PROMETHEUS
METABOLOMICS

Business Plan

PROMETHEUS METABOLOMICS LTD

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This document is confidential.

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Executive Summary

A. Vision/Mission Statement

To provide high-throughput solutions for clinical research through integration of statistical analysis with the biomedical sciences.
To foster new diagnostic approaches and achieve leadership in biomedical area, the development of novel technologies and to facilitate novel clinical applications.

B. Company Summary

The company is owned and managed by Mr Mirko Mori (Chief Executive Officer) and Mr Stefano Cacciatore (Chief Scientific Officer); the company management ensures an appropriate mix of expertise: operation/organization and scientific skills.

Mirko Mori PhD, has extensive and international expertise in quality, operation and project management in the pharmaceutical area.

Stefano Cacciatore PhD, has a highly personable scientific background in data analysis and in nuclear magnetic resonance (NMR) spectroscopy applied to the analysis of biological samples.

C. Products/Services

The study of the small-molecules (a.k.a. metabolites) has shown considerable promises in disease diagnosis and biomarkers discovery. Precise metabolite quantification is a prerequisite to move any chemical biomarker or biomarker panel from the laboratory to the clinic. PROMETHEUS METABOLOMICS LTD makes progress toward fully automated and reliable metabolite quantification for an efficient high-throughput tool of clinical analysis. Using NMR spectroscopy and advanced methods of data analysis, PROMETHEUS METABOLOMICS LTD offers an extensive portfolio of services for metabolite analysis in biological samples (e.g. urine, plasma/serum, faecal extract, tissue).

D. Market Assessment

To date, 689 clinical trials (registered at US National Library of Medicine) included metabolite analysis. Metabolite analysis represent a sector with an exponential trend of growth. Hospital, universities and research centers can take advantage by the analytical services offered by PROMETHEUS METABOLOMICS LTD for analysing biological samples.
The main advantage of PROMETHEUS METABOLOMICS LTD over other competitors is based on the usage of NMR spectroscopy as technique for chemical analysis. NMR spectroscopy offers higher reproducibility of the results at lower cost. This technique is still not fully exploited due to its time-consuming protocols. Using proprietary fully automatic procedures, PROMETHEUS METABOLOMICS LTD overcome these limitations offering in the market a very competitive tool of analysis at low price.

E. Strategic Implementation

PROMETHEUS METABOLOMICS LTD requires the involvement of high-level education employees for improving constantly its services of analysis and sale/marketing agents to promote its services to all potential customers. We estimate an initial investment of £200,000 for making fully operative the business of PROMETHEUS METABOLOMICS LTD and guarantee enough impact on the market. The initial investment gives us the opportunity to spread our services over the world and in the next future to patent worldwide the proprietary technology of PROMETHEUS METABOLOMICS LTD.

F. Expected Outcomes

For the short-medium term (within 3 years), we aim to acquire new clients for our consulting business by launching a marketing campaign, promoting our competitive services. This will allow us to grow our business and increase significantly our revenue.
For the long term (within 5 years), we would expand our portfolio increasing the number of services that we can offer to our clients becoming a world-wide company characterised by its acknowledged reputation and quality.

Vision/Mission Statement and Goals

A. Vision Statement

To provide high-throughput solutions for clinical research through integration of statistical analysis with the biomedical sciences.

To foster new diagnostic approaches and achieve leadership in biomedical area, the development of novel technologies and to facilitate novel clinical applications.

B. Goals and Objectives

PROMETHEUS METABOLOMICS LTD aims to offer high quality solutions for clinical research at a competitive price to meet the current market demand.

For the short term (within 12-18 months), we would acquire new clients for our consulting business by launching a marketing campaign, promoting our competitive services. This will allow us to grow our business and increase our revenue.

For the medium term (within 18-30 months), we would applicate to achieve a specific international patent of our technology.

For the long term (within 30-60 months), we would expand our portfolio increasing the number of services that we can offer to our clients.

C. Keys to Success

Keys to success for PROMETHEUS METABOLOMICS LTD will include:

- Providing the highest quality product available on the market
- Providing excellent and customized cutomers service
- Competitive pricing
- Growing and maintaing a referral network of clients
- Focususing expertise on samples commonly used in clinic area
- Assuring project flexibility
- Driving project performance
- Knowledge management and innovation attitude

Company Summary

A. Company Background

Our business is focused on offering a service of metabolomics analysis, an innovative method of chemical analysis of biological samples (e.g. urine, plasma/serum, tissue). PROMETHEUS METABOLOMICS LTD offers scalable, customizable research services to academic and industrial investigators in every area of the life sciences. Our technology is based on the state-of-the-art of nuclear magnetic resonance (NMR) spectroscopy techniques to detect small molecules (a.k.a. metabolites) in biological samples.

Our proprietary software allows the automatic detection and quantification of the metabolites by NMR spectroscopy. This quantitative information can be translated directly into clinical settings paying the way to the advance precision medicine and to the developing of novel clinical diagnostic tests that may improve early detection of several diseases. Our technology is designed to overcome the limitations due to the bottleneck of the current methods of data analysis of the information obtained by NMR spectroscopy.

The team is composed by Mirko Mori (*Chief Executive Officer*) and Stefano Cacciatore (*Chief Scientific Officer*). The company is owned and managed by its two partners and founders, which ensure an appropriate mix of expertise, quality and scientific skills, respectability.

Mirko Mori, PhD, has extensive and international expertise in quality and project management in the pharmaceutical area for more than ten years, working as external consultant for the major companies in the world (e.g. Teva Pharmaceutical, Baxter Healthcare, GlaxoSmithKline, Gilead Sciences, Novartis, Merck & Co, Johnson & Johnson, Sanofi, Pfizer). He worked for a world leader consultant company as project manager and then operation manager, managing projects proving direction, leadership and motivation to ensure that his team achieves the final target, the customer satisfaction and the operational goals. In this role, he got expertise on manufacturing and quality control processes applied to the pharmaceutical business, ensuring that all workings are manufactured in a correct, cost effective and timely manner in alignment with specifications and quality requirements.

Stefano Cacciatore, PhD, has a highly personable scientific background with over ten years of experience in NMR spectroscopy methodology and data analysis (i.e. machine learning and statistical analysis) with over 20 research papers published in peer-review journals. He worked for different academic institutes around the world: CERM (Florence, Italy), Dana-Farber Cancer Institute (Boston, USA), Imperial College of London (London, UK) and ICGEB (Cape Town, South Africa). His research focused on identifying metabolic profile to diagnose and predict the development and progression of several pathologies, including colorectal cancer, prostate cancer and pregnancy-related disease.

B. Resources, Facilities and Equipment

PROMETHEUS METABOLOMICS LTD has provides innovative solutions for improving individual health using NMR technologies. In the past few years, we have developed proprietary algorithms which allow us to extract and predict peculiar information from the NMR analysis in automatic way.

We have already established active collaborations with NMR Laboratories in Europe (i.e. Spain and Italy) for performing the data analysis of the NMR experiments.

Currently, NMR experiments are performed by the following laboratories:

- Biosfer Teslab (*http://biosferteslab.com*), a spin-off company from the Rovira Virgili University and the Pere Virgili Institute for Health Research (IISPV), Tarragona (Spain)
- Nuclear Magnetic Resonance Center (*http://molsim.sci.univr.it/nmr/*), University of Verona (Italy)

C. Marketing Methods

PROMETHEUS METABOLOMICS LTD has identified two market segments. The first segment is the physicians that work in clinical research. The second group is comprised of the managers of NMR laboratories.

PROMETHEUS METABOLOMICS LTD will provide services geared to two distinct customer segments:

- Physicians/Researchers
- NMR facilities

<u>Physicians/Researchers</u>

This segment is made up mainly of physicians that work in clinical research. There is a wide range of specialties represented, but predominantly secondary care practitioners. Most types of doctors want to investigate new strategies in the diagnostic field. They often need of new non-invasive diagnostic tools to improve the daily clinical practice. Urine and plasma/serum are an optimal source of information on the patient's health and their analysis would represent a way to discovery a new biomarker or biomarker panel that is possible to use in a non-invasive diagnostic test. In the same segment, we add researchers that need of a metabolomic analysis for their studies. Metabolomics analysis are included in many studies, ranging from the molecular mechanism of a pathology to the biochemical effect a drug treatment on murine models.

<u>NMR facilities</u>

This group is formed by NMR centers and laboratories that provides services using the NMR technology. They are located on all regions (mainly in US, EU, Asia), having a different structure and organization: from a small laboratory with a couple of NMR spectrometers until very big centers with many NMR spectrometers available, belonging to well organized international infrastructures.

Most of NMR facilities belong to a single University or a consortium of University, recognized in an international network of laboratories, offering hands-on spectrometers access, consulting services, technical assistance and training to everyone interested in NMR analysis (i.e. single user, companies, researchers) involved in biomedical, biochemical and pharmaceutical research and development.

Metabolomics is an area of research that has come to the fore in the biosciences in recent years and it has become an important service to be provided at the NMR community. NMR facilities need to include in their business portfolio a very competitive and attractive metabolomic service to meet the market needs and increase their clients.
PROMETHEUS METABOLOMICS LTD services would be attractive to this group. Our innovative services would increase the capability of a NMR facility in term of services provided in the NMR world. In this frame, PROMETHEUS METABOLOMICS LTD operates as a consultant company, collaborating with the NMR facility, and providing expertise and customized solutions in the metabolomic area.

D. Management and Organization

The management team is composed by the *Chief Executive Officer (CEO)* and the *Chief Scientific Officer (CSO)*. The responsibility is clearly divided as follow:

- CEO is the general responsible of the company; its activities include economic management, commercial strategy identification, explore and drive the company through new market opportunities, employee's selection

- CSO responds to the CEO; its activities include the management of Scientific department which is in charge for the development of customized solutions (i.e. algorithms) to elaborate data; he/she collaborate to select new potential candidate/co-workers.

