ROADMAP LARGE SCALE RESEARCH FACILITIES

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2. Title infrastructure

European **Bio**medical **Imaging** Infrastructure - from Molecule to Patient: **Euro-BioImaging Population Imaging**

3. Summary Infrastructure

The ESFRI Roadmap Working Group Biological and Medical Sciences (BMS) has given this new proposal a positive evaluation ranking it as number one of nine proposals that were submitted to BMS. The ESFRI Forum has been advised to put this infrastructure on the update of the ESFRI Roadmap.

Euro-BioImaging brings together key research areas in the imaging field stretching from basic biological imaging with advanced light microscopy, to the clinical and epidemiological level with medical imaging. Euro-BioImaging will address the imaging requirements of both basic and medical imaging communities by creating a coordinated and harmonized plan for infrastructure deployment in Europe.
Euro-BioImaging will be organized into strongly interlinked *nodes*, each focused on complementary imaging technologies addressing different aspects of biology, physiology and pathophysiology. These nodes are:

- <u>Common Nodes</u>: Large scale image processing and computing, Databases for quantitative biomedical imaging, and Imaging of tissues and animal models
- <u>Advanced light microscopy nodes</u>
- <u>Medical imaging nodes</u>, among which Population Imaging.

The Netherlands is strong in imaging and has interesting and compliant study populations. Adding imaging data to the genetic, lifestyle and other phenotypic information available on the populations will offer novel research opportunities. Objective is that the Netherlands will host the Node for Population Imaging within Euro-BioImaging, for which we are in an excellent position. To strengthen this position we propose to expand the research facilities for population imaging with dedicated, state-of-the-art imaging units and data handling and processing capacity. This will create an infrastructure for population-based research that is unique in the world, enhancing the Dutch science position and benefitting industry. Societal benefits are reduced health care costs due to identification of people at risk and a higher quality of life for patients due to new diagnostic markers and therapeutics.
This proposal is broadly supported by the Federation of the Netherlands University Medical Centers (NFU) and ZonMw.

4. Keywords

Medical imaging, Population-based studies, Epidemiology, Prevention, Imaging biomarkers

5. Science case

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Biomolecular imaging is a fundamental to basic and applied research. Innovative imaging techniques are key tools for life scientists to understand living systems at both the molecular and the physiological level, from biological model systems to patients.
In European and worldwide perspective, the Netherlands are at the forefront in basic and applied biomedical imaging sciences. All university medical centers have strong research programmes in biomedical imaging, covering the wide range from fundamental research (e.g. zooming in on disease processes at the molecular and cellular level) to large clinical studies. On average, imaging publications from the Dutch university medical centers are cited 35% more frequently than an average imaging publication. Indeed, publications from the Erasmus MC Departments of Epidemiology and Radiology — both partners in this proposal — are cited 97% and 121% more frequently than an average article in their field.
Strong biomedical imaging activities have been additionally established in the technical universities in Delft (e.g. optical imaging, acoustics, radiation and radioisotopes for imaging, biomedical image analysis), Eindhoven (molecular imaging, image-based modeling and analysis, MRI), and Twente (neuroimaging).

In particular, Dutch medical science has a track record in large population based studies which is acknowledged world-wide and which would benefit from imaging facilities, like:

- Generation R, a population-based cohort study from fetal life until young adulthood. The study is designed to identify early environmental and genetic causes of normal and abnormal growth, development and health.
- Integrated Primary Care Information database (IPCI), comprising longitudinal automated patient records of more than one million persons.
- Prospect-EPIC study, one of the two Dutch cohorts participating in the European Prospective Investigation into Cancer and Nutrition coordinated by the International Agency for Research on Cancer (IARC, Lyon).
- Leiden 85+, cohort of 1000 elderly from Leiden and vicinity
- Leiden Longevity Study, population-based cohort of 2000 people to study determinants of longevity.
- Longitudal Aging Study Amsterdam (LASA), interdisciplinary, longitudinal study (n=4500)
- Prevend Study, a prospective, observational cohort study (n=8000) focused to assess the impact of elevated urinary albumin loss in non-diabetic subjects on future cardiovascular and renal diseases.
- NLCS Study, cohort of 120,852 women aged 56-69 that have completed questionnaires. NLCS is followed up regularly by record linkage to the Netherlands Cancer registry, the national pathology registry PALGA, the municipal population Etiology, and specific molecular endpoints.

