Roadmap Molecular Diagnostics

Goal

Important issues and challenges in the further development and dissemination of new diagnostic tests based on molecular information are:

- The high number of candidate biomarkers identified in academia that do not progress to molecular diagnostic tools in clinical use
- There is limited integration of molecular diagnostic technologies and tools to provide straightforward diagnoses in a complex biological context
- Currently, there is a considerable disconnect and lack of integration between the science-driven discovery of molecular diagnostics, subsequently the development of a robust diagnostic, clinically validated test, the clinical application of such a biomarker test and last but not least clinical adoption including reimbursement.
- The coming decade new technology (e.g. high throughput genome sequencing) will result in massive data with unclear clinical relevance; this requires prioritized research efforts to transform this in valuable individualized clinical information
- All diagnostic test should have the intention to be developed into an in-vitro diagnostic device meeting all regulatory requirements (which are, at this point in time, highly insufficient for fast market penetration of these test)

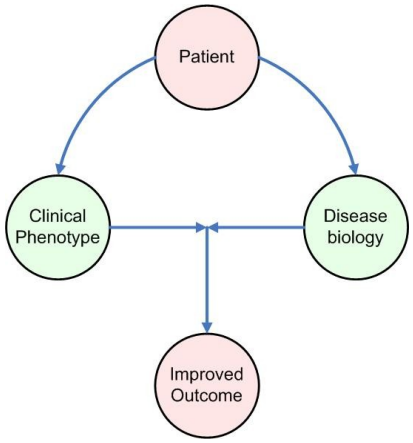
The ambition should be to define and implement a generic framework in NL that facilitates the development of candidate biomarkers into validated molecular diagnostics in clinical use, involving all stakeholders from the start in this process to ensure an integrated process from clinical needs to discovery and development resulting in reimbursed clinical application. It should be absolutely clear that all the stakeholders agree that the anticipated diagnostic test will serve an unmet medical need, has a high clinical additive utility and is commercially viable. In the process, the 3R goals will be served. In the end, this will result in the clinical application of specific molecular biomarkers for improved diagnosis and screening, patient segmentation and monitoring of therapy, ultimately contributing to cost-effective improvements of patient outcomes and quality of life.

Activities

Initial focus and being able to quickly assimilate new insights in technology and molecular biology to the major health care challenges will be essential to become successful in molecular diagnostics. Critical aspects are

- The identification of biological imbalances that drive clinical phenotypes, and the realization that this may be different between individual patients.
- The development of molecular read-out of disease biology that can provide important clinical information that affects the diagnosis, prognosis, triaging (prediction) and treatment of patients.
- A successful molecular diagnostic pipeline based on an integrated approach that starts with a well-defined clinical need that drives biomarker discovery and development, and ends with a reimbursed diagnostic test that is being applied in clinical use.
- Application of such generic framework involving all key stakeholders is not limited to specific disease areas.

- Molecular diagnostic read-out methods include a variety of technology platforms including e.g. simple laboratory tests and high-content imaging modalities.
- Biomarker based diagnostic tests hold great promise for increasing cost-effectiveness in healthcare by facilitating personalized therapies



The molecular biomarkers involved in molecular diagnostics address defined clinical needs like:

- (Genetic) predisposition for disease
- Screening/early detection of disease
- Prognosis for the individual patient
- Pretreatment classification for personalized therapy/prediction of response to therapy
- Early therapy response monitoring
- Follow-up and early detection of recurrence of the disease

Direct benefits of an operational molecular diagnostic development pipeline for the aforementioned needs will result in:

- Improved and personalized patient care
- More specific and earlier treatment based on individual case
- Prevention of (serious) adverse side effects
- Reduction in health care costs and increase in quality of life

The separate steps that can be identified in the molecular diagnostic development pipeline include:

- Discovery of biomarkers (‘Omics’, imaging, literature, etc)
- Development of initial diagnostic test (prototype)
- Discussion with the appropriate bodies to agree on development strategy leading to registration and reimbursement at the start of the development pipeline (precompetitive procurement !)
- Performance of prototype validation and cost effectiveness (including access to high quality clinical samples)
- Optimization of the prototype and development of the full (IVD) diagnostic test that meets regulatory requirements

- Analytical and clinical validation of diagnostic test
- Standardized application in clinical setting
- (GMP) production facilities for molecular kits

The process to convert these steps into one integrated pipeline include:

- Define and standardize the molecular diagnostic development pipeline from discovery to a reimbursed clinical service that will contribute to a cost effective health solution
- Involve key stakeholders in building such integrated pipeline
- Ensure early buy-in of end users (patients, clinicians, health care insurance)
- Support particularly those projects that demonstrate the added value in society and health

The required conditions and enabling technologies are:

- Accessible collections of well-defined biosamples (biobanks)
- Accessible data sets with clinical/phenotype annotations
- Appropriate and accepted molecular read-out technologies
- Facilitating IT infrastructure
- Appropriate Quality Assurance

Besides the technical challenge in Molecular Diagnostics to obtain the "highest level of information from the smallest amount of sample", the major roadblocks for an attractive R&D "ecosystem" are predominantly related to guidelines, inappropriate or lacking regulations and a reimbursement system unable to accommodate the evaluation ad implementation of complex molecular diagnostic products.

