JPND research

EU Joint Programme – Neurodegenerative Disease Research

Report on JPND Precision Medicine Workshop

Amsterdam, March 22nd 2017

Table of Contents

This report is not intended to be a comprehensive summary, but is instead an overview of topics and views contributed by the experts who attended the workshop.

1. Workshop background and remit

The findings summarised in this report are the result of a JPND workshop and explore the ways in which precision medicine (PM) can be applied to neurodegenerative disease (ND) research. The report also identifies what infrastructure and frameworks are required to achieve this goal. It will be used by the JPND Scientific Advisory Board (SAB) in preparing the 2018 edition of the JPND Strategic Research and Innovation Agenda (SRIA), which provides a framework for future investment in ND research.

The aims of the workshop were to provide the following:

- A view of the research opportunities and challenges to be addressed in applying the PM concept to ND, highlighting priorities for action

- A view of those areas that would benefit most from European-wide cooperation.

The workshop started with two 'scene-setting' talks followed by an overview on early ideas of stratification in ND. Workshop participants were then allocated to parallel discussion groups covering different topics under the theme *'What approaches and data are available for stratification of ND?'* In the afternoon, a second set of discussion groups explored topics under the theme '*Harnessing the power of 'big data' to advance PM in ND'*. The workshop finished with a roundtable discussion to bring together the key points and agree on recommendations.

2. List of attendees

Participant	Affiliation
Ole Andreassen	University of Oslo/Oslo University Hospital
Rudi Balling	University of Luxembourg
Monique Breteler	University of Bonn (DZNE)
Stefano Cappa (*JPND SAB*)	Institute for Advanced Studies, Pavia
Bruno Dubois (*JPND SAB*)	University Pierre & Marie Curie
Alexandra Dürr	University Pierre & Marie Curie
Yiu-Lian Fong	J&J Innovation
Nick Fox	University College London
Giovanni Frisoni	University of Geneva
Thomas Gasser *(Chair JPND SAB)*	University of Tübingen
Martin Hofmann-Apitius	University of Bonn
Esme Moniz-Cook	University of Hull
Agneta Nordberg	Karolinska Institutet
Alessandro Padovani	University Hospital of Brescia
Lara Passante	European Commission
Natasa Przulj	University College London
Olaf Riess	University of Tübingen
Craig Ritchie	University of Edinburgh
Martin Rossor (VC JPND SAB)	University College London
Bruno Vellas	University of Toulouse
Pieter Jelle Visser	Maastricht University /VU Medical Center
Gunhild Waldemar	University of Copenhagen
Jens Wiltfang	University of Göttingen
JPND	
Rob Buckle	JPND/MRC
Simon Fisher	JPND/MRC
Catherine Moody	JPND/MRC
Ness O'Sullivan	JPND/MRC

3. Introduction and overview of agenda

Professor Thomas Gasser presented an overview of JPND including the scope of the initiative, progress to date and the history of JPND calls followed by an explanation of the format and goals of the workshop.

4. Precision medicine of neurodegenerative diseases: What needs to be done?

- R.Balling, University of Luxembourg

Professor Rudi Balling outlined his perspective on the key requirements needed to implement PM for ND, noting the following points:

- Complex ND mechanisms need to be considered from a network perspective, adopting a systems biology approach to determine whether factors are a cause or a consequence
- The genetic approach to understanding ND remains valid but a complementary focus on cell biology and molecular machinery is required to accelerate progress[1]
- ND research will benefit from building alliances with other scientific disciplines (e.g. physics/engineering) to introduce novel approaches to understand the complexity of living systems
- PM is increasingly data driven requiring integration of experimental biology, clinical research, bioinformatics and the training of competent data scientists
- Academic institutes require better approaches to incorporate technological advances (e.g. machine intelligence/artificial intelligence) with digital tech. companies years ahead in these areas
- The gap between the ND research community and healthcare providers/patients needs to be bridged and new partnerships built across EU infrastructures (e.g CORBEL[2])
- Conduct in-depth phenotyping of existing ND cohorts, aided by comprehensive clinical and molecular assessment (e.g. utilising smart devices, phones, smart shoes, Fitbits)
- Streamline data sharing including contractual and legal issues (e.g. data passports) by learning lessons about advanced data access/control systems from the financial world
- Give greater consideration to comorbidities in ND e.g. link-up with the diabetes and vascular AD communities to identify common metabolic drivers

[1] Kosik KS, Sejnowski TJ, Raichle ME, Ciechanover A, Baltimore D. A path toward understanding neurodegeneration. Science 353(6302):872-3

[2] Coordinated Research Infrastructures Building Enduring Life-science Services an initiative of eleven new biological and medical research infrastructure. Resources include biological data, physical biobank samples, imaging facilities and molecular screening centres e.g ELIXIR, ECRIN, , Euro Bioimaging, Instruct, ISBE, MIRRI (see Annex 1 for full resource names).