- Utrecht Health Project (LRGP), cohort of 10.000 inhabitants of the Utrecht area with still increasing participation
- NEO-study, population study of 6000 persons from Leiden and vicinity to study the consequences of obesities.
- Rotterdam Study, a prospective population-based study aimed at investigating determinants of chronic and disabling diseases in the elderly.
- LifeLines, cohort of 165.000 participants, based on a 3-gereration design.

This is only a part of the existing population cohort that might include imaging. More population studies will start in the coming years.

As the Dutch scientists also have extensive expertise in handling and processing large imaging databases, the Netherlands is an ideal country to host the population based imaging node. The different and well documented populations combined with new imaging studies will keep the Netherlands at the forefront as a center of excellence for Europe. This requires new investments in imaging infrastructure to gather, to store and to analyze imaging phenotypes. This information can be combined with the analysis of biological material, lifestyle factors and genotyping of these populations. Ongoing population-based studies which already include imaging, for example the Rotterdam Study, have recently demonstrated that this approach delivers extremely important new knowledge. These studies will lead to many more scientific breakthroughs in crucial areas of medicine like oncology, cardio-vascular, neurodegenerative diseases, in chronic musculo-skeletal or developmental disorders.

The identification of biomarkers and risk factors of pre-symptomatic disease and the development of predictive models for functional and structural alterations require large, prospective epidemiological studies in unselected populations in which sub-clinical pathology can be assessed. It is now widely recognized that we need biomarkers to make accurate diagnoses early in the disease process and to monitor changes in organs of individuals even before the first symptoms of disease become clinically manifest. Although biochemical markers have promising value in the early stages of diseases, many of them are non-specific and lack the possibility for localization of the ongoing functional and structural alterations.

Imaging allows non-invasive assessment of structural and functional changes in intact organisms that may reflect specific pathology. Recent developments in image data acquisition and analysis make it feasible to use these techniques at a large scale. This opens the possibility to investigate specific pathophysiological substrates of disease in a pre-symptomatic phase, in an epidemiological context, and at the population level.

MRI, with its lack of ionizing radiation and capacity to provide exquisitely accurate details of in vivo anatomy and function, is particularly well suited for pediatric studies and has become a valuable tool for investigating developmental disorders in childhood. While many studies of developmental disorders and possible underlying brain or cardio-vascular abnormalities have been done, little is known about normal development. However, the characterization of normal development during the period when many developmental disorders emerge is important for our understanding of the underlying mechanisms and possible etiology of these disorders.

A large, prospective, population-based imaging study is not original in the sense that nobody else has ever perceived of the idea or need of such a study. On the contrary, the urgent need to find non-invasive and early biomarkers of disorders is commonly recognized. The innovation lies in actually conducting such studies on a large scale. Innovations in epidemiology typically do not come from the development of novel techniques, but rather from the creation of unique databases that allow the investigation of correlations that till then could not be studied. The combination of novel imaging data with the already existing and continuously increasing data potential of the different Dutch population cohorts will create an infrastructure for population-based research that is internationally unique and scientifically on the forefront of epidemiologic research.

The *ultimate aim* of the population-based imaging node is to help the development and implementation of strategies to prevent or effectively treat disease. In order to accomplish this, we must first investigate the etiology of disease and identify specific imaging markers of incipient disease that can be used both to investigate causes of pathologic alterations and to identify people at risk. These can be used to develop diagnostics, therapeutics and other types of interventions.

The consortium has a solid record of producing high-impact publications on a regular basis. Examples of some of these publications relating to this proposal are:

2007 N Engl J Med 357:1821 — Vernooij MW, Ikram MA, Tanghe HL, Vincent AJ, Hofman A, Krestin GP, Niessen WJ, Breteler MM, van der Lugt A. Incidental findings on brain MRI in the general population.

2005 Circulation 112:572 — Vliegenthart R, Oudkerk M, Hofman A, Oei HH, van Dijck W, van Rooij FJ, Witteman JC. Coronary calcification improves cardiovascular risk prediction in the elderly.

