set of assays. However, the overall strategy and direction of the concerted efforts were not immediately obvious. The team is encouraged to provide greater quantification of their deliverables and define future milestones more clearly.

Data processing is a critical component in quantitative profiling. At the moment it is not clear how the Quantitative Profiling data processing groups are interacting with the other computational groups within the NMC such as the Biostatistics Research Theme and the Data Support Platform.

The productivity in terms of papers is average. Therefore, the team should put in place a more aggressive publication strategy; a 'culture for publishing' should be fostered. Although the Committee acknowledges that the Dutch PhD model also leads to longer 'run-in' times before projects deliver. The team has generated a number of patents, however, at the moment the value of these patents is unclear. Identification of specific commercial partners for the patents would be beneficial.

The network of the team appears to be mainly Dutch. This is understandable given the fact that they are building a technology infrastructure in The Netherlands. However, the team is encouraged to look for input from around the world and to continue to benchmark their work to the leading international groups.

The Committee recommends flux analysis as a potential future focus area.

- **Metabolite Identification Research Theme**

Theme Leader:	Albert Tas (TNO)
Research years (NGI Grant):	20
NGI Grant:	€ 2.116.555
Matching:	€ 1.100.000
% of total grant used by Dec 2010:	62%

Assessment

Quality:	3
Productivity:	3
Relevance:	4
Valorisation:	3
Vitality and feasibility:	4*

**The vitality and feasibility of this theme is rated as 'very good' (4). However, to maintain this current score in the future, actions have to be taken by the NMC management team to adjust this Theme. The NMC has indicated that they are already implementing changes.*

Qualitative assessment and recommendations

The aim of this Theme is the development of new databases, methods and tools to aid in the identification of currently unknown metabolites. This Theme operates in an important area and there is a compelling need for confident metabolite identification strategies as this is fundamental to providing a biochemical context to profiling data.

In the Metabolite Identification Research Theme there is a substantial emphasis on MSn fragment trees as a primary mechanism for identification. However, progress towards this goal has been somewhat unclear. Furthermore, it is not clear how other orthogonal data and alternative approaches to metabolite identification such as traditional tandem MS/MS, chromatographic retention and UV absorption data are being utilized.

A substantial focus has been invested in the technical research components, but substantially less effort has been invested in addressing the metabolite identification needs of the application areas.

The current trajectory of the overall group appears somewhat fragmented, i.e. in that most groups appear to operate independently and there was not a clear sense of interactions between the groups; it is advised to further strengthen the team leadership.

The Committee found it difficult to truly gauge what outputs have been produced. When the team was queried, clear quantifiers of output were not provided. The team needs to be more explicit with respect to the numbers and types of metabolites identified; they should also develop a more strategic and interactive plan for this group. Furthermore, the Committee had some questions about the uniqueness of the approach, there are also other tools that can enable confident identifications based upon MS/MS data, which is typically easier and faster to obtain.

The Committee urges the team to build clear pipelines for metabolite identification, defining what has been achieved now, what will be ready in 1 or 2 years and how they can offer their achievements to the world. This should also be understandable to the external community. According to the Committee, the team should also aim to review and align with the Metabolomics Standards Initiative's suggestions with regards to chemical identification.

- **Biostatistics Research Theme**

Theme Leader:	Renger Jellema (DSM)
Research years (NGI Grant):	26
NGI Grant:	€ 2.495.850
Matching:	€ 1.400.000
% of total grant used by Dec 2010:	44%

Assessment

Quality:	5
Productivity:	4
Relevance:	5
Valorisation:	4
Vitality and feasibility:	4

Qualitative assessment and recommendations
The aim of the projects within the Biostatistics Research Theme of the NMC is to develop statistical tools that will serve in creating information from metabolomics data.

Robust data analyses are key in order to design metabolomics experiments as well as to analyse robustly the results of these measurements. This Theme of the NMC brings together some excellent scientists in the area with an international metabolomics presence. The team seems to be able to address the important challenges to metabolomics: how to manage the different streams of data that are generated. Good outputs have been generated and novel algorithms developed in MATLAB and R, which have been released for NMC users and beyond.

The Biostatistics team appears to be a strong team with a great capacity. There seems to be a lot of interaction within the team, and with the Associate Projects of the NMC (e.g. through data provision by the Nutrition & Health projects).