CEO brings in the company a very extensive experience acquired working in the pharmaceutical sector for all the most important worldwide pharma companies. Since years, CEO has acquired a specific know-how on manufacturing and quality control processes applied to the pharmaceutical business, one of the most complex and regulated sector of the global market. CEO has a huge experience on projects management relevant for pharmaceutical companies. CEO capability is recognized due to several projects directly managed at corporate level for the bigger pharmaceutical companies.
CSO brings in the company the scientific knowledge which is needed for our business. CSO has acquired specific and strong experience on the elaboration/processing of data collected form NMR experiments, working in well-known NMR Centers recognized at international level. CSO has developed innovative and customized algorithms for data processing which are the core of our business. CSO capability is documented due to a several scientific articles published in many scientific journals with international relevance.

E. Ownership Structure

PROMETHEUS METABOLOMICS LTD is incorporated in the UK. The company is owned and managed by its two partners and founders which share the company stocks, as follow:

- Mirko Mori, owning 49% of company's shares
- Stefano Cacciatore, owning 51% of company's shares

F. Social Responsibility

PROMETHOUS METABOLOMICS LTD will financially support fellowships for PhD students, investing in the career of young scientists. Students from developing nations will be taken in major consideration. We consider the multiculturalism a competitive advantage for our company.

G. Internal Analysis

Internal examination is shown through the following *SWOT* analysis:

- *Strengths*
  - The ownership of developed algorithms
  - Innovative approach
  - No direct competitors on the market (using the same approach)
  - Better quality of provided services (i.e. more medical information provided) compared to competitors (working with other solutions)
  - Final cost significant less than the other competitors (operative on the market and comparable with us in term of services provided)
  - Team open mind oriented

- *Weaknesses*
  - Poor financial resources
  - No capital available to immediately invest on the market
  - Poor commercial capability
  - Slow rate of spreading our innovative services

- *Opportunity*
  - Escalate the market on metabolomic sector with an innovative approach
  - Proving new services without direct competitors
  - Impose our company as one of global leader on the metabolomic sector
  - Enlarge our business to other medical sectors

- *Threats*
  - Fast grow of the business without an adequate company structure in place (i.e. financial capability, persons, infrastructure)
  - Initial limited economic capability

Products and/or Services

The emergence of personalised and precision healthcare requires detailed knowledge of human molecular pathology. The concentrations of small molecules (a.k.a. metabolites), such as lipids, oligopeptides, nucleotides, amino acids, sugars and metabolic intermediates, represent a snapshot of the metabolic dynamic that reflects the response of living systems to environmental factors, pathophysiological stimuli (e.g. cardiovascular diseases) or genetic modifications (e.g. cancer). This information can be extracted from a biofluid (i.e. urine and blood) or a tissue by NMR spectroscopy. However, due to its complexity, NMR profiling has remained manual resulting slow, expensive and error-prone procedure that have hindered its clinical and industrial usage.
Current preclinical methods are limited in predicting successful outcomes. Such failure exacts enormous cost, both financial and in the quality of human life. Drug development and preclinical trials are challenging processes and more than 80% to 90% of drug candidates fail to gain approval from the US Food and Drug Administration. Predictive and efficient tools are required to discover high quality targets and increase the probability of success in the process of new drug development. One such solution to the challenges faced in the development of new drugs and combination therapies is the use of low-cost and high-throughput experiments specifically designed for animal models. New technological innovations are improving the process of preclinical testing by generating richer data, resulting in higher validation of results.

PROMETHEUS METABOLOMICS LTD makes progress toward fully automated and reliable metabolite quantification for an efficient high-throughput tool of clinical analysis. The study of the ensemble of all metabolites (metabolomics) by NMR spectroscopy has shown considerable promise in disease diagnosis and biomarker discovery in both biofluids and tissues. Precise metabolite quantification is a prerequisite to move any chemical biomarker or biomarker panel from the laboratory to the clinic.

PROMETHEUS METABOLOMICS LTD operates in the life science area. We started our adventure after a deep investigation of metabolomic sector, focusing the attention on the quality and quantity of data which can be extracted using the current solutions available on the market. Our investigation has established that the number of information, potentially providing medical predictions of patient health, are not enough stressed with the common technologies used routinely and many other data can be extracted and/or predicted from a set of biological samples. For this reason, a new approach would be attractive, allowing a significant increase of collected data. In this view, we have developed an innovative approach to analyse data, improving the number of information collected form a single experiment.

PROMETHEUS METABOLOMICS LTD offers a service of NMR spectra analysis. Each single service was customized and adapted to the typology of the samples.
Our services include:

- Blood analysis
- Urine analysis
- Faecal extracts analysis
- Saliva analysis

At the present time, we already commercially developed these services only for human samples. We are optimising different services for murine models and cell/tissues extracts. The objective of PROMETHEUS METABOLOMICS LTD is to offers a large portfolio of different services that include the analysis from all common samples used in clinic. NMR spectra of urine samples from different patients are showed in **Figure 1**.

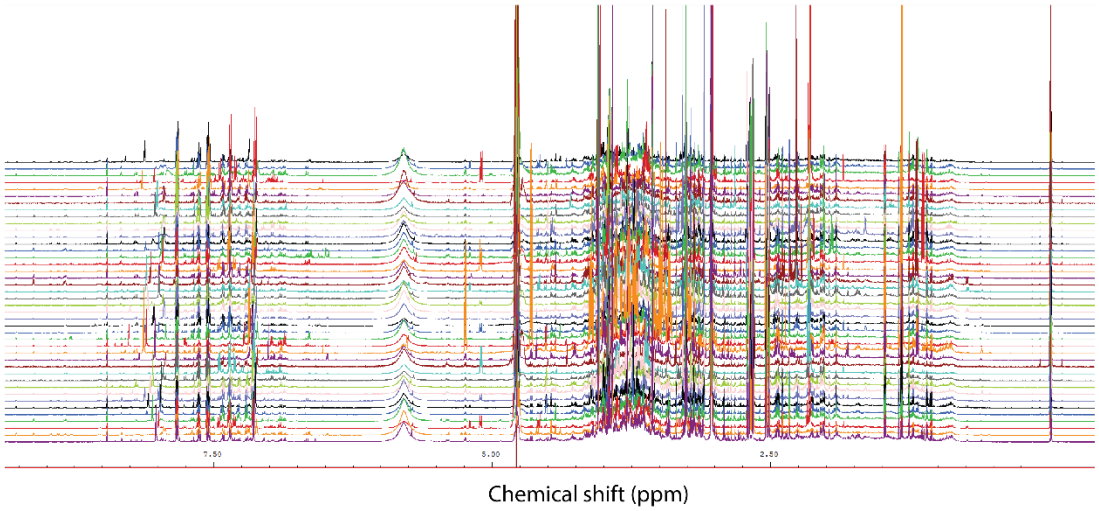

Figure 1. NMR spectra of urine samples.

Using the proprietary algorithm, we are able to quantify the concentration of metabolites from NMR spectra (**Figure 2**).

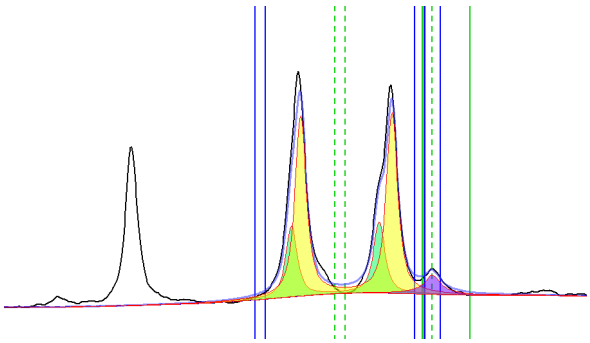

Figure 2. Deconvolution of lactate, threonine and alpha-hydroxyisobutyrate.

Up to now, we operate in the metabolomic area, providing services mainly as private consulting for doctors, researchers, public foundations and private companies.

Since company foundation (2016), the overall volume of sales has been £21,000 thank to the projects successfully executed for the customers mentioned in the table below.

Table 1. Customers (2017)

CUSTOMERS	SALE VOLUME
PRIVATE CONSULTING (DOCTOR)	£10,500.00
UNIVERSITY COLLEGE OF LONDON	£4,500.00
PRIVATE CONSULTING (CAVIAR)	£720.00
FUNDACIO URV	£2,500.00
INSTITUT D'INVES	£2,000.00
IBSA FARMACEUTICI	£1,700.00

Market Assessment

A. Examining the General Market

Metabolomics is an emerging field which combines strategies to identify and quantify cellular metabolites using sophisticated analytical technologies with application of statistical and data analysis methods for information extraction and data interpretation. Metabolomics – the newest "omics" – is a dynamic and developing field, joining genomics, trascriptomics and proteomics in empowering an integrative frameworks science methodology to drug discovery and development. In spite of the fact that metabolomics is still at an early evolutionary stage it is conjecture that throughout the following decade the pharma business will apply this innovation all the more generally in drug development and information. Metabolomics is now being extensively used in pharmaceutical and biotechnology industries for biomarker and drug discovery; pharmaceutical and biotechnology industries are expected to grow at a high rate in coming years, which is expected to boost the growth of the market.

Global market for Metabolomics is projected to reach US$1.4 billion by the year 2020, and US$2.1 billion by 2024 (at CAGR of 11.3% over the forecast years), driven by increasing investiments in Metabolomics research and rising adoption of the technology in pharmaceutical and biotechnology sectors. Other factors driving growth in the market include increasing volume of clinical trials, rise in toxicological studies, growth of metabolomics data analysis solution and software and increasing use of metabolomics as a diagnostic tool for biomarker screening of various diseases. The United States represents the largest market worldwide supported by the presence of a sophisticated healthcare infrastructure conducive to pharmaceutical R&D. Asia-Pacific ranks as the fastest growing market with at CAGR of 18.4% over the analysis period, led by factors such as increase in age-related chronic illnesses, improving healthcare infrastructure, growing number of pharmaceutical and biotech companies, rising demand for improved pharmaceutical products and increased investiments in life science research.