2004 N Engl J Med 350:2033 — van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, van der Klift M, de Jonge R, Lindemans J, de Groot LC, Hofman A, Witteman JC, van Leeuwen JP, Breteler MM, Lips P, Pols HA, Uitterlinden AG. Homocysteine levels and the risk of osteoporotic fracture.

2003 N Engl J Med 348:1215 — Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline.

2001 N Engl J Med 345:1515 — in t' Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, Breteler MM, Stricker BH. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease.

6. Talent case

The proposed imaging node for population-based studies will provide a research infrastructure that is unique in the world. Recent investments in imaging infrastructures, like the 7-tesla MRIs (VISTA) , an MR centre for population-based imaging, and imaging facilities within the Cyttron project, have proven that these attract talented researchers, young as well as established ones. This project, however, will provide a multidisciplinary infrastructure based on the top-level research in epidemiology and imaging science that already occurs in the Netherlands. This infrastructure can be used by researchers in many fields (imaging science, epidemiology, genetics, physics, image processing, information technology, as well as disease-specific fields), attracting researchers from different disciplines and further enhancing the multidisciplinary aspect. Especially important will be the opportunity to examine the relationship between genotype and phenotype in major clinical disease areas, which can only be done in large populations and which will make this infrastructure invaluable to genetic researchers world-wide. The multidisciplinary research groups can provide students, PhD students, technicians and more established researchers with excellent education and training opportunities. This extended multidisciplinary interaction is fertile soil for innovative ideas and will attract top researchers from others countries to the Netherlands as well as holding our top researchers here. Recent, excellent immigrants who would be susceptible to 'brain-drain' are Dr. Christiane Reitz from Heidelberg/DE and Columbia University/US, Dr Fernando Rivadeneira from Madrid/ES, and Dr Elisabeth Devore from Harvard University/US. In addition, any of the VIDI/VICI awardees listed in 'Section 12: Critical Mass' could be susceptible to offers from other countries if the facilities there outweigh those in the Netherlands. We are confident that new imaging infrastructures will lead to brain gain and reduce the brain drain to the US and other countries.

7. Innovation case

The relevance of Euro-BioImaging for innovation at the European level is evident from the strong collaboration with industrial partners in Europe and worldwide that already exists. Both the large industrial partners and SMEs that have activities in, e.g., microscopic imaging, optical imaging devices, software, MRI equipment, biomarkers, florescence assays, histological stains, measuring equipment, et cetera will strongly benefit from the activities and infrastructure of Euro-BioImaging.

In the Netherland a large number of industrial companies will benefit from an infrastructure for population-based imaging. Concrete examples are:

- The production, installation and maintenance of the equipment for this infrastructure
- Development of methods and programs for automated quantitative imaging analysis
- Discovery of biomarkers of disease mechanisms that may lead to new or improved diagnostics and therapeutics.

The societal impacts are:

- the development and implementation of strategies to prevent disease
- (early) identification of people at risk
- differential diagnosis and treatment strategies that are optimized for the individual

Societal impact will be in all major disease areas. For example, imaging will play an important role in unraveling the relation between obesity, the metabolic syndrome, diabetes, cardiovascular diseases, high blood pressure, et cetera. These conditions are very common. Patients often develop complications, which lower their quality of life considerably and impose a heavy burden on the health care budget. Identifying people at risk and implement preventive interventions.

Examples of specific disease populations that will benefit from *Population Imaging*:

Dementia

Dementia is the most common neurologic disease in the elderly. Dementia is a syndrome and sub typed according to presumed etiology. Alzheimer's disease (AD) and vascular dementia are considered the most common sub-types, with AD accounting for about 70% of cases. Traditionally, AD and vascular dementia have been studied as separate diseases. It is however a question to what extent Alzheimer’s disease and vascular dementia are truly distinct and separable entities. The clinical distinction between Alzheimer disease with vascular pathology and vascular dementia is difficult and maybe even impossible.

Most research on neuro-imaging in relation to dementia has been clinic-based and concentrated on finding appropriate modalities and techniques to follow people as they develop cognitive impairment and Alzheimer’s disease. However, therapeutic strategies for dementia and Alzheimer’s disease have largely failed and the current focus in dementia research is shifting from treatment of disease to possible prevention. The importance of early, preferably in a presymptomatic stage, detection of dementia is widely recognised. However, the US Preventive Services Task Force recently concluded that currently available evidence is insufficient to recommend for or against routine screening for dementia in older adults, let alone screening for preclinical stages of dementia. However, in view of huge ongoing efforts to develop disease modifying strategies that may prevent or reverse the early development of Alzheimer’ disease pathology, the need to be able to identify individuals at risk, will soon become more pertinent.