A current challenge for the team seems to be to acquire 'real' data, representative of typical metabolomics investigations (in particular those from longitudinal studies). The Committee encourages the team to look outside of the NMC and abroad for data; this has not been done thus far. The team should do this in a more pro-active fashion. Acquiring 'real' data does have a preference over synthetic data, but the lack of 'real' data must never hold the team back. If 'real' data cannot be acquired, the team should go forward using synthetic data, but should reassess whether they are trying to address is a relevant problem.

The group should take a good look at its valorisation activities: are they doing enough? The Biostatistics team should work closely with the Data Support Platform to make results more accessible. For example, the algorithms should be made easily available on the NMC website and elsewhere, and logs should be kept of downloads as this can be a useful additional metric for valorisation.

- **Data Support Platform**

Theme Leader:	Margriet Hendriks (UMCU)
Research years (NGI Grant):	22 (programmers)
NGI Grant:	€ 804.408
Matching:	€ 300.000 (excl. co-financing by NBIC)
% of total grant used by Dec 2010:	70%

Assessment

Quality:	5
Productivity:	5
Relevance:	5
Valorisation:	4
Vitality and feasibility:	4

Qualitative assessment and recommendations
The aim of this project is to develop a data support platform for metabolomics studies to support storage of experimental metabolomics data and their processing. This bioinformatics support platform will provide a means for communication between the partners of the NMC for the exchange of data, software, and tools.

It aims to create:
- A metabolomics data warehouse as a repository of metabolomics data which can be researched as a whole (including analytical (raw) data, processed data (e.g. metabolite concentrations), study design information and other meta-data);
- A data processing infrastructure, containing tools supporting the metabolomics workflow. These can be used in connection with the data warehouse, or separately from it. The platform wants to provide web services, support for software development, and set standards.

The Data Support Platform is developed in collaboration with the Netherlands Bioinformatics Centre (NBIC). Funding of personnel was shared between NBIC and NMC.

This group provides a critical infrastructure for the NMC and warrants priority funding in the future should tough budget decisions be necessary. The viability could be threatened by lack of long-term support and it is vital that this is not lost. This team appeared to be a cohesive group of individuals that embedded themselves in the more global community as well as other national efforts in The Netherlands.

The Committee would like to recommend the team to try to engage with the European Bioinformatics Institute, which is setting standards for metabolic databases.

The Data Support Platform has a lot of potential, but is not yet delivering up to full capacity; they require a clear strategy to achieve their valorisation potential. This strategy is not yet in place.

- **Demonstration & Competence Lab**

Theme Leader:	Rob Vreeken (Leiden University)
Research years (NGI Grant):	30 (analysts)
NGI Grant:	€ 3.611.473
Matching:	€ 1.000.000
% of total grant used by Dec 2010:	60%

Assessment

Quality:	4
Productivity:	4
Relevance:	4
Valorisation:	4
Vitality and feasibility:	4

Qualitative assessment and recommendations
The Demonstration & Competence Lab's primary role is the application of state-of-the-art technologies and tools for demonstration purposes and/or feasibility studies for members & collaborators of the NMC and the dissemination of knowledge via the analysis of cohorts and through the use of identification services, hosting associate researchers and providing training courses for scientist.

The team seems actively engaged, and the quality of work is good and the flow of methods from development to Demonstration & Competence Lab is admirable.

The report by the team was lacking in core statistics such as the number of analyses per year, number and types of molecules quantifiable, including the level of quantification (absolute or relative) and the ability to map these onto pathways. The utility and uniqueness of the spectral database is not fully convincing to the Committee. In addition, the strategy for systematic identification is not clear, as is the strategy for achieving robustness. The overall capability needs to be much more visible on the NMC website. There is clear opportunity for improvement here.

Considerable viability for the Demonstration & Competence Lab is expected beyond 2012 if a sound business plan is in place. In this context: the Demonstration & Competence Lab has chosen not to acquire full ISO certification at the moment. However, if the NMC wants to exploit the Demonstration & Competence Lab as a provider to third parties, this may be important. The Committee also recommends the team to invest in monitoring and continuously improving customer service, customer satisfaction and analytical quality to better ensure success and long-term viability.