Todate, 689 clinical trials registered at the ClinicalTrials.gov of the United States National Library of Medicine included metabolomic analyses. Clinical trails affering to metabolomic sector were significantly increased in the past 10 years and the trend is continoulsy in rapid grow (**Figure 3**). In 2017, the number of clinical trials registred at ClinicalTrials.gov using metabolomic technologies was over a hundred.

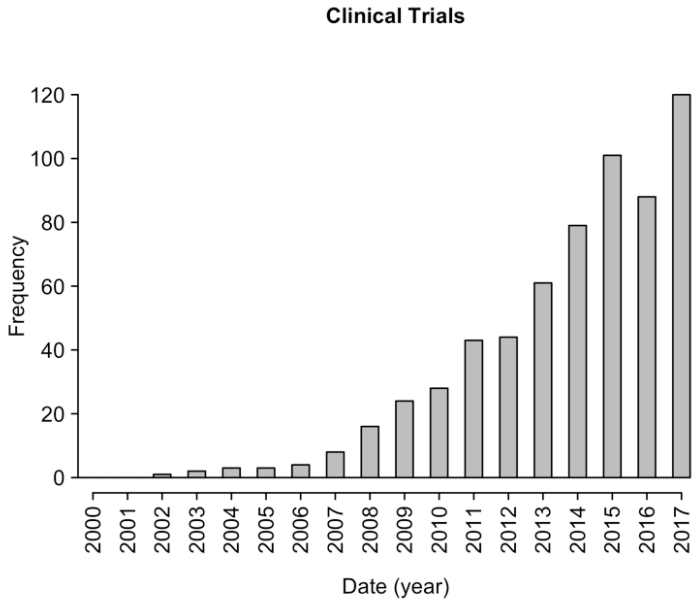

Figure 3. Clinical Trials (US ClinicalTrials.gov)

The largest clinicals trials are listed in **Table 2**. In 2017, USA registrated 40 clinical trials on ClinicalTrials.gov representing almost the 35% of all clinical studies. Over 40% of the clinical trials were registred in Europe, with 13 and 11 clinical trials performed only in UK and France, respectively.

Table 2. Largest Clinical Trails worldwide

NCT Number	Title	Enrolment	Year	Country
NCT03364582	Dietary Patterns, Metabolomics and Colorectal Cancer Risk	173230	2016	USA
NCT00005152	Nurses' Health Study (Cardiovascular Component)	121700	1980	USA
NCT02306096	Sweden Cancerome Analysis Network - Breast: Genomic Profiling of Breast Cancer	15000	2010	Sweden
NCT02429362	Obstetrical Repository of Biological Materials	10000	2015	USA
NCT03004898	Population-based Chronic Kidney Disease Cohort at Northern Taiwan	10000	2013	Taiwan
NCT01431326	Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care	10000	2011	USA
NCT03131414	The IMAGINE-SPOR CIHR Chronic Disease Network	8000	2017	Canada
NCT03049254	Mayo AVC Registry and BioBank	6000	2016	USA
NCT00435734	Obesity Intervention "Obeldicks" for Obese Children, Adolescents and Their Parents	6000	1999	Germany
NCT03491280	Diagnostic Research in Patients With Rare Diseases - Solving the Unsolved Rare Diseases	5500	2018	Germany
NCT01891240	IMproved PRegnancy Outcome by Early Detection	5000	2013	Ireland
NCT03027401	Clinical Sequencing of Cancer and Tissue Repository: OncoGenomics	5000	2017	USA
NCT01410318	Progression of Early Subclinical Atherosclerosis	4184	2010	Spain
NCT03308916	Screening At-risk Populations for Hepatic Fibrosis With Non-invasive Markers	4000	2017	Denmark

Nowadays, the Americas is set to be the leading region for the metabolomics market growth followed by Europe. The Asia Pacific and the rest of the world are set to be the

emerging regions. The markets in India, China, and Japan are also expected to grow at a rapid pace during the forecast period due to refining biopharmaceutical research infrastructure, huge population, and growing healthcare requirements.
The metabolomic analysis of plasma/serum samples represents the largest sector with the histest rate of growth as demostrated by the number of scientific publication (**Figure 4**).

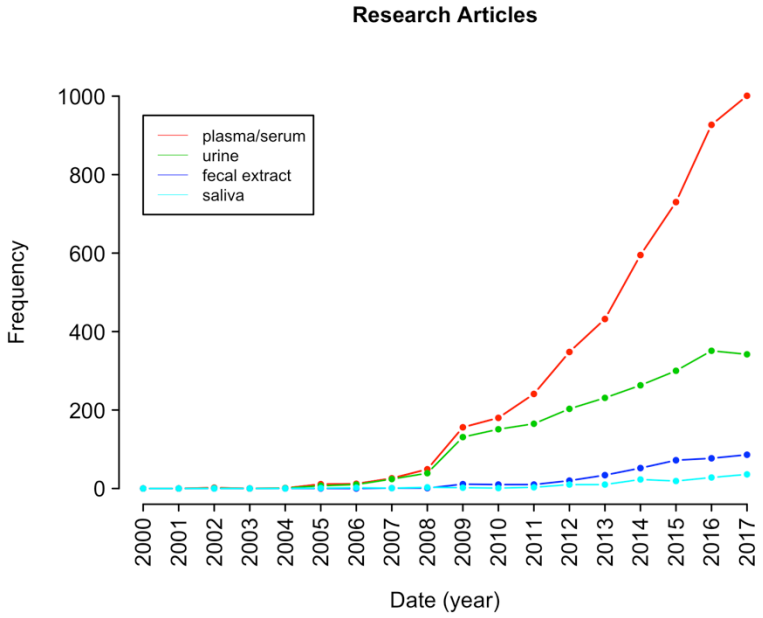

Figure 4. Metabolomics publication metrics from 2000 through 2017. The line graphs show the annual number of publications (derived from the search in PubMed database) that contain the word "metabolomics" and a key words among plasma/serum, urine, fecal extract and saliva.

Generally, metabolomics applications are segmented into the following: *Biomarker Discovery*, *Toxicity Assessment* and *Nutrition*.

Biomarker discovery
It has been suggested that metabolomics greatest potential lies in disease marker discovery and detection. For instance, many in-born errors of metabolism (IEMs) and numerous acquired metabolic disorders (i.e. obesity, iabetes, cachexia and hyper-cholesterolemia) are characterized by unusually high (or low) concentration levels of certain metabolites.
Much of the promise of the future precision medicine rests on robust biomarkers, and market forecasts continue to reflect big expectations.
Metabolomics is being used to produce key new insights into important disease areas, such as cancer, liver and metabolic disease, importantly traslating across both clinical and research applications. Thus metabolomics is poised to dramatically expand the scope and utility of the clinical reference laboratory, and emerging metabolic-derived testes and expected to play significant roles in precision medicine and patient management of the future.
A summary of clinically useful biomarkers used in clinical practice are provided in **Table 3** (summarised from a test catalogue provided by Mayo Clinic, US available at http://www.mayomedicallaboratories.com). Whilst these biomarkers are very valuable for

diagnosing disease there is an urgent need to have many more that are highly predictive and robust.

Table 3. A selection of small molecule biomarkers and their clinical relevance; summarised from an available test list at the Mayo Clinic, US. The biological matrix investigated (U- urine, P-plasma, Sm-serum, Sa-saliva, Se-semen, WB-whole blood, BS-dried blood spot & C-CSF) and the analytical method/test applied is detailed.

Biomarker	Clinical Relevance	Biological Matrix								Analytical Test
		U	P	Sm	Sa	Se	WB	BS	C	
5-Hydroxyindoleacetic acid	Intestinal carcinoid syndrome									LCMS
Acylcarnitines	Fatty acid oxidation disorders, several organic acidurias & new born screening									ESI-MS
Acylglycines	Inborn errors of metabolism									Capillary GCMS
Allo-isoleucine	New born screening: branched-chain amino acids elevations									LCMS
Amino acid (Panel)	Inborn errors of metabolism - evaluation of endocrine & neurological disorders, liver, muscle & neoplastic diseases									LCMS
Aminolevulinic acid	Various acute hepatic porphyrias									LCMS
Bile acids	Liver dysfunction									Enzymatic & LCMS
Carnitines	Organic acidemias, fatty acid oxidation disorder and primary carnitine deficiency									MS
Carotene, Beta	Fat malabsorption									HPLC
Ceramides	Myocardial infarction, cardiovascular disease and mortality within 5 years									LCMS
Cholesterol	Evaluation of cardiovascular risk									Enzymatic
Citric acid	Metabolic diseases									Enzymatic Spectrophotometry
Cortisol	Cushing syndrome & adrenal insufficiency									LCMS & Immunoenzymatic Assay
Creatinine	Renal function									Enzymatic
d-Lactate	d-lactate acidosis									Enzymatic
Ethylmalonic acid	New born screening									LCMS
Fatty acid profiles	Identifying deficiency of essential and other nutritionally beneficial fatty acids									Capillary GCMS
Fructosamine	Glyceamic control									Colourmetric
Fructose	Azoospermia									Qualitative Test
Galactitol	Galactosemia									GCMS
Glucose	Diabetes & carbohydrate metabolism disorders									Photometric
Glutaric Acid	New born screening									LCMS
HDL cholesterol	Cardiovascular risk									Colorimetric & Enzymatic
Hippuric acid	Liver function									LCMS
Histamine	Allergies and mast cell disorders									Immunoenzymatic Assay
Homocysteine	Inherited disorder of methionine metabolism									ESI-MS
Homovanillic acid	Screening children for catecholamine-secreting tumors									LCMS
Hydroxyglutaric acid	New born screening									LCMS
Insulin	Insulinoma									Electrochemiluminescence immunoassay
Lactate	Lactic acidosis & differentiating between bacterial and viral meningitis									Photometric
LDL Cholesterol	Cardiovascular risk									Colorimetric & Enzymatic
Methylmalonic acid	Methylmalonic acidemia									LCMS
Methylsuccinic acid	New born screening									LCMS
Organic acid screen	Inborn errors of metabolism									GCMS
Phenylalanine and tyrosine	Hyperphenylalaninemia									MS
Phospholipids	Ecithin-cholesterol acyltransferase deficiency									Colourmetric
Pipecolic acid	Peroxisomal biogenesis									GCMS
Purines and pyramidines (Panel)	Disorders of purine and pyrimidine metabolism									LCMS
Pyridoxal 5-phosphate	Progressive nerve compression disorders									LCMS
Pyruvate	Disorders of mitochondrial metabolism									Spectrophotometry
Riboflavin vitamin B2	Ariboflavinosis									LCMS
Thiamine	Behavioural change, delierium, dietary concerns									LCMS
Triglycerides	Elevated cholesterol values									Enzymatic
Urea	Renal failure									UV
Uric acid	Acute uric acid nephropathy from other causes of acute renal failure									Enzymatic & Photometric