This program aims to find brain imaging parameters that can predict later development of neurodegenerative disease. Currently, no specific biomarkers are available that can identify persons at risk for neurodegenerative disorders. Imaging parameters hold promising value. Now that the focus in dementia research is gradually shifting from treatment of disease to possible prevention quantification of an individual’s risk becomes more and more important. Brain imaging may become of major importance to identify people that could benefit from preventive intervention.

The importance of early detection of dementia is widely recognized. An intense effort is underway to develop disease modifying therapies for Alzheimer’s disease and dementia. Notwithstanding a recent setback for an Alzheimer’s disease vaccine, similar and parallel efforts continue at full speed. The realistic expectation that disease modifying strategies may become shortly available accentuates the need for the development of methods to identify individuals at risk. Considerable progress has been made in recent years in neuro-image analysis and automated tools are now available for segmentation of the brain and brain regions, and for the subsequent volume and shape analysis. The further development of such analytical tools is dependent on the availability of large databases of repeated measures in unselected populations. The data generated under this program can serve as reference material enabling the assessment of normative values and brain maps that will be instrumental for the development of new imaging techniques and systems for neuro-image analysis.

Osteoarthritis

Osteoarthritis (OA) is the most common joint disease and is among the most frequent and symptomatic health problems for middle aged and older people. The total economic burden of arthritis is estimated at 1 to 2.5% of the gross national product of Western countries; OA accounts for the major share of this burden. Because of the aging of the population, the prevalence of OA is expected to increase substantially in the next decades. A clear insight in the etiology of OA, the cascade of osteoarthritic processes, and the factors influencing these processes is lacking. Such knowledge is highly desirable to develop research into disease modifying or preventive interventions; until now only symptomatic treatment is available but such treatment cannot relieve the progressive symptoms in the long run.

It is widely believed that the cause of OA is multi-factorial, including inherited, metabolic, nutritional, and local mechanical factors. The golden standard technique – still -- to image and identify osteoarthritis is X-ray, which can identify joint space narrowing and bony changes such as osteofytes and subchondral densification as hallmarks of osteoarthritis. However, correlation of the radiological parameters with clinical signs of osteoarthritis such as pain and immobility are weak. Therefore accurate measures for (early) OA detection and progression are needed to enable quality research.

The advantages of MRI, although costly, are obvious. Cartilage lesions, cartilage volume, cartilage quality (amount of proteoglycans and water content) can all be visualized using specific MRI sequences. In addition information concerning the surrounding soft tissues and bone or bone edema can be visualized as well. Using MRI in populations with existing osteoarthritis or in high risk sub-populations we expect to find early pathological characteristics that can be used to identify the status of osteoarthritis; and to describe disease development at the structural (tissue) level and find the most essential characteristics that can predict disease progression.

Atherosclerosis
Atherosclerosis begins to develop early in life and progresses with time. Individuals may differ in the speed of plaque progression and their propensity for plaque vulnerability, arterial remodeling (compensatory vessel enlargement) and arterial thrombosis. Each of these factors will contribute to the susceptibility of individuals to develop symptomatic disease. Furthermore, due to heterogeneity in vascular anatomy and physiology, atherosclerosis in different vessels may represent conditions with different risk factors and distinct courses. Therefore, it is important to distinguish vascular territories when studying the natural history of atherosclerosis.
Our current concept of the different stages of atherosclerosis has mainly been derived from autopsy studies, with obvious limitations. The development of new noninvasive techniques allows accurate assessment of the course of atherosclerosis in the living for the first time. While assessment of plaque burden has evolved in the past decade, fast CT and high-resolution MRI to assess plaque composition has been applied in small patient series by only a few centers worldwide. By using these newest imaging techniques in subjects aged 30 years and older, the program will provide novel insight in the life course of atherosclerosis and subsequent clinical disease in the general population.
High-resolution MRI is particularly appealing for the longitudinal study of the natural history of atherosclerosis as it allows accurate assessment of arterial dimensions (for remodeling studies) without radiation. The process of remodeling over time at different sites of the arterial tree and its relation to clinical events is not well understood. Serial studies that measure changes in arterial dimensions at the same site over time are the optimal way to assess arterial remodeling because they are not subject to the limitations of using a reference site of normal wall.
This type of project combines the use of the newest non-invasive imaging techniques in radiology with longitudinal, population-based research. The technology to detect asymptomatic atherosclerotic burden is already available for several vascular territories including the coronary arteries (coronary calcification). Combining serial measures of plaque burden and plaque composition in a large population would create a research setting that is worldwide unique.