- **Nutrition & Health Associate Project**

Theme Leader:	John van Duynhoven (Unilever)
Research years (NGI Grant):	14
NGI Grant:	€ 2.446.066
Matching:	€ 6.400.000
% of total grant used by Dec 2010:	64 %

Assessment

Quality:	5
Productivity:	4
Relevance:	5
Valorisation:	4
Vitality and feasibility:	5

Qualitative assessment and recommendations
The Nutrition & Health Associate Project consists of a number of 3-year projects, involving 21 fte. The Associate Project consists of four components: Diet-Gut Interactions (Food Formats), Gut and Immune Health, Diet and Global Cardiometabolic Risk and Plasma Driven Network Biology.

The team looks strong and cohesive, with an important involvement of private partners (DSM and Unilever). The Committee noted and strongly endorsed the decision of the team to abandon the focus on applying metabolomics solely to longitudinal dietary intervention studies and moving toward acute intervention studies. Such studies can of course be incorporated into longitudinal intervention studies as 'acute-on-chronic' studies, particularly where a cross-over design is involved.

Overall, the work is impressive but, for reasons of the strategy change mentioned above, has obviously had a low initial output making it difficult in a Mid-Term Review to exactly match the original deliverables with the achievements. However, the trajectory for the research output looks very productive. The results of the Diogenes and ADMIT studies will be important for the reputation of the NMC.

Despite rather low sample numbers in Diogenes, there is potential for GWAS-metabolite correlations to give considerable added value for nutritional studies (and indeed clinical ones), this should be explored more fully.

The team may need to consider whether the studies they are conducting will be suitable for providing 'proof of principle' to regulators such as FDA (e.g. due to sample size). In addition, interpretation of metabolite data from gut microflora (microbiome), which may be present in circulatory biofluids, needs to be carefully considered given the vast variability between individuals.

The collaboration with TI Food & Nutrition will gave a basis for the future and the likely success in EU FP8 grants bodes well for the sustainability of this area.

- **Plant Associate Project**

Theme Leader:	Ric de Vos (Plant Research International)
Research years (NGI Grant):	6
NGI Grant:	€ 949.842
Matching:	€ 500.000
% of total grant used by Dec 2010:	50%

Assessment

Quality:	5
Productivity	4
Relevance:	5
Valorisation:	4
Vitality and feasibility:	4

Qualitative assessment and recommendations
The Plant Associate Project within the NMC consists of two research projects. For these research projects the NMC works closely together with the Centre for BioSystems Genomics (CBSG). The Plant Associate Project is relatively small compared to other NMC projects. It consists of two subprojects of 1 fte each for a period of three years. The first project started in August 2008 and aims to develop new statistical tools to cope with the wealth of data from large-scale metabolomics, phenotyping and genotyping studies, focusing on the data generated within the tomato quality cluster of CBSG. The second project will start in 2011 and aims to develop and use metabolomics tools to get a better insight into the mechanisms and cellular processes underlying plant-pathogen interactions. This second project is still under development, thus difficult to assess.

CBSG/Wageningen is one of the best places in the world to conduct plant metabolomics research, and the Committee is assured that the NMC's work in this area will be an integral part of a world-class plant research environment and will deliver high quality results. The Plant Associate Project is strongly dependent on it being embedded in the CBSG, the project does not seem feasible without the support of the CBSG.

Since only the first project has started, the Committee can only incorporate this project in its assessment. This project is mainly computational in nature and data fusion tools appear to have been developed. However, the final outcomes were still unclear, i.e. which genetic markers, metabolites and sensory characteristic were associated with each other and how these will be used in future studies or commercial applications. It was also hard to assess the true potential for valorisation. For these and other projects in this area business cases may be hard to define due to the, potentially, high costs of targeted breeding based on metabolomics, compared to alternatives.

- **Industrial Biotech Associate Project**

Theme Leader:	Marcel van Tilborg (DSM)
Research years (NGI Grant):	8
NGI Grant:	€ 1.098.000
Matching:	€ 1.100.000
% of total grant used by Dec 2010:	27%

Assessment

Quality:	5
Productivity:	4
Relevance:	5
Valorisation:	4
Vitality and feasibility:	5

Qualitative assessment and recommendations
The Industrial Biotech Associate Project is a small project (2 PhD students, 8 research years). The focus of the project is on the influence of the exometabolome, the metabolites present in the environment of the microorganism, on the intracellular metabolome. Better understanding of disturbances will lead to better performance of industrial fermentation processes. Within this context, two industrial problems were chosen in the area of the 'meaty' taste of yeast extracts and biofuels.