Toxicity assessment

Metabolic profiling (expecially of urine or blood samples) can be used to detect the physiological changes casued by toxic insult of a chemical (or mixuture of chemical). In many cases, the observed changes can be related to specific syndromes, e.g. a specific lesion in liver or kidney. Metabolomics allows rapid identification of the potential targets of a hazardous compound. It can give information on target organs and often can help to improve our understanding regarding the mode-of-action of a given compound. Such insights aid the discovery of biomarkers that either indicate pathophysiological conditions or help the monitoring of the efficacy of drug therapies. This is of particular relevance to pharmaceutical companies wanting to test the toxicity of potential drug candidates if a compound can be eliminated before it reaches clinical trials on the grounds of adverse toxicity, it saves the enormous expense of the trials.

Nutrition

Functional foods and nutraceuticals have received considerable interest in the past decade largely due to increasing consumer awareness of the health benefits associated with food. Diet in human health is no longer a matter of simple nutrition: consumers are more proactive and increasingly interested in the health benefits of functional foods and their

role in the prevention of illness and chronic conditions. This, combined with an aging population that focuses not only on longevity but also quality of life, has created a market for functional foods and nutraceuticals. In general, a metabolome in a given body fluids is influenced by endogenous factors, such as age, gender, body composition and genetics as well as underlying pathologies. The large bowel microflora are also a very significant potential confouder of metabolic profiles and could be classified as either an endogenous or exogenous factor. Metabolomics is one means to determine a biological endpoint, which reflects the balance of all these forces on an individual's metabolism.

B. Customers Analysis

PROMETHEUS METABOLOMICS LTD has identified several potentials customers, which can be grouped in two main categories as follow:

- Hospitals, Universities and Research centers (Physicians/Researchers)
- NMR facilities

Hospitals, Universities and Research Centers (Physicians/Researchers)

With the goal of basic research begins moved to clinical practice, research-related clinicians and opinion leaders must incorporate advanced molecular profiling in the usual practice. This segment is made up mainly of physicians that work in clinical research. There is a wide range of specialties represented, but predominantly secondary care practitioners. Most types of doctors want to investigate new strategies in the diagnostic field. They often need of new non-invasive diagnostic tools to improve the daily clinical practice. Urine and plasma/serum are an optimal source of information on the patient's health and the metabolomic analysis of these fluid would represent a way to discovery a new biomarker or biomarker panel that is possible to use in a non-invasive diagnostic test.

Researchers that need of a metabolomic analysis for their studies are part of this segment. Metabolomic analysis can provide important information in many studies, ranging from the molecular mechanism of a pathology to the biochemical effect a drug treatment on murine models.

There has been a general exponential growth in the number of metabolomics publications and a continuing growth in number of industrial reports. Interestingly, the publications ratio does not significantly change across the years, which illustrates very similar growth in interest in metabolomics applications between different fields (**Figure 5**).

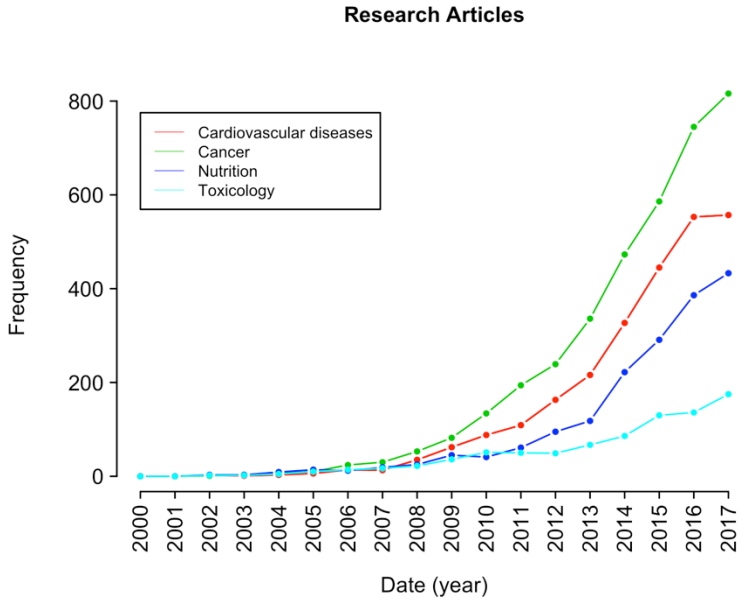

Figure 5. Metabolomics publication metrics from 2000 through 2017. The line graphs show the annual number of publications (derived from the search in PubMed database) that contain the word "metabolomics" and a key words among cardiovascular disease, cancer, nutrition and toxicology.

The top 30 pharmaceutical companies using metabolomics in research illustrate the growing number of publications in industry (**Figure 6**).

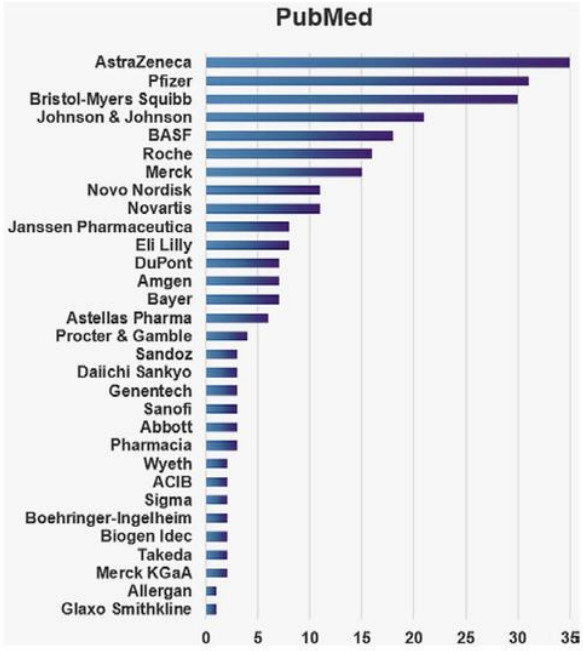

Figure 6. Metabolomics publication metrics from 1999 through 2015. The bar graph shows a number of publications that list key words "metabolomics" and company name derived from the search in PubMed database.

PROMETHEUS METABOLOMICS LTD offers to Hospitals, Universities and Research Centers (Physicians/Researchers) an analytical service of analysis of tissues, cell line and biofluids (i.e. plasma/serum, urine, saliva and faecal extract). The service will cover the

NMR analysis of the samples and the retrieval of metabolite concentrations. Upon request, a service of statistical analysis is provided.

NMR facility

NMR facilities are centers that offer analytical services using the NMR technology. They are located in all Western countries (mainly in US, EU) as showed in **Figure 7**. China is continuously investing new resource in the development of new NMR centers.

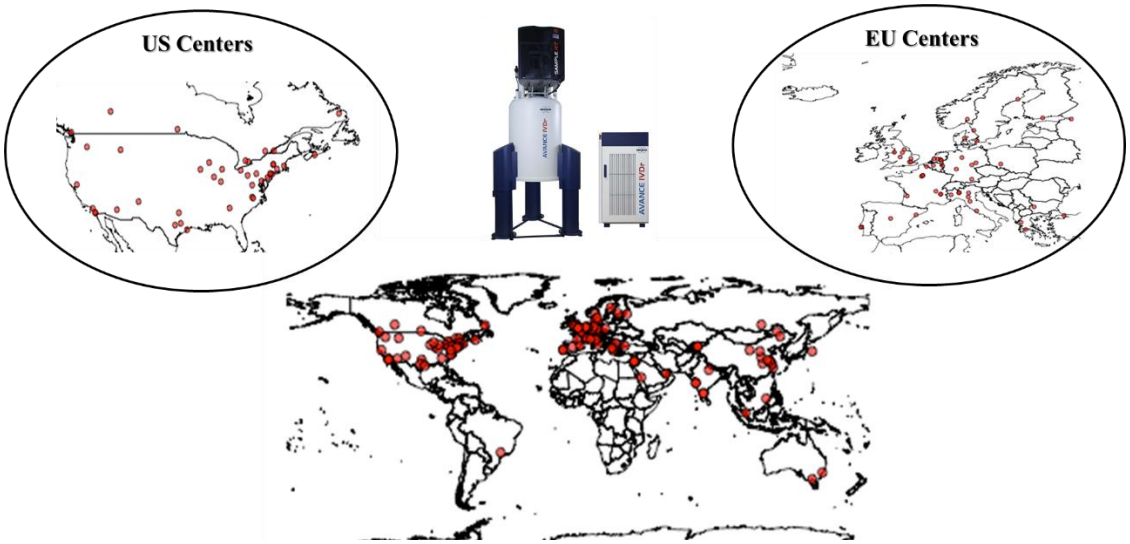

Figure 7. NMR facilities.