8. Partnership case

In the present European context, the awareness of the need to organize long term imaging infrastructures for Europe is well known and expressed among the members of the imaging community. Euro-BioImaging integrates the existing networks and will serve as a launching pad to guarantee the participation of the major actors in the field. Euro-BioImaging will be lead by two major imaging organizations, EMBL and EIBIR, both of which are ready to start the work immediately.

At national level several cooperative networks are formed around the present imaging infrastructures, for example Virtual Institute for Seven Tesla Applications (VISTA including UMCU, Radboud UMC, FC Donders Institute, UL en LUMC), Medical Delta (Universities of Leiden, Delft and Rotterdam, LUMC and ErasmusMC), Center for Translational Molecular Medicine (CTMM), NIMIC and Cyttron.
The Dutch Federation of University Medical Centers (NFU) supports this European initiative. In NFU opinion the Netherlands should play the leading role in the population based imaging node.
The already existing and continuously increasing data potential of the different Dutch population cohorts combined with novel imaging data will create an infrastructure for population-based research that is internationally unique and scientifically on the forefront of epidemiologic research. To gain and maintain this position the Netherlands needs to decide quickly to invest substantially in population imaging infrastructures. These infrastructures can easily be integrated in the existing infrastructure of the UMC's. Be it, that these infrastructures are dedicated to research. Alternative equipment is hardly available because it is in use for patient care and fully booked. However knowledge and expertise will be shared between research and patient care, creating synergies.

Population imaging infrastructure needs to be close to the populations under research. Therefore the infrastructure will consist of a network of dedicated facilities, like many other facilities within the biomedical field, for instance biobanks.
Each location will have one or more imaging facility under its local management. Each facility may include more than one imaging device. The facilities may be located adjacent to or within the medical center complex, but may also be placed at a remote location so that they are accessible to the population being studied. One option to be explored is the usefulness of mobile imaging facilities. As these can be placed in different locations on a regular schedule, they provide opportunity for efficient utilization of facilities by groups looking at physically separated populations.
Data management will be centralized as much as possible in order to insure the availability of high-quality systems and tools. Archiving, backups, data processing, data mining, and quality control will be arranged by the central data management facility, to be located at Erasmus MC, Rotterdam/NL.
Each location will name a management committee to oversee use of the facilities. This management committee will in any case include representatives of the Departments of Radiology and Epidemiology as important stakeholders in the facility. Further groups to be represented on the management committee will be decided at the local level, depending on the groups using the facilities. The management committee is responsible for maintenance, upgrading, and exploitation of the facilities, as well as for preparing reports on the local facilities and their use.
Each location will appoint 1 representative to the central Steering Committee. The Steering Committee will additionally include members from the Erasmus MC Departments of Radiology, Epidemiology, and Medical Informatics as coordinators of the central data management facility and the national infrastructure. The Steering Committee is responsible for communication with and reporting to the EC.
Access to scan facilities will be granted by the consortium based on high scientific quality. Data-acquisition protocols will be harmonized over the different facilities and studies.

The eight Dutch university medical centers have proven with Parelsnoer that they are capable of implementing a governance structure that complements the needs of the research infrastructures and the network participants. In order to fully exploit the rich data that will be collected within the population imaging structure, the infrastructure will also need to support large scale image storage, effective data access, and provide advanced infrastructure and tools for large scale image computing, automated quantitative image analysis, and integrated analysis with other clinical data and biobanks.