This project is embedded in a very strong industrial context. The projects are dependent on the Kluyver institute and DSM, their infrastructures and intellect brings considerable added benefit. The Committee expects that the project should deliver very interesting results. However, at the moment of evaluation only one project has started.

The yeast lines selected in this first project that has already started are based on industrial relevance and have excellent support from DSM in terms of genome sequence, transcriptomics, enzymatic kinetics as well as mapping these onto metabolic pathways. The genetics/environmental experiments could be world class if delivered.

The meat flavour focus of the second project would have excellent valorisation opportunities if it can deliver; this will be dependent on NMC's ability to identify novel compounds. The Committee is positive about the experimental design chosen in this project (e.g., with the inclusion of an olfactory panel). If successfully executed, the results from this project could lead to a good pool to draw from for future projects and funding.

- **Biomedical Associate Project**

Theme Leader:	Ton Rullmann (Merck)
Research years (NGI Grant):	35
NGI Grant:	€ 5.115.016
Matching:	€ 6.900.000
% of total grant used by Dec 2010:	12%

Assessment

Quality:	4
Productivity:	-*
Relevance:	4
Valorisation:	-*
Vitality and feasibility:	4

** The Committee did not rank the productivity and valorisation, as many of the projects in this Theme were still in their early stages.*

Qualitative assessment and recommendations
The Biomedical Associate Project of the NMC aims to identify biomarkers for several important diseases, and to contribute to the biological understanding of the underlying pathologies. The emphasis is on metabolomics-based phenotyping of diseases or drug treatment effects in humans and in animal models.

The Biomedical Associate Projects appeared quite diverse and were designed in a manner to optimize coverage of other NGI programs. The selection of projects was based on maximizing synergy with other NMC initiatives, and aimed at the validation of the rich pipeline of metabolomics platforms within NMC. This is seen as an important first step towards using metabolomics platforms for translational research and biomedical applications. The Committee appreciates this approach. For the future the Committee suggests that the NMC may want to focus more strategically on a smaller number of projects initially, so as to ensure better success and elevated impact. A clear success story ('home run') will provide greater recognition for the NMC and will better demonstrate the capabilities of metabolomics.

The team is attracting external funding for elements in the project; this is a sign of added value of this project within the context of the NMC.

The Committee has noted that a pipeline with respect to biostatistics and measurement is in place, and that clinicians appear to be signed up to this. This is a positive sign. A risk for this project is the uncertainty about the future of the R&D facility of MSD in The Netherlands; the NMC management is encouraged to monitor developments and their effects on the two projects involved.

Although the Theme is still in an early phase, the Committee is positive about its prospects and looks forward to learning about future results.

Chapter 4 General conclusions and final recommendations

The overall judgment of the Committee on the NMC is that the approach within the NGI is very unique; this has led to a world class Centre where the various relevant technologies, disciplines and application expertise's for metabolomics research come together in a unique manner at a world-class level.

In addition to the Theme-specific recommendations and suggestions, for which the Committee trusts that they are approached in an appropriate way by the NMC management team, there are several points the Committee would like to make for immediate action:

- International Scientific Advisory Board

The Committee perceived a strong need during the interviews to have in depth scientific discussions, challenges and guidance, which the Committee, unfortunately, could not provide, as this would be far beyond the scope of the assignment of the Committee. Therefore, the Committee strongly recommends establishing an International Scientific Advisory Board, with the right briefing with respect to the depth of the discussions, its objectives and with sufficient time to truly contribute to the development of NMC through a detailed critical review. This advisory board should bring together technological and biological knowledge and expertise from the clinical and application sides.