NMR facilities can have different structure and organization: from a small laboratory with a couple of NMR spectrometers until very big centers with many NMR spectrometers available.

Most of NMR facilities belong to a single University or a consortium of University, recognized in an international network of laboratories, offering hands-on spectrometers access, consulting services, technical assistance and training to everyone interested in NMR analysis (i.e. single user, companies, researchers) involved in biomedical, biochemical and pharmaceutical research and development.

Metabolomics is an area of research that has come to the fore in the biosciences in recent years and it has become an important service to be provided at the researcher community. NMR facilities need to include in their business portfolio a very competitive and attractive metabolomic service to meet the market needs and increase their clients.

PROMETHEUS METABOLOMICS LTD offers to NMR facilities a service of data analysis of the NMR experiments. Upon request, a service of statistical analysis is provided. In **Table 4**, a list of the most important NMR facilities around the world is provided.

Table 4. List of NMR facilities.

University	Location	Country	Reference's name	Reference's email
Asia				
China Agricultural University	Beijing	China	Zhu W	wentaozhu@cau.edu
Heilongjiang Bayi Agricultural University	Daqing	China	Xia C	xcwlxyf@sohu.com
Zhejiang University	Hangzhou	China	Meirong Zhao	xyycz@zjut.edu.cn
Henan University	Henan	China	Huijuan Wang	juanjuan5891@163.com
China Pharmaceutical University	Nanjing	China	Kong L	10199208871@cpu.edu.cn
Nanjing University of Science and Technology	Nanjing	China	Jun-Song Wang	wang.junsong@gmail.com
Shanxi University	Taiyuan	China	Qin XM	qinxm@sxu.edu.cn
Wenzhou Medical University	Wenzhou	China	Zheng H	123zhenghong321@163.com
University of Chinese Academy of Sciences	Wuhan	China	LIU Maili	ml.liu@wipm.ac.cn
Xningxia University	Yinchuan	China	J Z Tao	tao_jz@nxu.edu.cn
Indian Institute of Science	Bangalore	India	S. Vasudevan	svipc@iisc.ac.in
Institute of Medical Sciences	Lucknow	India	Jaideep Saha	jaideep.saha@cbmr.res.in
IIT Bombay	Mumbai	India	Ashutosh Kumar	ashutoshk@iitb.ac.in
TIFR	Mumbai	India	Mamata Joshi	nmr@tifr.res.in
St Petersburg University	St Petersburg	Russia	Peter M Tolstoy	peter.tolstoy@spbu.ru
Nanyang Technological University	Singapore	Singapore	Li Hoi Yeung	vd-sbs-acad@ntu.edu.sg
Europe				
Vrije Universiteit Brussel - VUB	Brussel	Belgium	Monique Biesemans	mbiesema@vub.ac.be
Bulgarian Academy of Sciences	Sofia	Bulgaria	Svetlana Simova	sds@orgchm.bas.bg
University of Aarhus	Aarhus	Denmark	Niels Chr. Nielsen	ncn@chem.au.dk
Carlsberg Research Laboratory	Copenhagen-Valby	Denmark	Sebastian Meier	smeier@crc.dk
University of Helsinki	Helsinki	Finland	Hideo Iwai	grp-nmrservice@helsinki.fi
CBMN-IECB	Bordeaux	France	Antoine Loquet	a.loquet@iecb.u-bordeaux.fr
ICSN	Gif sur Yvette	France	Eric Guittet	eric.guittet@cnrs.fr
IBS	Grenoble	France	Bernhard Brutscher	bernhard.brutscher@ibs.fr
Très Hauts Champs	Grenoble-Lyon	France	Gilles Rautureau	lyndon.emsley@ens-lyon.fr
UCCS-UGCF	Lille	France	Olivier Lafon	olivier.lafon@univ-lille1.fr
ISA-CRMN	Lyon	France	Guido Pintacuda	guido.pintacuda@isa-lyon.fr
Universite Paris-Saclay	Paris	France	Zinn Justin Sophie	sophie.zinn@i2bc.paris-saclay.fr
Pasteur Institute	Paris	France	Muriel Delepierre	muriel.delepierre@pasteur.fr
LBM-ENS	Paris	France	Geoffrey Bodenhausen	geoffrey.bodenhausen@ens.fr
RWTH Aachen University	Aachen	Germany	Bernhard Blümich	bluemich@itmc.rwth-aachen.de
Goethe University	Frankfurt	Germany	Harald Schwalbe	schwalbe@em.uni-frankfurt.de
Leibniz University	Hannover	Germany	Teresa Carlomagno	teresa.carlomagno@oci.uni-hannover.de
Leibniz Institute for Age Research	Jena	Germany	Matthias Görlach	matthias.goerlach@leibniz-fli.de
University of Leipzig	Leipzig	Germany	Jörg Matysik	joerg.matysik@uni-leipzig.de
Technische Universität München	München	Germany	Steffen Glaser	glaser@tum.de
University of Ioannina	Ioannina	Greece	Vassiliki Exarchou	vexarc@cc.uoi.gr
University of Patras	Patras	Greece	Spyroulias Georgios	g.a.spyroulias@upatras.gr
University of Florence	Florence	Italy	Claudio Luchinat	luchinat@cerm.unifi.it
Ospedale San Raffaele	Milano	Italy	Giovanna Musco	musco.giovanna@hsr.it
Bicocca	Milano	Italy	Cristina Airoldi	cristina.airoldi@unimib.it
Politecnico di Milano	Milano	Italy	Franca Castiglione	franca.castiglione@polimi.it
Università degli studi di Modena e Reggio Emilia	Modena	Italy	Adele Mucci	adele.mucci@unimore.it
Sapienza	Rome	Italy	Maurizio Delfini	maurizio.delfini@uniroma1.it
Politecnico di Torino	Torino	Italy	Francesco Svorani	francesco.savorani@polito.it
University of Verona	Verona	Italy	Michael Assfalg	michael.assfalg@univr.it
Leiden University	Leiden	Netherlands	Hugo van Ingen	h.van.ingen@lic.leidenuniv.nl
Radboud University	Radboud	Netherlands	Ed Koster	info@radboudresearchfacilities.nl
Utrecht University	Utrecht	Netherlands	Hans Wienk	H.L.J.Wienk@uu.nl
Wageningen University	Wageningen	Netherlands	Jacques Vervoort	jacques.vervoort@wur.nl
Unilever	Wageningen	Netherlands	John van Duynhoven	John-van.Duynhoven@unilever.com
University of Oslo	Oslo	Norway	Frode Rise	frode.rise@kjemi.uio.no
University of Wrocław	Wrocław	Poland	Piotr Młynarz	piotr.mlynarz@pwr.wroc.pl
Technical University of Lisbon	Lisbon	Portugal	Ana Teresa Lopes	analopes@fct.unl.pt
ITQB-UNL	Oeiras	Portugal	Pedro Lamosa	lamosa@itqb.unl.pt
Universidad Complutense	Madrid	Spain	Juan Manuel Garcia Segura	jmgsegura@ucm.es
Universitat Rovira i Virgili	Reus	Spain	Oscar Yanes	oscar.yanes@urv.cat
Göteborg University	Göteborg	Sweden	Anders Pedersen	nmr@science.gu.se
Umeå University	Umeå	Sweden	Gerhard Gröbner	gerhard.grobner@umu.se
University of Birmingham	Birmingham	UK	Ulrich Günther	u.l.gunther@bham.ac.uk
University of Cambridge	Cambridge	UK	Daniel Nietlispach	dn206@cam.ac.uk
University of Liverpool	Liverpool	UK	Lu-Yun Lian	Lu-Yun.Lian@liverpool.ac.uk
King College of London	London	UK	Sasi Conte	sasi.conte@kcl.ac.uk
Imperial College of London	London	UK	Jeremy Nicholson	j.nicholson@imperial.ac.uk
University of Sheffield	Sheffield	UK	Mike Williamson	M.Williamson@sheffield.ac.uk
University of York	York	UK	Jennifer Gilmartin	business@york.ac.uk
Middle East				
Bar-Ilan University	Bar-Ilan	Israel	Keren Keinan-Adamsky	Keren.Adamsky@mail.biu.ac.il
Hebrew University	Jerusalem	Israel	Debbie Shalev	debbie@macbeth.ls.huji.ac.il
Weizmann Institute	Rehovot	Israel	Tali Scherf	tali.scherf@weizmann.ac.il
Tel-Aviv University	Tel-Aviv	Israel	Limor Frish	limorf@post.tau.ac.il
King Abdullah University of Science and Technology	Thuwal	Saudi Arabia	Jorge Gascon	jorge.gascon@kaust.edu.sa
Fatih University	Istanbul	Turkey	Fatih İnci	fatihinci@itu.edu.tr
New York University	Abu Dhabi	United Arab Emirates	Gennaro Esposito	ge22@nyu.edu
North America				
University of Alberta	Edmonton (Alberta)	Canada	Michael Overduin	overduin@ualberta.ca
Dalhousie University	Halifax (Nova Scotia)	Canada	Josef W. Zwanziger	jzwanzig@dal.ca
McMaster University	Hamilton (Ontario)	Canada	Philip Britz-McKibbin	britz@mcmaster.ca
McGill University	Montreal (Québec)	Canada	Robin Stein	robin.stein@mcgill.ca
Memorial University	Newfoundland (Newfoundland and Labrador)	Canada	Celine Schneider	cmschnei@mun.ca
University of Ottawa	Ottawa (Ontario)	Canada	Glenn A. Facey	gafacey@uottawa.ca
British Columbia University	Vancouver (British Columbia)	Canada	Zhicheng Paul Xia	zcxia@chem.ubc.ca

