APPENDIX 3

EXPECTED ECONOMIC IMPACT, LONG TERM SUSTAINABILITY AND POTENTIAL REVENUES OF THE HUMAN TECHNOPOLE

The expected economic impact of HT should be evaluated on a time scale of at least 10 years. The development of:

- a precision medicine and preventive nutrition strategy for public health,
- new technologies for food traceability, production and packaging,
- new medical diagnostics approaches and the development of new software,
- new algorithms and predictive models,

will impact remarkably at technological as well as social and economical level. There are three main indicators of impact to be considered:

1- direct fund raising of the research;
2- creation of new jobs and entrepreneurial activities;
3- reduction of public expenditure induced by the HT technologies on the public health system and other public domains

Direct fund raising will be a primary target of HT. Competitive fund raising channels include: European programs (eg Horizon 2020 and ERC), other national and international individual awards, including charity funds, industrial grants and sponsored research agreements. We also expect patent licensing and IP related revenues (eg royalties) to contribute to the global fund raising of HT. **At steady state HT targets to raise yearly up to 40% of the research cost.**

In addition to fund raising, a positive impact of HT on GNP is expected by the creation of new startup and new jobs and by the transfer of technologies to companies and hospitals. Enhanced attractiveness of international companies in Italy and establishment of joint public/private R&D laboratories between HT and industries should also be considered. Despite these actions do not impact directly on the finances of HT, they represent positive indicators of impact on the country's economy, which is ultimately measured by the number of new jobs created around the Human Technopole activities. **A good target could be to double the number of jobs around the HT initiative at steady state**.

The most important indicator is obviously the expenditure reduction induced by the massive impact of the HT program on the public health system, food and nutrition system, predictive models for social needs and decision making system in the long term. It is very difficult to make quantitative prediction at this stage. However, considering that the social cost of Cancer and Neurodegenerative diseases in Italy amounts to about 2% of the GNP (> 30 Billion Euro) per year, even a partial success of the precision medicine strategy would by far compensate the investment of the first 10 years of HT. Similar arguments apply to the food/nutrition pipeline and to the predictive models applied to other social domains (such as the tax system).

A more detailed analysis of expected impact of the different HT centers is provided in the following.

CENTER C1 and C2: IMPACT ON THE PUBLIC HEALTH AND PUBLIC EXPENDITURE

Biopharma and care executives are optimistic that Personalised Medicine will improve efficacy, safety and public health (through improved disease prevention, management of disease in early stages, prediction of a

specific patient's clinical response to various medical interventions). It is also generally perceived that Personalized Medicine may be economically viable, due to: i) improved primary and preventive care (expected to greatly reduces future health care costs) and ii) improved disease control (expected to reduce global costs of current disease treatments by increasing efficacy).
There is, however, a widespread skepticism about the financial impact of Personalized Medicine in the short term. In particular, since Personalized Medicine is based on innovation through science and technology, it is automatically suspected to be unsustainable in terms of spending (advances in medical technology are widely thought to contribute significantly to the escalating costs of health care). This is mainly due, however, to the fact that there are only a few studies available that analyzed Personalized-Medicine interventions (economic evaluations are largely based on drugs designed to treat the whole patient population). Accurate measurements of the economical effects of Personalized Medicine is indeed among the top priorities of HT. The few available studies, however, demonstrate the potential of Personalized Medicine to reduce costs of Health.
Measurements of cost-effectiveness or cost-utility of health interventions are usually performed through analyses of the incremental impact of the single outcomes on quality-adjusted life years (QALY) and costs associated with the health gain. A threshold of 50000 US$ is considered as cost-effective. A recent review of all published studies that examined cost-effectiveness and cost-utility of Personalized Medicine interventions (1998–2011) showed that the majority (~70%) fall under 50000 US$ per QALY gained, with 20% that are cost saving. This is confirmed by another study that analysed the 47 Personalized-Medicine intervention currently approved (mainly in oncology) in years 2000-2015, which showed, in the majority of the analysed studies, that Personalized Medicine therapies represent a cost-effective/cost-saving treatment option.