- Valorisation

Some valorisation activities have been successfully started, such as the submission and filing of several patents (quantitatively below target but fully in line with the actual NGI average) and the preparations for at least two spin-off companies. Companies are heavily involved as partners in the research program, and the NMC provides expertise to several other centres in the life sciences fields. Still, the targets, metrics and strategy should be reviewed urgently and rigorously. The Committee made the following observations:

- NGI sets targets on, e.g., the number of patents. To the Committee many of these targets (including the target for patents) seem unrealistic. This is especially true as the NMC develops enabling technologies, where much of the valorisation will occur in other life sciences areas that will use the developed technology. According to objective data on this matter presented to the Committee by a valorisation professional, the NGI targets are a factor three too high. This is also reflected in the total number of patents which have been produced within the NGI overall. Based on these independent international criteria the NMC actually scores above average. Moreover, the true value of technology-based patents should be critically reviewed. The Committee thought it would be a waste of valuable resources to patent for the sake of it without these patents going onto commercial fruition.
- The definition of valorisation is unclear to various scientists. In the self-assessment activities are put forward as 'valorisation' that in the opinion of the Committee are the normal results of work packages handed over to another project/Theme within the NMC according to the research plan.
- The valorisation strategy and priorities are unclear. There are many interesting initiatives listed, but without a proper analysis, it is difficult to establish their true value, what the risks are and what resources are needed to achieve this value. These points seem essential for a proper prioritization.
- There seems to be insufficient recognition by the NGI/the Dutch government of the value of obtaining grants from international sources. As one of the Committee Members put it: "Should you focus on making a few hundred thousand dollars from patent licensing or many millions of dollars

through high level grants?" However, for this the NMC needs a much better visibility to the outside world. It is therefore also recommended to consider investing the valorisation budget in making the NMC much more visible as THE partner for metabolomics research.

- Overall, the Committee advises the NMC to develop another valorisation strategy, based on other objectives. The Committee finds the use of the developed knowledge (for instance by measuring the number of downloads of a software package) at least as relevant as the number of patents filed. The NMC should develop itself as a highly visible, world-renowned metabolomics centre.

- International reputation and visibility

For a good international reputation it is crucial and essential to have an excellent publication portfolio. In almost all of the themes, publications are lagging behind both in quantity and quality. There should be a strong focus on correcting this, as the scientific progress in the NMC does make this possible. Moreover, it should be considered whether a few topics could be identified which are especially suited for this purpose ('home-runs') and get the required resources in place for these projects.

Furthermore, the NMC is not well known yet and recognized for its real value globally. It is recommended to put in place an "outreach" policy addressing which stakeholders (from international scientists up to the R&D heads in major companies) should be approached and in what way. Also, information brochures, and most importantly, an up-to-date exciting websites should be a central part of this outreach strategy. Organization of training and courses can further strengthen the profile of the NMC

- Organization and management

The management states correctly that the way in which the NMC is organized and has to operate is rather complex and a significant challenge. However, this organizational structure is also one of the key differentiators and therefore success factors of the NMC. The Committee realizes that government subsidies are to be spent on research rather than management and overheads, but the Committee is of the opinion that the management of the NMC needs, for the reasons above, more attention of all involved than other institutes should require. The Committee sees the following improvement opportunities (in addition to the immediate installation of an International Scientific Advisory board):

Theme Leaders are in place for all of the nine Themes, but increasing their leadership, empowerment and accountability for delivery can have a strong impact on the effectiveness of the scientific work and the implementation of the various recommendations made by the Committee. It might require some further training of Theme Leaders on the non-scientific aspects of these roles. Evaluation of each of the Theme Leaders and an assessment of whether they can live up to this more demanding role seems appropriate. If functioning in this way, they can form an excellent team under the leadership of the scientific director.

The Committee understood that flexible allocation of resources is not easy to execute for reasons that are inherent to the Dutch funding system. Nevertheless, the Committee would recommend to analyse whether some form of flexible allocation can be made possible as this is key to identifying potential 'home-runs' and subsequently executing them. This is also a very important element for achieving a better international visibility.

The Supervisory Board of the NMC has, as perceived by the Committee, a role that is somewhat at a distance, as is usual for these types of bodies. However, given the phase the NMC is in with respect to short- and long-term strategy adaptation to rapidly changing requirements, activities to develop, and uncertainties about budgets, the Committee recommends a 'closer' and more active position of the Supervisory Board.

This allows the management to make use of a more frequently available sounding board but avoids detailed management by the Board.

The management twin construction, with a scientific and a managing director, is seen as a good and strong concept. The Committee has high expectations that the newly appointed managing director can tackle the management challenges mentioned above.