University	Location	Country	Reference's name	Reference's email
University of British Columbia	Vancouver (British Columbia)	Canada	Suzana K Straus	sstraus@chem.ubc.ca
University of Waterloo	Waterloo (Ontario)	Canada	Janet Venne	jan.venne@uwaterloo.ca
Uni Manitoba	Winnipeg (Manitoba)	Canada	David Davidson	david.davidson@umanitoba.ca
Siena College	Albany (New York)	USA	Kristopher Kolonko	kkolonko@siena.edu
ABQMR	Albuquerque (New Mexico)	USA	Eiichi Fukushima	eiichi@abqmr.com
Emory University	Atlanta (Georgia)	USA	Shaoxiong Wu	SWu@Emory.edu
University of Texas	Austin (Texas)	USA	Steve Sorey	s.sorey@utexas.edu
John Hopkins University	Baltimore (Maryland)	USA	Ananya Majumdar	ananya@jhu.edu
Indiana University Bloomington	Bloomington (Indiana)	USA	M. Kevin Brown	brownmkb@indiana.edu
Montana State University	Bozeman (Montana)	USA	Joseph Seymour	scodd@coe.montana.edu
MIT	Cambridge (Massachusetts)	USA	Robert Griffin	rgg@mit.edu
Case Western Restern Reserve University	Cleveland (Ohio)	USA	Matthias Buck	matthias.buck@case.edu
Texas A&M	College Station (Texas)	USA	Gregory P. Wylie	gregory.wylie@chem.tamu.edu
UT Southwestern Medical Center	Dallas (Texas)	USA	Qiong Wu	Qiong.Wu@UTSouthwestern.edu
UC Davis	Davis (California)	USA	Gary Smith	gmsmith@ucdavis.edu
Duke University	Durham (North Carolina)	USA	Benjamin G. Bobay	ben.bobay@duke.edu
UConn Health	Farmington (Connecticut)	USA	Jeffery C. Hoch	hoch@uchc.edu
The University of Texas	Galveston (Texas)	USA	Tianzhi Wang	tiawang@utmb.edu
James Madison University	Harrisonburg (Virginia)	USA	Daniel M. Downey	downeydm@jmu.edu
The University of Iowa	Iowa City (Iowa)	USA	Santhana Velupillai	santhana-velupillai@uiowa.edu
University of California, Irvine	Irvine (California)	USA	Philip R. Dennison	dennison@uci.edu
University of California, La Jolla	La Jolla (California)	USA	Stanley J. Opella	sopella@ucsd.edu
University of Wisconsin-Madison	Madison (Wisconsin)	USA	John Markley	markley@nmrfam.wisc.edu
American Chemical Society	Morris Township (North Jersey)	USA	Mary Harner	mary.harner@bms.com
Albert Einstein Collge of Medicine	New York (New York)	USA	Sean M. Cahill	sean.cahill@einstein.yu.edu
The Rockefeller University	New York (New York)	USA	Chingwen Yang	yangc@rockefeller.edu
City College of New York	New York (New York)	USA	Bruce Johnson	Bruce.Johnson@asrc.cuny.edu
University of Notre Dame	Notre Dame (Indiana)	USA	Jaroslav Zajicek	jzajicek@nd.edu
University of Pennsylvania	Philadelphia (Pennsylvania)	USA	Mark Elliott	melliott@pennmedicine.upenn.edu
Rutgers University	Piscataway (New Jersey)	USA	Gaetano T. Montelione	guy@cabm.rutgers.edu
North Carolina State University	Raleigh (North Carolina)	USA	Xiaoyan Jennifer Sun	xsun9@ncsu.edu
San Diego State University	San Diego (California)	USA	Bennett Addison	baddison@sdsu.edu
University of California, San Diego	San Diego (California)	USA	Brendan M. Duggan	sopnmr@ucsd.edu
Pennsylvania State University	State College (Pennsylvania)	USA	Carlos N. Pacheco	cnp14@psu.edu
Arizona State University	Tempe (Arizona)	USA	Brian Cherry	Brian.R.Cherry@asu.edu
Rensselaer Polytechnic Institute	Troy (New York)	USA	Scott A.	mccals@rpi.edu
University of Illinois	Urbana-Champaign (Illinois)	USA	Dean Olson	dolson@illinois.edu
Oceania				
University of Melbourne	Melbourne	Australia	David Keizer	dkeizer@unimelb.edu.au
RMIT	Melbourne	Australia	Robert Brkljaca	robert.brkljaca@rmit.edu.au
University of New South Wales	Sydney	Australia	James Hook	j.hook@unsw.edu.au
South America				
UFSCar	Sao Carlos	Brazil	Antonio Gilberto Ferreira	giba@ufscar.br

C. Industry Analysis

The companies that offer a service of metabolomic analysis can be divided in two groups characterized by the analytical method used to quantify the metabolite concentration: Mass Spectrometry or NMR spectroscopy.

Mass Spectrometry (MS) based Companies

MS-based approaches are the most sensitive of all techniques. There are many types of mass analysers, and each analyser type has its strengths and weakness. MS is usually coupled with gas chromatography (GC) or liquid chromatography (LC) to separate different classes of metabolites.

Major players in MS based metabolomic are the following companies: Thermo Fisher Scientific, Inc. (U.S.), Agilent Technologies, Inc.(U.S.), Biocrates Life Sciences AG (Austria), Shimadzu Corporation (Japan), Waters Corporation (U.S.), Human Metabolome Technologies, Inc.(Japan), LECO Corporation (U.S.), Metabolon, Inc. (U.S.), Bio-Rad Laboratories, Inc.(U.S.), Evotec (German), MtoZ Biolabs (CRO, U.S.)
They are very consolidated companies with a solid structure and operating in the life science area since many years.
Minor players belonging to the same company type are the following: OWL Metabolomics (Spain), Afekta Technologies (Finland), MetasysX (German), MS-Omics (Denmark), Metanomics Health (German), Stemina Biomarker Discovery (U.S.), Matrix Bio (U.S.).
These players are constituted by small and medium size companies up to 50 employees and mainly located in USA, UK and Northern Europe.

NMR Spectroscopy based Companies

The other company group, operating in the same market, is constituted by companies using NMR spectroscopy as analytical method for providing metabolomic services.
NMR spectroscopy is particularly useful in the detection of compounds that are less tractable by GC-MS and LC-MS, such as amines, sugars, and volatile and nonreactive compounds. NMR spectroscopy is a particularly powerful approach when applied to the high-throughput analysis of biofluids such as blood. NMR spectroscopy has been confirmed to be a straightforward and useful technique for the qualitative and quantitative analysis of a wide range of components, including low-molecular-weight metabolites, lipids, and lipoproteins (different for size and composition).Compered to MS based companies, the companies that use NMR technologies to offer a metabolomic service are of smaller dimensions, less than 50 employees, located in Canada, USA and Northern Europe. Their business is mainly focused on bioinformatic analysis, metabolomic profiling determination and clinical tests.

Competitive Analysis

PROMETHEUS METABOLOMICS LTD acts on the market providing a metabolomic service using NMR based technology and proprietary algorithm to analyse data.
Two company groups defined above (MS-based and NMR based-) were assessed to screen our potential competitors. First, companies are divided in *direct* and *indirect* competitors based on the technology used to provide the same metabolomic service.

- Direct Competitor:
  company providing a similar service using the same technology (NMR based company)

- Indirect Competitor:
  company providing a similar service using a different technology (MS based company)

Second, the performance of all competitors was evaluated on a select choice of competitive factors (key service features) which has allowed us to clear identify our competitive advantage. The key service features (values driver) identified are reported in the following table:

Table 5. Value driver definition for the competitive analysis

Value Driver	***Description***
Service	*The overall service value provided from the definition of projects needs to the delivering of service*
Flexibility	*The capability to provide customized / not standardised solutions*
Benefits	*The overall benefit that the metabolomic service is able to provide (i.e. number of metabolites extract and/or predict from a sample)*
Price	*Average cost for the metabolomic service provided*
Sensitivity of Technology	*The sensitivity level of technology used for providing the metabolomic service*
Reproducibility of Technology	*The reproducibility level of technology used for providing the metabolomic service*
Quality	*The current reputation of the metabolomic service provided for being a leader in its category*
Innovation	*The innovation level of provided service*
Convenience	*Service meets or exceeds customer/consumer requirements (i.e. potential medical information provided)*

Evaluating each feature for all competitors, a general values proposition has been calculated and then a positioning map obtained which determines our market position in relation to our main competitors (see figures below).