Personalised medicine may decrease the average research and development costs for new medicines. Clinical trials are the most expensive part of R&D (nearly 50% of the investment; risen by one third between 2005 and 2007). Biomarkers may enhance the efficacy of clinical trials of new drugs by investing more heavily in early research to identify key biomarkers, and in targeting relevant sub-groups of patients. Smaller (and maybe even shorter) clinical trials are likely to reduce development costs.

CENTER C3 and C7: IMPACT ON THE MARKET AND PUBLIC EXPENDITURE

There are several market segments that may be targeted by the development of rapid tests for genetic traceability of food and food safety. These include, for instance, producers of food ingredients, producers of finished processed food, distributors and suppliers, as well as the mass market retailers (MMR). On the other side, given the important weight on the public health expenditure of foodborne illnesses (detailed below), the development of rapid tests for food safety is expected to produce a large indirect impact on the reduction of public sanitary costs. The innovative tests developed by this HT platform will foster the creation of several new start-ups, specialized in the production and on-demand customization of these technologies to meet the needs of the final users.

Genetic traceability of food
According to Coldiretti, the Italian food industry has a loss of 60 B€/year due to food counterfeiting, which includes both trademark sophistications (false Made in Italy), and substitutions of food ingredients with similar but cheaper food varieties. Additionally, according to the World Customs Organization, food fraud is costing 49 BUS$ annually.
Allied Market Research estimates that the food traceability market is expected to reach 14 BUS$ by 2020, growing with a CAGR of 8.7%. This forecast is based on current technologies that allow for “production chain traceability”, such as RFID/RTLS, barcodes, infrared, biometrics and GPS. Genetic traceability of food

(varietal identification) represents a different technology that addresses a part of the food traceability market, in particular that regarding food frauds by substitution of an ingredient with a different food variety. Standard technologies that could allow genetic traceability of food are those currently employed in traditional diagnostics, which requires expensive instrumentation or time consuming procedures, and thus are not routinely used for food analysis. Compared to these technologies, the low-cost colorimetric tests for food DNA barcoding, that will be developed in this platform, display several technical advantages (Table 1).

Table 1. *Substitute technologies on the market (adapted from: Wong, E.H.K., et al., Food Research International, 41, 2008, 828.)*

	Applicable to degraded material	Low DNA requirement	Simple protocol	Mixture detection	Time efficient	No prior knowledge required	Reproducible between labs
Hybridization	×			×			
Species-specific primer	×	×	×	×	×		×
RFLP		×	×		×	×	×
SSCP		×			×		
RAPD		×	×		×		
Traditional sequencing	×	×	×		×	×	×
DNA barcoding	×	×	×		×	×	×
Human Technopole	×	×	×	×	×		×

These tests for genetic traceability of food represent, thus, a novel technology with no equivalent on the market, especially in terms of costs. Due to the high market size and absence of substitute products, the tests that will be developed by this HT platform have a huge potential impact on the market, and could create a new, substantial demand for genetic traceability tests, spinning from an existing and unmet market needs.

Food safety

The food safety testing world market is expected to reach 16.1 BUS$ by 2020, according to Markets & Markets (India). Another analysis, from Global Industry Analysts (GIA), predicts an impact of 19.7 BUS$ by 2018.

Only in U.S., according to BCC Research, the food safety testing market will reach 4.3 BUS$ in 2017, increasing at a five-year compound annual growth rate (CAGR) of 5.6%. According to report "Global Markets and Technologies for Food Safety Testing", issued by BCC Research:

"The food safety testing market can be split into five segments based on contaminant type: pathogens, toxins, GMOs (genetically modified organisms), residues, and others. […]

- *The pathogens segment is expected to increase from nearly US$3 billion in 2012 to US$3.9 billion in 2017, a CAGR of 5.7%.*
- *Toxins are expected to jump from US$141 million in 2012 to $US162 million in 2017, a CAGR of 2.8%.*
- *GMOs, worth US$125 million in 2012, are expected to increase to US$167 million in 2017, a CAGR of 6%.*
- *Residues are expected to climb from US$110 to US$140 million from 2012 to 2017, a CAGR of 4.9%.*
- *The segment made up of other contaminants should increase from US$10 million in 2012 to US$13 million in 2017, a CAGR of 5.4%."*