Appendix 1: Brief Curricula Vitae of Committee members

Dr. Nico Overbeeke (chairman):
My scientific research education started with a major in molecular biology (Vrije Universiteit), followed by a thesis in this area on Pore proteins in the Outer Membrane of E.coli (University of Utrecht). It developed further through a post-doc on the replication of the chloroplast DNA in Petunia for which several grants were obtained and a team with 4 PhD students formed (Vrije Universiteit). After that, my molecular biology expertise was applied and further developed through cloning and expressing a gene from the Guar plant in various yeast strains with the aim to produce in a commercial way the α galactosidase enzyme (Unilever). In this total period I produced more than 20 original papers in peer reviewed journals, more than 10 reviews and chapters in books, several patents and numerous poster presentations on international symposia and congresses. I started with some colleagues from universities in The Netherlands a community of scientists working with yeasts and was one of the organizers of the 15th International Conference on Yeast Genetics and Molecular Biology (1990, The Hague). After this, I switched to Research and Business management within Unilever with a.o. the development of margarine flavours for the worldwide product portfolio, company development manager Foods in Germany, with a big expansion to the eastern part of Europe, Board member of Langnese Iglo (rolling out e.g. Magnum from Germany to the world). In this period the first GMO products were coming from the USA to Europe (soy). Managing all the various stakeholders through the whole chain (scientists, suppliers, producers, retail, consumers) was a very interesting challenge. After that, as member of a business unit team (small multi-functional teams) I was responsible for the innovation strategy, project portfolio, execution and implementation, worldwide, usually with a total sales volume of several billions of dollars. One of the highlights was the first worldwide launch of a 'functional food', Becel Pro.Activ with plant phytosterols. In this role there was always a strong research element, from basic academic science up to application and development. Amongst others, set-up of a new way of open innovation cooperation with academic scientists, suppliers, where a new way of networking was established.

The common theme in all past and present activities is finding breakthrough scientific challenges and identifying ways to apply these for social and commercial benefit.

Dr. Mike Gibney:
I graduated from UCD with an MAgrSc in 1971 working on lipid metabolism in lambs and took up a teaching fellowship at the University of Sydney's Veterinary School and was awarded a PhD in 1976 for work on the digestive physiology of the neonatal lamb. From there I moved to human nutrition with a lectureship at the University of Southampton Medical School in 1977 and then returned to Dublin to take up a post at Trinity College Dublin in the Department of Clinical Medicine as professor of nutrition. During that time I served as Dean (Vice President) of Research. Twenty-three years later in 2006, I moved to UCD to take up the post of Professor of Food and Health. I served on the EU Scientific Committee for Food from 1985 to 1997 and chaired the working group on nutrition. From 1997 to 200 I served on the EU Scientific Steering Committee and was chair of its working group on BSE. In 2010, I was appointed to the Scientific Advisory Board of the European Joint Programme Initiative on Food and Health Research.

Dr. Roy Goodacre :
Educated in University of Bristol, UK where he was awarded his BSc in Microbiology and his PhD in analytical methods applied to microbiological problems. After which he did a three-year PDRA in University of Wales, Aberystwyth, UK and then four years as a Wellcome Trust Fellow where he investigated chemometrics and artificial neural networks for the analysis of spectroscopic data. Following this he was appointed a Lecturer in Microbiology. He moved in Feb 2003 to take up the position of Reader in Analytical

Science in the School of Chemistry , The University of Manchester, UK. His current position since Aug 2005 is as Professor of Biological Chemistry.

Dr. Rima Kaddurah–Daouk:
Dr. Kaddurah-Daouk trained in biochemistry at the American University of Beirut with post graduate training in molecular biology and genetics at Johns Hopkins where she worked with Nobel Laureate Hamilton Smith. She did subsequent training at the Massachusetts General Hospital followed by appointment in the Biology department at the Massachusetts Institute of Technology. She is currently Associate Professor at the Duke Medical Center and head of the newly established Pharmacometabolomics Center. Dr. Kaddurah-Daouk has been a seminal force in the development and evolution of the metabolomics field. She cofounded the Metabolomics Society, served as its founding president and for over four years coorganized national and international meetings and workshops on metabolomics and helped bring membership of society to over 500. She also cofounded a leading biotechnology company devoted to metabolomics applications. Dr. Kaddurah-Daouk has extensive experience in assembling teams of researchers to work collaboratively on large scientific projects and has lead scientific programs from an early stage of discovery through clinical trials. She established and leads the Metabolomics Research Network with funding from NIGMS (R24 grant and RC2 stimulus funding) with the goal of integration of metabolomics and clinical pharmacology in an effort to personalize treatment. Additionally she has built a comprehensive metabolomics program at Duke for mapping biochemical underpinnings of neuropsychiatric diseases. Her work with the creatine kinase system earlier in her career resulted in the identification of neuroprotective properties of creatine and partnerships she established between academia, NIH, biotech and the non profit organizations lead to phase III clinical trials that are ongoing in over 50 centers for Parkinson's and Huntington's Diseases with one of the largest investment from NIH for a natural compound for the treatment of a CNS disease.