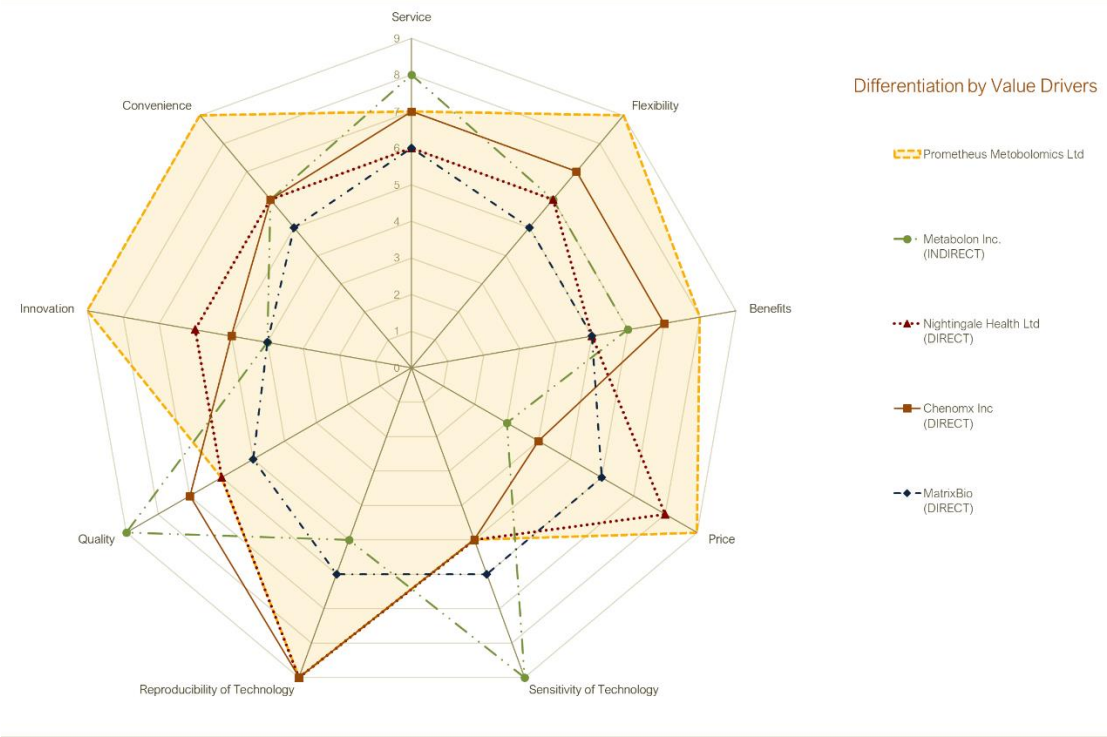

Figure 8. Differentiation Chart, the rankings from the value driver scoring are displayed visually

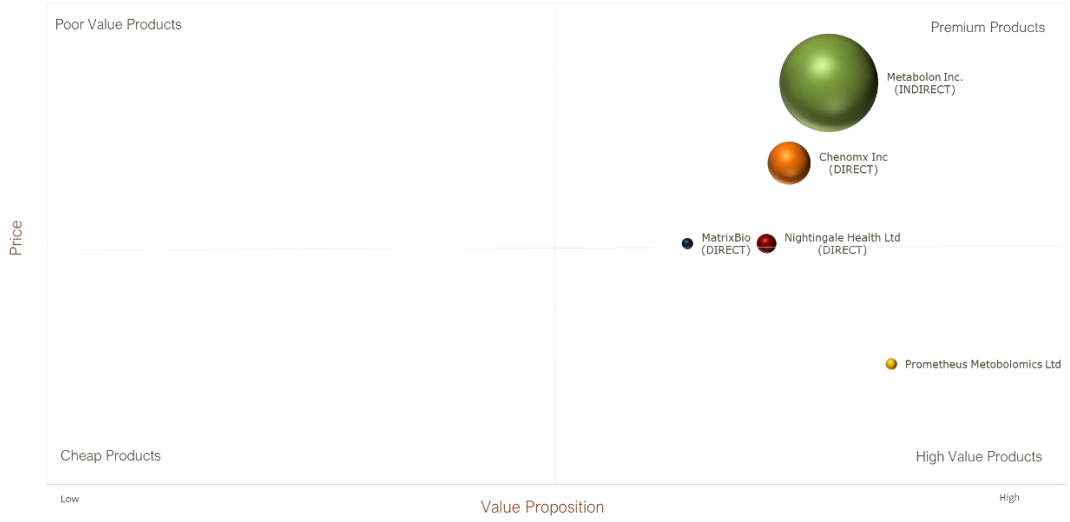

Figure 9. Positioning map: market position evaluated with the key service features described. Bubble size shows the company size

Companies that offer metabolomic analysis based on MS technologies cannot be considered as direct competitor. Beyond the higher sensitivity of MS, the advantages of

NMR spectroscopy are its higher reproducibility and its minor cost. For this reason, the competitive analysis has focused the attention only at the major player of this company category, Metabolon Inc, as representative actor of the others.
The direct competitors of PROMETHEUS METABOLOMICS LTD are Nightingale Health Ltd (Finland), Chenomx Inc (CAN) and Matrix Bio (USA).

These competitors are constituted by NMR based companies with a general value proposition less than PROMETHEUS METABOLOMICS LTD and an average cost of provided service generally higher than ours. Beside the cost, our competitive advantage is represented by having a very high innovation factor due to our developed algorithms which determines more benefits to the customers. Overall, our service is a more convenient than others due to a higher number of potential medical information potentially extracted (a higher satisfaction of customer expectations).

Finally, considering the Metabolon service's as the top on the market, PROMETHEUS METABOLOMICS LTD is able to offer almost the same service level (i.e. value proposition slightly higher) at a cost significantly minor.
Below a company profile description of each is provided, which includes key information about the players addressed in this competitive analysis such as company overview (year of foundation and company size), business core description, technology applied, specialties and average services cost.

Chenomx
Chenomx patented Targeted Profiling turns complex NMR spectra into easy-to-use tables of metabolites and their concentrations in the mixture under investigation. The key is a combination of advanced software methods and an extensive library of reference compounds developed using both experimental data and theoretical spectral predictions.
The company was founded in 2000 and is based in Canada (company size 2-10 employees).
They provide metabolomic services at US$300 (as average) per sample.

Matrix Bio
Matrix-Bio's goal is to be a leading provider of metabolomics-based testing in the fast-growing molecular diagnostic testing market. The company's first product, VeraMarker™ BCR, a blood test for detecting breast cancer and cancer recurrence monitoring, is being commercialized as the first metabolite-based test in the world. Matrix-Bio is currently exploring the commercial feasibility of additional diagnostics tests using its VeraMarker technology platform, including colon, esophageal, liver and pancreatic cancer; for identifying liver cancer in patients with hepatitis C; and for predicting preoperative chemotherapy effectiveness for breast cancer treatment. The company was founded in 2009 and is based in USA (company size 2-11 employees). They provide metabolomic services at US$150 (as average) per sample.

Metabolon
Metabolon, Inc., a technology company, develops analytical methods and software for biomarker discovery using metabolomics. It offers MS profiling platform that analyses

and identifies biochemicals in the research of pharmaceutical, biotech, agriculture, cosmetic, and consumer products. The company provides biochemical markers and information for understanding biochemical processes, such as drug action, toxicology, and bioprocess monitoring. Its metabolomics platform is used to develop diagnostics for cancer, amyotrophic lateral sclerosis, diabetes, and metabolic diseases. The company was founded in 2003 (company size 200 employees) and is based in Durham (North Carolina) and it represents the world leader in the metabolomics sector. They provide metabolomic services at 400 US$ (as average) per sample.

Nightingale Health ltd

Nightingale Health Ltd. is a pioneering Finnish biotech company (founded in 2013, company size 11-50 employees), transforming healthcare and research through use of its innovative blood analysis service. By providing comprehensive and cost-effective data on blood, Nightingale's mission is to solve the world's number one health problem - chronic diseases. At the heart of its technology is a combination of NMR-based analysis and proprietary software that generates data used by researchers and clinicians to improve risk prediction of diseases, such as diabetes and cardiovascular diseases. There are currently over 100 scientific publications that have successfully applied Nightingale's method, including major metabolomics and epidemiological studies.

Nightingale is built on an unrivalled scientific foundation, comprising of an interdisciplinary team of experts in computational medicine, healthcare IT and business. With headquarters and laboratory facilities in Finland (along with two franchising laboratories in the UK), Nightingale routinely provide services for academic research and industrial R&D customers internationally. They provide metabolomic services at 150 US$ (as average) per sample.

Strategic Implementation

A. Production

Our services consist in the elaboration and processing of data acquired with NMR experiments. To produce these services is only needed a dedicated IT infrastructure (i.e. PCs, servers, network access) because the NMR experiments are performed in selected NMR centers collaborating with us.

The implementation of our innovative approach foresees the following steps:

- Project analysis as per customer needs (algorithms fixing)
- Protocols preparation for samples management
- Samples delivering to NMR center
- Execution of NMR experiments
- Data elaboration and processing
- Results delivering

The solutions provided are innovative and allow the detection and quantification of metabolites in the NMR spectra, giving a clearer understanding of experiments and rapid translation into clinical settings. Our business is designed to overcome the limitations of current clinical diagnostics and enables focus on improving individual health.

In this frame, PROMETHEUS METABOLOMICS LTD operates as a consultant company, collaborating with the NMR facilities and Physicians/Researchers, and providing expertise and customized solutions in the metabolomic area.

B. Resource Needs

PROMETHEUS METABOLOMICS LTD has identified the following needs to speed up its project.

- **Human**

  The project requires the involment of high-level education employes for performing sofistacaed statistical data analysis. For this activity, we will hire PhD employees with the right skills for executing data analysis, data processing, algorithms elaboration. Moreover, our business requires sale/marketing agents to promote our services to all potential customers.

  The company intends to implement the following resources plan:

  - *Short Term (within 12-months)*: hiring 1 full time employee with sales/marketing skills (i.e. new customers scouting, company services promoting) and 2 part-time collaborators working on pre-established projects with data analysis skills
  - *Medium Term (within 36 months)*: transforming the 2 part-time collaborators in full time ones and hiring 1 collaborator to handle day to day operations (i.e. projects handling)
  - *Long Term (within 60 months)*: hiring 1 full time collaborator to handle day to day operations (i.e. projects handling)

- **Financial**
  We estimate an initial investment of *£200000* for making operative our business to guarantee enough impact on the market and to overcome the competitors.