9. Business case

	2010	2011	2012	=> 2013	Total 15 Years
Invest-ments *total*	25	10.5	4.5	0	40
details	Building 5 x 2 IT 1.5 MRI 5 x 1.5 CT 3 x 1.0 US 3 x 0.15 PET-CT 1 x 2.5	IT 1.5 MRI 3 x 1.5 CT 2 x 1 PET-CT 1 x 2.5	MRI 3 x 1.5		
Running costs *total*	0	13.2	13.2	13.2	198
details		Deprec. 6.0 Service 2.0 Tec. Pers 5x0.2 IT Pers 5 x 0.1 Material 5 x 0.2 Storage 0.5 Data mng. 0.2 Diverse 5 x 0.4	Deprec. 6.0 Service 2.0 Tec. Pers 5x0.2 IT Pers 5 x 0.1 Material 5 x 0.2 Storage 0.5 Data mng. 0.2 Diverse 5 x 0.4	Deprec. 6.0 Service 2.0 Tec. Pers 5x0.2 IT Pers 5 x 0.1 Material 5 x 0.2 Storage 0.5 Data mng. 0.2 Diverse 5 x 0.4	
Grand Total	**25**	**23.7**	**18.7**	**13.2**	**238**

Population imaging: 40 m€. This budget is needed for:

- 10 to 12 (1.5 or 3 Tesla) MRIs 3-4 MS CTs, 3-4 PET-CTs dedicated for research purposes (see technical case)
- infrastructures enabling collection and storage of large image datasets, data processing based on GRID technology, development of quantification tools, link to existing clinical data, biobanks, etc.
- First years operating costs, technical personnel and maintenance costs over the period of the project

Additional operating costs and particularly scientific personnel will be covered by the participants out of their first stream funding and project funding.

The infrastructure is open to Dutch and international researchers, however populations usually are imaged close to where they live. So it is very unlikely that populations for other countries are imaged in the Dutch facilities, although the option to invest in mobile units will be considered. However, international interest in the results, databases and expertise will be large.

10. Technical case

The technical risk of this infrastructure is relatively small as the equipment is mainly the same as present in many hospitals. However research requires dedicated equipment. It needs to be located as closely as possible to the research populations. Moreover, to be able to compare the follow-up data, long-lasting consistency of the equipment has to be guaranteed. Use of existing equipment in patient-care facilities is limited by the large populations that need to be included as well as the consistency requirements. However, dedicated research infrastructures can also be used to test and validate new technologies in the field (optical imaging, elastography, etc). For this reason Philips Medical Systems and other industrial parties are highly interested in Euro-BioImaging. The analysis of large imaging databases and the integrated analysis of imaging data with other type of data (e.g. genetic data, clinical data) is highly challenging. However, both Dutch industry and research groups at Dutch University Medical Centers are internationally at the forefront of the developments in these fields, and have large expertise in the analysis of biomedical image data. In addition, there is a good infrastructure for data storage and data handling, and there is expertise in the performance of large medical image computing tasks on computer grids.

11. Potential Focus for The Netherlands

The node Population Based Imaging within Euro-BioImaging fits the Dutch research strengths. Especially the different and well documented populations combined with new imaging infrastructure and studies will keep the Netherlands at the forefront as a center of excellence for Europe. Investment in population imaging infrastructure is necessary to ensure and enhance this position, and to become the Population Based Imaging node.

The Netherlands can play also a significant (but not the leading) role in other Euro-BioImaging nodes like:

- The common nodes:
  - Imaging of tissues and animal models
  - Large scale image processing and computing
- Advanced Light Microscopy nodes
  - Correlative light and Electron microscopy
  - Functional imaging of live cells
- Medical Imaging Nodes
  - Minimally invasive image-guided interventions

The Population Based Imaging node will support imaging in large, prospective epidemiological studies in unselected populations. This enables identification of imaging biomarkers and risk factors of pre-symptomatic disease as imaging phenotypes play an essential role in the early detection of people at risk. It will benefit form the embedding within Euro-BioImaging and create strong synergies with the other nodes. Also the links with infrastructures like VISTA (7-tesla MRIs) will be strong. Knowledge generated by research in VISTA might be translated for use in population based imaging in near future.

At European level Euro-BioImaging will connect to and create synergies with other relevant large research Infrastructures like BBMRI (Biobanks) and EATRIS (translational research). At national level the population based imaging node will connect to and create synergies with the equivalent national initiatives, like CTMM and Parelsnoer.