Dr. Lloyd Sumner:
Dr. Sumner acquired his B.S. degree in chemistry and mathematics in 1989 from Cameron University in Lawton, OK and a Ph.D. in analytical chemistry in 1993 from Oklahoma State University in Stillwater, OK. He then joined Texas A&M University, College Station TX, where he was the Director of the Mass Spectrometry Applications Laboratory and where he later served as the cofounder and Associate Director of the TAMU Laboratory for Biological Mass Spectrometry with Prof. David H Russell. He joined The Noble Foundation in 1999 and has risen to the rank of Professor in the Plant Biology Division. While at the Noble Foundation, Dr. Sumner has built a research program focused around large-scale profiling of plant proteins and metabolites (proteomics and metabolomics) which provide greater insight into the physiological and biochemical consequences of gene expression and system responses to genetic and environmental perturbations. Much of this work has focused upon secondary metabolism. In the process, he has published close to 90 peer reviewed articles and book chapters. Dr. Sumner's research is supported by The Samuel Roberts Noble Foundation, The NSF 2010, NSF Molecular and Cellular Biosciences, and The Oklahoma Commission for the Advancement of Science and Technology. Dr. Sumner is currently a Fellow of The American Association for the Advancement of Science, Treasurer and past President of the Metabolomics Society, Founding Member of the International Advisory Committee for Plant Metabolomics, Adjunct Professor at Oklahoma State University Department of Biochemistry and Molecular Biology, and a Distinguished Alumni of Cameron University. Dr. Sumner serves as a Managing Editor for Plant Physiology. He is also an Editorial Board member for the journal Metabolomics and the newly formed journal Frontiers in Plant Biotechnology.

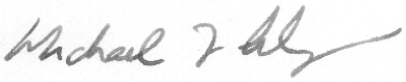
Appendix 2. Statement of independence

I declare that my assessment of Netherlands Metabolomics Centre is unbiased and independent. I will report any existing professional relationships with research groups under review in the Committee meeting.

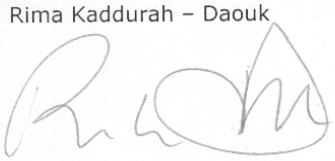
Leiden, 20 March 2011

NicoOverbeeke (chairman)

Mike Gibney

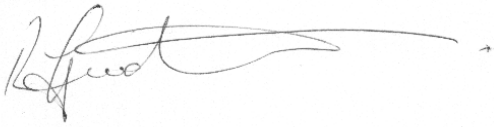


Rima Kaddurah – Daouk



Lloyd Sumner

Roy Goodacre



Appendix 3. Overview of the Committee scores

	Centre overall	Quant. Profiling	Metabol. Identific.	Biostat.	Data Support Platform	Dem. Comp. Lab	Nutrition & Health AP	Plant AP	Industrial Biotech AP	Biomed. AP
Quality:	5	4	3	5	5	4	5	5	5	4
Productivity:	4	4	3	4	5	4	4	4	4	-[b)]
Relevance:	5	4	4	5	5	4	5	5	5	4
Valorisation:	4	4	3	4	4	4	4	4	4	-[b)]
Vitality & feasibility:	4	4	4[a)]	4	4	4	5	4	5	4

a) If actions are taken by the NMC management team to adjust this Theme.
b) The Committee did not rank the productivity and valorisation, as many of the projects in this Theme were still in their early stages.