Ultimately, the compelling arguments for increased investments in Molecular Diagnostics and the rationale for its use are :

- Cost containment by early detection allowing secondary prevention and early treatment of less advanced (and more costly) disease states
- Keeping patients as active society members (labor participation) for longer time
- Defining target population avoids unnecessary treatment and prevents toxicity from treatment
- Monitoring results avoids unnecessary continuation of ineffective treatment and also avoid Rx related complications

Case

A. Priorities

Priority setting in this Roadmap is directly related to addressing a therapeutic area that has a high medical need for improved application of molecular diagnostics and should involve all parts of the molecular diagnostic development pipeline with a phased but connected approach from discovery to application and implementation of effective healthcare solutions. An important aspect will be to use molecular diagnostics to bridge research to clinic, thus also reducing animal experimentation following 3V guide lines.

B. Strengths

Scientific landscape in Netherlands

The public-private partnerships that have been operational in NL since 2006 have changed the mindset of researchers and industry towards an integrated team approach. Experts in their individual disciplines work closely together towards an innovative solution that would not have been possible by the separate parts. Several groups have succeeded in creating highly effective multi- and cross disciplinary teams where industry meets academia. This is unique in the world.

Technologies

Within these partnerships, much expertise has been built around basic research, biomaterials, clinical applications, shared infrastructure and enabling technologies (ESFRI (EATRIS, BBMRI. ELIXIR, ECRIN), PSI, PALGA, etc). The Netherlands has state-of-the-art molecular diagnostic activities closely integrated with clinical practice within the setting of the UMC's and through the public-private partnership network. Based on a firm academic presence in molecular biology, a spectrum of small and medium enterprises from an excellent industrial base for innovations focused on unmet clinical needs. Dutch research groups are highly productive in both application development and biological discovery. The continued development of technologies within the NGI technology centers has brought the field to a level that allows molecular diagnostic development with methodologies that have proven to be robust.

The implementation of this knowledge and technical capabilities to improve health in real life is still a major hurdle. Applied research institutes, the government, payers and patients should help implementing these findings. Provided that the molecular diagnostic development pipeline can now be extended to clinical care and reimbursement involving key stakeholders as we propose in this Roadmap, these characteristics put the Netherlands in an excellent position to be an example worldwide of integrated applied diagnostic development.

Embedding

There are direct links with other top sectors, e.g. High Tech Systems & Materials (nanomedicine) and DTL (enabling technologies)

Molecular diagnostics comprise the tools that enable improved biological and clinical research. As such, this Roadmap relates to many other disciplines and stakeholders in the Life Sciences and health Sector:

- Enabling technologies and infrastructure: application of technologies, biobanking (BBMRI, PALGA, data analysis into the integrated molecular diagnostic development pipeline.
- Imaging and image guided therapies: application of the developed integrated molecular diagnostic development pipeline into imaging applications in health care.
- ICT and clinical decision support: application of molecular diagnostic information into clinical decisions, supported by ICT e.g. electronic medical record, TraIT/DISC/DTL.
- Pharmacology & pharmacotherapy, Regenerative medicine, Nutrition & health: flow of candidate biomarkers into the integrated molecular diagnostic development pipeline to mature into robust tests that support research in these Roadmaps
- Health economics: application of health technology assessment to support selection of those therapeutic areas based on calculated costs and effects
- Ethics: involvement CSG (Center the Society and the Life sciences), VSOP (Vereniging Samenwerkende Ouder- en Patiëntenorganisaties) and other organizations addressing societal impact and acceptation of new health care solutions

Many different stakeholders are directly involved in and impacted by the development and implementation of molecular diagnostics: (e.g. Nederlandse Hartstichting (NHS), Koningin Wilhelmina Fonds (KWF) , Diabetes fonds, Nierstichting, Reumafonds, etc.)

A large number of on-going public-private partnerships within the existing TTI's (CTMM, BMM, TI Pharma) are engaged in all kind of activities directly related to Molecular Diagnostics. There is a need for further coordination and integration between different programs that range from biomarker discovery to diagnostic assay development and implementation, particularly in the area of technology adoption and data handling (TraIT, DTL, NBIC, Parelsnoer, eSience).

Other relevant initiatives comprise the TNO programs "Preventie enTherapie Opmaat" en "3V", as supported by ministry of VWS, The NGI program Pre-Seed and the ZonMw Program Translational Research.

Relevant European programs include Biomedical ESFRI programs for infrastructure (e.g. EATRIS, Elixir, BBMRI), IMI (OpenPhacts, Portrait).