12. Critical Mass

The Netherlands has, compared to world, high quality and quantity output in related fields to medical Imaging (like radiology, neurology, cardiology and endocrinology) and Advanced light microscopy (like molecular cell biology, endocrinology) scores 20-35 % above the world average.
Several researchers in imaging research and population-based imaging studies have been awarded VIDI and VICI grants and are now in a position of consolidating their research lines. Examples are:

VICI 2003:	Prof. dr. M.M.B. (Monique) Breteler (v) 26-01-1961 Erasmus MC – Epidemiology & Biostatistics
VIDI 2004:	Dr. H.M. (Erik) Meijering (m) 31-07-1971 Erasmus MC - Radiology/Medical Informatics
VICI 2005:	Prof. dr. W.J. (Wiro) Niessen (m) 15-11-1969 Erasmus MC - Radiology/Medical Informatica & TUD - Applied Sciences
VICI 2006:	Dr. J.C.M. (Jacqueline) Witteman (v) 27-07-1960 Erasmus MC - Epidemiology & Biostatistics
VICI 2005:	Prof. H. (Harold) Bekkering (m) 19-10-1965 RU - Cognitive Psychology
VICI 2005:	Prof. dr. G.S.E. (Guillén) Fernández (m) 12-08-1964 RU - Neurology & F.C. Donders Centre for Cognitive Neuroimaging

VIDI 2007:	Dr. G. (Gabriele) Janzen (v) 24-08-1968 Radboud University Nijmegen – F.C. Donders Centre for Cognitive Neuroimaging
VIDI 2007:	Dr. S.A.R.B. (Serge) Rombouts (m) 24-08-1970 UL – Leiden Institute for Brain and Cognition / LUMC – Radiology / UL – Institute for Psychological Research
VIDI 2007:	Dr.ir. G.J. (Gustav) Strijkers (m) 06-12-1971 TU/e - Biomedical NMR
VIDI 2007:	Dr. B. (Bram) v. Ginneken (m) UMC Utrecht - Image Sciences Institute

The Netherlands have been able to maintain and attract excellent researchers with the present infrastructures. Indeed, the NIHES research school, a nationwide collaboration for training and research in the Health Sciences in which many of the *Population Imaging* institutes participate, was recently evaluated by an international committee as "a model for other countries" with "an outstanding research and teaching programme meeting the highest international standards." The evaluation committee recommended that NIHES "strengthen … cohort and data infrastructure" as they felt that this would enable NIHES to reach its full potential. We expect to educate, train and attract more excellent researchers with the improved position we hope to acquire through participation within Euro-BioImaging.

13. Embedding

The Population based imaging infrastructure will very likely be embedded within the university medical centers. They have an excellent research infrastructure and the expertise needed. They run research project with population in the areas that population based imaging will add significant new knowledge, like dementia, cardiovascular diseases like atherosclerosis, osteoarthritis, diabetes, metabolic syndrome, longevity, development of children, et cetera. Their first stream research money is invested in these research lines. Other research money is acquired from the national research council, charities, EU, industry and other sources.

Several national cooperative networks are formed around the present Dutch infrastructures, for example Virtual Institute for Seven Tesla Applications (funded by NWO BIG), CTMM (FES), Parelsnoer (FES), Medical Delta (Universities of Leiden, Delft and Rotterdam, LUMC and ErasmusMC), Cyttron (Bsik) and NIMIC (Smartmix). Moreover, population-based imaging can play a crucial role for TI Pharma. The population imaging node connects to all these cooperative networks through the participating university medical centers, related universities or other existing partnerships.

Europe-wide Euro-BioImaging will be linked to research infrastructures that are identified on the first ESFRI Roadmap: ELIXER (European Life Sciences Infrastructure for Biological Information, INSTRUCT (Integrated Structural Biology Infrastructure for Europe), EATRIS (European Advanced Translational Research Infrastructure in medicine) and ECRIN (Network of Distributed Infrastructures for Clinical Trails).
Euro-BioImaging will also be linked to the existing large scale physics facilities such as CERN or ultra-high field MR systems becoming available within NEUROSPIN to integrate new ideas for the development of novel, innovative imaging procedures and with the Bioinformatics resource infrastructures for accessing the most efficient procedures for handling the acquired imaging data.