- **Physical**
  We are proving innovative solutions based on proprietary algorithms. To improve the efficiency and the amount of data processed per time, we need an adequate IT infrastructure available such as PCs, servers, network access, a web-based platform. To start the business is not mandatory a physical structure as offices, but our services can be handle from home by our collaborators. Moreover, the development of a dedicated web-based platform will guarantee the full project control at the final customer

C. Sourcing/Procurement Strategy
PROMETHEUS METABOLOMICS LTD has identified the following strategy to obtain its needs to catch the requirements for its business.

- **Human resources**
  PROMETHEUS METABOLOMICS LTD wants to build a team composed by the following figures:

  - Analysts
    People involved in the statistical data analysis with the capability to understand the NMR data collected during the experiments and then process NMR data, generating the final result; preferibly, people with a PhD

  - Sales Agent
    People involved in the promotion of our services to all potential customers, with the cabability to build and to maintain a network of clients over the world

- **Financial resources**
  PROMETHEUS METABOLOMICS LTD estimates an initial investment of *£200000* for making operative our business to guarantee enough impact on the market and to overcome the competitors.
  The initial investment will cover the hiring of new employees, a general re-organization of our IT infrastructure (see next section) and the development of other innovative solutions in the metabolomic area (i.e. novel approaches and algorithms to extract data from NMR experiments for the metabolomic area). As mentioned at pages 10, 13, metabolomic is an optimal source of information on the patient's health and the metabolomic analysis of patient fluids would represent a way to discovery a new biomarker or biomarker panel that is possible to use in a non-invasive diagnostic test.

For the medium term (within 36 months), PROMETHEUS METABOLOMICS LTD would finalize our innovative approach, optimizing the statistical platform, and then start the process to achieve a specific patent about our services.

To increase our business capability, our intention is asking financing to the market, offering our business plan to potential investors.

- **Physical resources**
  PROMETHEUS METABOLOMICS LTD are proving innovative services based on proprietary algorithms. To improve the efficiency and the amount of data processed per time, we need an adequate IT infrastructure available (i.e. servers, PCs).
  Moreover, it's our intention to create a dedicated platform, web based, to guarantee a full access to the end-user for project management, data sub-mission, results monitoring and delivering. The final user will have the complete and 24h control of each step of the project.
  To handle this needs we will ask the collaboration to a specific company selected on the market, specialized on IT services delivering

D. Marketing Strategy

PROMETHEUS METABOLOMICS LTD has identified two market segments. The first segment is the physicians that work in clinical research. The second group is comprised of the managers of NMR laboratories.
The marketing strategy foresees to drive our services through NMR centres already operative in the world. Our plan consists in the following steps:

- Worldwide search and selection of all NMR centres
- Promote and stipulate a strategic alliance with the selected ones
- Offering our services through the selected NMR lab to the final customers

Based on the successful alliance with the NMR centres in Spain and Italy, collaborating with us (see page 7, section B), we want to expand this strategy over the world.
It is our intention to offer the same approach to others NMR centres in the world. The single NMR centre will expand its markets, performing more experiments in its laboratory while we will be able to provide our services to all final clients, collaborating with the NMR centre. We will provide a list of services to all selected NMR centres which will be our main channels for delivering our business from us directly to final customers.
An advantage of our approach is given by the possibility to perform NMR experiments close to the location of our clients reducing the cost of shipment. The potential customer sends physically the samples directly to the selected NMR centre (collaborating with us) via express courier. The results of the NMR experiments are sent to us through the web with no additional cost and we preform the analysis of NMR experiments. After the analyses are complete, we sent the final result directly to the clients by email. The final cost is decided by the cost of the NMR experiments. The overall amount of NMR experiments cost is around US$30-40 per sample (raw estimation) but this price can decrease a lot due to a constructive competition between NMR Centers, collaborating

with us. A cost decrease of 10-15% can be predictable. This is the only cost which is strictly needed to start and continue our business.
The cost of IT infrastructure (i.e. PCs, printers, servers) required for data processing is a fix price which is included in the closing price, paid by customers.

NMR centres are not the only channel to drive our services but another important market segment is represented by all persons involved in research activities, working in public and/or private institutes.
It's our intention to promote our services via internet, contacting directly all potential clients (researchers).

E. Performance Standards
At the end of this round, we will able to put our company as one of the leader services providers in the metabolomic area. During the spreading of our services, we will continuously monitor the market to promptly react for keeping our products as the best solution available on the market.
PROMETHEUS METABOLOMICS LTD has identified the following KPIs to monitor its business:

- Recurring Revenue Rate
- Cost of Goods and Services
- Gross Profitability
- Average Revenue Per User
- Infrastructure Capacity Utilization
- Availability Rates
- Sales Activity
- Customer Satisfaction and Retention Rates
- Return on New Investments
- Compared to Competitors
- Average Resolution Time
- Employee Productivity
- Active / resolved Issues
- Complaint Escalation Rate
- Cash Flow

Financial Plan

A. Financial Projections

At to now, the business is auto-financed with our sales coming from the market. To increase our business capability, our intention is asking financing to the market, offering our business plan to potential investors.

This financial plan is based on a Capital Improvement of £200,000.

The financial plan for the next five years is described below (see Figure 10) and it is based on the planned operations, mentioned above in the strategic implementation section.

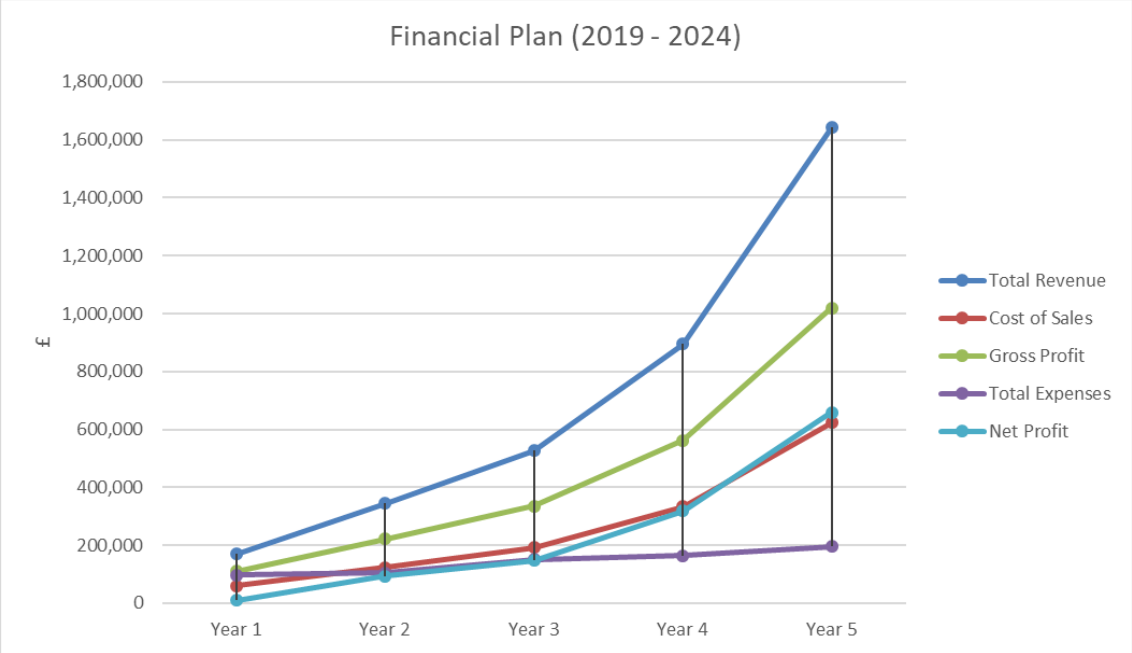

Figure 10. 5-years financial plan

The details of the financial plan are available for reference under written request.

- *Forecasted Revenue*

PROMETHEUS METABOLOMICS LTD provides metabolomic services which can be divided in three main groups:

1. Metabolites Quantification (without statistical evaluation)
2. Metabolites Quantification (with statistical evaluation/multivariate analysis)
3. Metabolites Quantification (unknown matrix)

For each group, the required effort to reach the target (metabolites quantification) is different and determines the closing price of the service itself which can be estimated

as average, as follow: £55 per unit (for services belong to group 1), £85 per unit (for services belong to group 2), £140 per unit (for services belong to group 3).

At the end of first year, we estimate to sell our services for 2000 unit overall, divided as follow, reaching a total revenue of £169,000:

- Group 1: 400 unit
- Group 2: 1400 unit
- Group 3: 200 unit

For the following years, we estimate a significant increase of annul unit sold due to the strong improvement of sales/marketing operations:

- after 3 years: 8000 unit with a total forecasted revenue of £527,000
- after 5 years 32000 unit with a total forecasted revenue of £1,642,000

- *Cost of Sales*

The cost of sales is represented by the cost of the NMR experiments needed to collect the raw data on samples provided by customers.
PROMETHEUS METABOLOMICS LTD sales its services by performing a specific analysis of data collected by NMR facilities over the world which have a strategic alliance with us. The current estimation of the cost of sales is based on the current agreement with the NMR centre collaborating with us. Due to the planned extensive and efficiency sales/marketing campaign, PROMETHEUS METABOLOMICS LTD will be able to decrease the cost of each NMR experiment by increasing the available portfolio of NMR facilities collaborating with us. This element should be considered for the future but in the proposed financial projections, we analyse the cost of sales variable in the worst scenario (i.e. same cost as today and annual inflation rate at 2%)

- *Expensive*

The expensive item is mainly constituted by the number of human resources hired. PROMETHEUS METABOLOMICS LTD wants to implement the HR plan as described at page 27. That plan foresees to hire 5 FTE within the next 5 years with an increase of overall expenses consequently (from £96,500 to £196, 400 after 5 years).
Compared to the amount of HR related expensive, the other items are very less significant and are represented by operating expenses as travel costs and sales/marketing activities. The cost associated to samples delivering from the customer laboratory to the NMR centre selected is sustained directly by the client itself.

Sincerely,

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Date: 16 July 2018

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