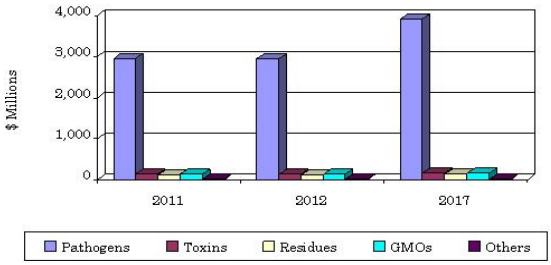

Figure 1. *Segmentation and projections for the US food safety testing market (source: BCC Research, Global Markets and Technologies for Food Safety Testing – FOD011G).*

Currently, the majority of food safety tests relies on standard instrumental technology, which mostly requires samples shipment to external certified laboratories. This represents an additional and important cost for all the companies involved in the production and distribution of food. Consequently, there is a huge market demand for low cost, rapid tests, that can be performed on field in the food processing/distributing chain.

Moreover, food contamination by foodborne pathogens, occurring in production facilities or along packaging, distribution and storage lines, with the risk of outbreaks of fatal foodborne illnesses, represents a serious public health issue. At least 250 foodborne pathogens have been reported globally (source: ISS, Epicentro). According to WHO (Foodborne Disease Burden Epidemiology Reference Group 2007-2015), approximately 600M of foodborne illnesses have been reported worldwide in 2010, which caused more than 350.000 deaths, and 30.000 cases of various degrees of disability. Moreover, according to "The European Union summary report on trends and sources of *zoonoses*, *zoonotic* agents and food-borne outbreaks in 2014 (EFSA and ECDC)", 5,251 food-borne outbreaks were reported only in the EU in 2014, which caused more than 6000 hospitalizations and 27 deaths.

The development of low-cost rapid tests for food safety has thus an important impact on the prevention of foodborne epidemics and consequent reduction in connected sanitary expenses. This is exemplified in the following table.

The following table 2, exemplifies the main areas of impact of the HT research in the field, and the main beneficiaries.

Innovation	**Societal gain**								**Beneficiaries**						
	Increased output	Reduced input	Reduced waste	Increased choice	Better quality	Increased competitiveness	Healthier option	Cleaner technology	Agbiotech industry	Food industry	Healthcare industry	Service industry	Farmers	Retailers	Consumers
Bioactives from microrganisms	√	√			√		√		√	√	√		√	√	√
Bioactives from plants	√			√	√	√	√		√	√	√		√	√	√
Bio-control strategies		√					√	√	√	√		√	√	√	√
Cosmeceuticals				√		√	√				√	√		√	√
Crop genomics tools						√			√	√		√			
Decision support systems in agriculture		√	√					√		√		√	√	√	
Fecal transplant				√		√	√				√				√

Fermented products	√			√	√	√	√	√		√	√	√		√	√
Food safety tools					√	√	√			√		√	√	√	√
Functional foods				√	√	√	√			√	√	√		√	√
Health/disease markers				√		√	√				√	√		√	√
Improved crop varieties	√	√	√	√	√	√	√		√			√	√	√	√
Intervention nutrition				√	√	√	√			√	√	√		√	√
Medical foods				√	√	√	√				√	√			√
Metagenomics tools	√	√	√				√	√	√	√	√	√	√		√
Packaging technologies		√	√		√	√	√	√		√				√	√
Personal care				√	√	√	√				√	√		√	√
Personalised nutrition			√	√	√	√	√				√	√	√	√	√
Prebiotics	√			√	√	√	√		√	√	√		√	√	√
Precision agriculture	√	√	√				√	√				√	√		√
Preventive nutrition			√	√	√	√	√			√	√	√		√	√
Probiotic strains				√	√	√	√		√	√	√		√		√
Traceability of food origin					√	√	√			√		√		√	√
Yeast collections	√			√	√	√	√	√	√	√	√	√	√	√	√
food tracability tool					√	√									
Bioprospecting	√	√			√		√								
Lab in a chip for food analysis					√	√									
Food dna barcoding database	√			√	√	√	√	√							
increased food shelf life			√		√		√								