About the scores:

5= Excellent	Research is world leading. Researchers are working at the forefront of their field internationally and their research has an important and substantial impact in the field.
4= Very good	Research is internationally competitive and makes a significant contribution to the field. Research is considered nationally leading.
3= Good	Work is competitive at the national level and makes a valuable contribution in the international field. Research is considered internationally visible.
2=Satisfactory	Work adds to our understanding and is solid, but not exciting. Research is nationally visible
1=Unsatisfactory	Work is neither solid nor exciting, flawed in the scientific and or technical approach, repetitions of other work, etc.

Appendix 4. Meeting schedule Committee

Netherlands Metabolomics Centre Peer Review 2011 March 20 – 22nd
Nico Overbeeke (chair) [NO], Mike Gibney (University College Dublin) [MG], Rima Kaddurah – Daouk (Duke University) [RK], Lloyd Sumner (Noble Foundation) [LS], Roy Goodacre (University of Manchester) [RA] and Pieter Stolk (secretary)

Sunday, March 20th 2011

17.00 Arrival and check-in at Holdiday Inn, Leiden

18.00 Drinks

19.00 Dinner
[Douwe Breimer, Thomas Hankemeier and Merlijn van Rijswijk]

Monday, March 21st 2011 (Leiden)

07.30 Working breakfast Peer Review Committee and transfer to Leiden University

09.00 Introduction Peer Review by director Netherlands Genomics Initiative
[Colja Laane]

09.45 Interview Founding Fathers on background NMC and future perspective
[Thomas Hankemeier, Marcel van Tilborg, John van Duynhoven, Ruud Berger and Age Smilde]
Committee Lead: [NO] Back-up: all

10.45 Interview Quantitative profiling research theme
[Hans- Gerd Janssen, Thomas Hankemeier, Arjan Brenkman]
Committee Lead: [LS] Back-up: [RK]

11.45 Interview Metabolite Identification research theme
[Albert Tas, Theo Reimers, Ric de Vos, Jacques Vervoort, Leon Coulier en Rob Vreeken]
Committee Lead: [LS] Back-up: [RG]

12.45 Lunch

13.30 Interview Biostatistics research theme
[Renger Jellema, Age Smilde, Fred van Eeuwijk, Margriet Hendriks, Huub Hoeksloot en/of Johan Westerhuis]
Committee Lead: [RG] Back-up: [RK]

14.30 Interview on Valorisation activities
[Merlijn van Rijswijk, Thomas Hankemeier, Bob Smailes (LURIS), Frits Fallaux (UU)]
Committee Lead: [NO] Back-up: [RK]

15.30 Break

15.45 Interview Data Support Platform initiative
[Margriet Hendriks, Theo Reimers, Jildau Bouwman]
Committee Lead: [RK] Back-up: [MG]

16.30 Visit and interview Demonstration and Competence Lab
[Rob Vreeken, Adrie Dane, Thomas Hankemeier]
Committee Lead: [MG] Back-up: [RG]

17.30 Interview Supervisory Board
[Douwe Breimer, Robert Hall, Jan Maat]

18.30 Evaluation and discussion by Committee

20.00 Dinner with members of Executive and Supervisory Board

22.30 Transfer to Vlaardingen

Tuesday, March 22nd (Vlaardingen)

07.30 Working breakfast Peer Review Committee and transfer to Unilever Research Laboratory (within walking distance)

09.00 Welcome and visit of Unilever Research Laboratories

09.30 Interview Nutrition and Health associate projects
[John van Duynhoven, Age Smilde, Thomas Hankemeier, Marcel van Tilborg and Ben van Ommen]
Committee Lead: [MG] Back-up: [LS]

10.30 Interview Plant associate projects
[Ric de Vos, Robert Hall, Fred van Eeuwijk]
Committee Lead: [LS] Back-up: [RG]

11.00 Interview Microbial driven associate projects
[Marcel van Tilborg, Peter Punt]
Committee Lead: [RG] Back-up: [RK]

11.30 Interview Biomedical associate projects
[Ton Rullmann, Thomas Hankemeier, Ruud Berger, Michel Ferrari]
Committee Lead: [RK] Back-up: [MG]

12.30 Lunch with management team NMC, possibility to ask questions
[Thomas Hankemeier, Merlijn van Rijswijk, Douwe Breimer]

13.30 Evaluation and discussion by Committee

15.00 Presentation of conclusions by Peer Review Committee
[Thomas Hankemeier, Merlijn van Rijswijk, Douwe Breimer]

16.00 End of visit / departure