14. Track Record in Collaboration

Especially the research infrastructures Euro-BioImaging will offer are suitable for multidisciplinary research. Examples of these intra or extra-institutional research cooperations are:

- Cyttron (LU, LUMC, UU, NKI, TUD, Bruckner, and foreign institutes),
- the Leiden Institute for Brain and Cognition (LUMC, fac. of Social Sciences and fac. of Linguistics of Leiden University)
- VISTA (UMCU, LUMC, FC Donders, UMCN, Philips)
- Parelsnoer and BBMRI (ESFRI)
- Medical Delta (TU Delft, LUMC, ErasmusMC, EUR en UL), but also many national and European cooperative research projects.

- TI Pharma projects
- Many collaborative national and European research projects
- Netherlands Forum for Biomedical Image Analysis (multiple research groups and industry members, led by LUMC, Erasmus MC, UMC Utrecht)

These examples prove that the commitment to cooperate at national and European level is high. The examples also prove that the availability of advanced research infrastructures to lead new and enhanced cooperation between research groups, within and across disciplines.

15. Relevance to Developments in Society

Improved health care for European citizens will translate into economic advantages for the society, and the discovery of new products, new equipment, and new diagnostic and therapeutic procedures will represent important income for the institutions involved. The health care market is growing fast and the activities carried out in Euro-BioImaging are expected to yield a marked increase in European IP in fields ranging from imaging methods to innovative diagnostic methods.

Euro-BioImaging will establish strong ties with European industry. The Nodes will cooperate closely with companies to apply new technologies to the needs of the imaging community. European companies will actively contribute to the development of technologies and biological application at Euro-BioImaging nodes, where a multidisciplinary environment and cutting edge research applications will be ready available. This will allow the industry partners to define new concepts faster and deliver prototypes closer to the final product, significantly increasing their competitiveness and generating added European value.

Euro-BioImaging will have a major impact on the training of European scientists. First, this will be done by training external users at the Euro-BioImaging nodes for the specific technologies they offer. This training will cover all aspects necessary to obtain conclusive data using the technology, ranging from specimen preparation to data collection and analysis. This will disseminate expert skills in the scientific community and ensure maximum return in the use of the advanced technologies. Second, Euro-BioImaging will provide training in new technologies to the existing local imaging facilities. This "training of the trainers" will ensure that the needs of European scientists can be addressed at the closest possible physical distance. Third, Euro-BioImaging will provide basic training in imaging technologies through the well established initiatives in ELMI, EAMNET and ESOR that have already made successful and widely recognized contributions to training and trans-national access.

Euro-BioImaging will consider itself a success once Europe has a world leading infrastructure in terms of both equipment and the critical mass required to develop, maintain and use it. A key measurement of success is the user satisfaction of those who access the infrastructure and receive the necessary training for its use. Processes will be established to obtain feedback on essential points and to implement corrective measures where necessary. Once Euro-BioImaging meets the needs of the user communities it will be considered a success.

In national perspective, hosting of the population imaging node is in line with the innovation programme on Life sciences & Health. Life sciences & Health aims to eliminate hurdles to and create a leading climate for health-related life sciences valorization. It completes a unique innovation infrastructure, designed to **build**, **bundle** and **benefit.**

Creating a population imaging research infrastructure in the Netherlands contributes to the objectives of Life sciences & Health. It creates an enormous knowledge base that can be scientifically exploited for research for many years. It is also of great value to industry and public-private partnerships like CTMM and TI Pharma. The knowledge generated can be translated into new or better diagnostics and therapeutic interventions. The knowledge can lead to new or better methods to detect people at risk in an early stage, preferably before clinical symptoms are manifested. The knowledge can be translated differential diagnosis and treatment strategies that are optimized for the individual. Discovery or development of new biomarkers is very likely to be valorized commercially. The societal impact will be in all major disease areas. There patients will benefit. But also healthy people will benefit from prevention strategies if they are identified as person at risk. This might result in substantial reduction of loss of quality of life.

EuroBioImaging and its population imaging in the Netherlands contributes to:

- the **building**:, by the data recourse that will be build up with the population imaging infrastructure
- the **bundling**, by developing cooperative projects with industry, TI Pharma and CTMM, and by its European and international cooperation
- the **benefit**, by implementing new prevention, diagnostic and treatment strategies in the clinic and at primary health care level.