*Table 2 Areas of impact of C3 and C7 and main beneficiarie*s

CENTER C4 and C5 and Facility F3: IMPACT ON THE MARKET AND PUBLIC EXPENDITURE

Centers C4 and C5 will be devoted to the design and the development of novel formalisms, algorithms, and codes, with the goal of obtaining predictive models for life sciences and health. In addition, we envision a well-structured pipeline of activities "from equation to software", and through this pipeline, we seek to develop user-friendly and professional software solutions fostering their widespread distribution and exploitation. These new algorithms can also represent the technological core of high-tech startup companies, enabling them to commercialize software solutions to pharmaceutical, food, and cosmetic industries, in the fields of big data analytics, multiscale computational modeling, and bioinformatics. Small biotech companies will also be reached by these innovative solutions with diverse business models and co-development agreements. In addition, teams of C4 and C5 will apply to H2020 and future framework programs in Health and ICT, as well as to specific technological calls for HPC and data storage infrastructures.

Facility F3 will be devoted to the design and development of a national data repository, which will store administrative, epidemiological, pharmaceutical, clinical, and research data in the domains of health, bioinformatics, and life sciences. This will remarkably improve diagnoses and treatments benefiting the entire health system, including the ultimate goal of precision medicine and personalized treatments for cancer, neurodegenerative diseases, rare diseases, etc.

Three KPI could be assumed as indicators of potential economical impact derived by the construction of a national data repository and by the development and application of predictive computational models in life sciences and health: i) optimization of the management of the public health system through a massive informatization of all processes (expected impact of 2-3% on the health system budget); ii) improvement of the reliability of diagnoses and the quality of treatments, which in turn will reduce hospitalization and will impact on the overall population quality of life; iii) development of new enabling technologies thanks to professional data warehousing and computational predictive models, which can have an impact of about 5% on the pharmaceutical and biotech industry-segment that approximately represents the 8% of the national GDP. Table 3 summarizes the expected direct and indirect revenue sources of centers C4 and C5.

Item	Sources
DIRECT REVENUES	
HORIZON 2020	FET (Health and ICT) Center of Excellence for Computing Applications
ERC	YES (three, one ongoing, one starting at Y2, the other starting at Y3)
THER EUROPEAN PROJECTS	Flagship HB
INDUSTRIAL PROJECTS	IBM
LICENSES & PATENT TRANSFER	NA on short term
CHARITIES	Bank Foundations (CRT, CSP)
SOFTWARE – MODELS – ANALYTICS	YES: Open Access
SCIENCE DISSEMINATION	YES: Free
OUTREACH	YES: Free
INDIRECT REVENUES	
START UPS	AI in healthcare (one, starting Y3)
PERSPECTIVE REDUCTION OF THE HEALTH SYSTEM COSTS	National Health System, WHO
CLINICAL TRIALS	Data storage and computational design
PERSPECTIVE REDUCTION OF SOCIAL COSTS INDUCED BY PREDICTIVE MODELS	Public health-care running costs, social costs of diseases: in particular neuro-degenerative diseases and cancer

Table 3 Analysis of the direct and indirect revenue sources of centers C4 and C5 (NA: Not Applicable)

CENTER C6: IMPACT ON THE MARKET AND PUBLIC EXPENDITURE

The main mission of C6 will be to process and analyze high throughput data gathered or generated by Humane Technopole. In addition C6 will manage, explore, and analyze large-scale and high dimensional data on socio-economic decisions and interactions. CADS will integrate and manage massive databases to design and measure the impact of policy decisions on an unprecedented scale, speed, and resolution. Table 1 and 2 synthesize the impact of research activities performed at CADS on attraction of additional resources and on societal benefits. Table 4 exemplifies the main areas of impact of C6 and the main beneficiaries.

Innovation	**Societal Gain**					**Beneficiaries**			
	Sustainability	Predictive capabilities	Industrial Competitiveness	Healty ageing	Human capital	Public Sector	Healthcare industry	Service industry	Citizens
Data integration and analytics for policies	√	√	√	√	√	√	√	√	√
Analytics for health and the life sciences		√	√	√		√	√	√	√
Foundational data science		√			√	√	√	√	√
Analysis of industrial and financial systems		√	√		√	√	√	√	√
From now casting to long term projections	√	√	√	√	√	√	√	√	√
Management systems and solutions	√		√	√	√	√	√	√	√

*Table 4 Areas of impact of C6 and main beneficiarie*s