- Further exploiting the potential of epigenetic signatures to understand the influence of environmental factors on ND
- A greater understanding of the gut microbiome, personalised nutrition and utilising mechanistic models of gut physiology is required in relation to the pathogenesis of ND
- The concept of disease maps should be explored further, including storing and visualizing data in modules and providing advice on knowledge-management in ND
- Utilising computer modelling and simulation to bridge basic science with the commercialisation of products. For example, the Avicenna Alliance[3] is creating a research and technological development roadmap for predictive or *in silico* clinical trials
- Improve data access and integration and measure communication between research communities to promote innovation[4]. Social dynamics and collaboration among different scientific disciplines will be critical for a systems biology approach[5].

5. Developing personalised medicine at EU level: Opportunities & challenges - *L.Passante, European Commission*

Dr. Lara Passante presented an overview of key personalised medicine[6] initiatives and research programs across the EU to provide context on the existing investments in this area.

Personalised Medicine (PerMed,2013-2015)

- PerMed was established to form a road map for personalised medicine in Europe
- The PerMed Strategic Research and Innovation Agenda (SRIA) identified five challenges to improve the science base (Developing Awareness and Empowerment, Integrating Big Data and ICT Solutions, Translating Basic to Clinical Research and Beyond, Bringing Innovation to the Market and Shaping Sustainable Healthcare).

International Consortium for Personalised Medicine (2016-2020)

- Collaboration of 30 research funders and policy makers from EU and beyond
- Aims to provide support/coordinated approach and to implement the PerMed SRIA[7].

Horizon 2020 - Research Developments relating to PM

[3] Association for Predictive Medicine, http://avicenna-alliance.com/

[4] Reference made to *Henn & Allen: The organisation and architecture of innovation*

[5] Kitano et al., 2011 Social engineering for virtual 'big science' in systems biology, Nature Chemical Biology 7, 323–326.

[6] *EC Council Conclusions 2015*: Personalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. It relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs.

[7] The International Consortium on Personalised Medicine has published its Action Plan, based on some of the challenges identified in its strategic research agenda. The document can be downloaded here http://www.icpermed.eu/en/activities-action-plan.php

- *Ubiquitous Pharmacogenomics (U-PGx)*: consortium with plans to implement pharmacogenomic testing in patient care
- Comprehensive EU portfolio in PM exists from molecular pathogenesis and epidemiology through to clinical trials and care & support
- *PROPAG AGING*: utilising existing cohorts to identify specific cellular and molecular perturbations deviating from healthy ageing trajectories towards PD
- Current H2020 call:SC1-HCO-03-2017 - implementing key areas of PerMed SRIA.

Innovative Medicines Initiative (IMI)

- Partnership between EC and European Federation of Pharmaceutical Industries and Association. Provides open collaboration in public-private consortia, non-competitive collaborative research and competitive calls for proposals
- Focus on unmet needs, ND is a priority area
- IMI Alzheimer's Research Platform: EMIF-AD, EPAD, AETIONOMY.

Personalised Medicine - available resources

- European Reference Networks for rare diseases
- The Human Brain Project (HBP), Information and Communications Technology infrastructure for neuroscience, medicine and computing to catalyse collaborative efforts to better understand the brain and its diseases
- ELIXIR: distributed infrastructure - intergovernmental organisation linking life science resources across Europe (e.g. databases, cloud storage, software tools)
- Biobanking and BioMolecular Resources Research Infrastructure (BBMRI-ERIC), aims to develop a pan-European distributed research infrastructure of bio-resources.

Attendees noted the wealth of opportunities created by EC funding that could and should complement any future JPND activity.

6. Early ideas on stratification in neurodegenerative disease - *Craig Ritchie, University of Edinburgh*

Professor Craig Ritchie discussed the current and potential stratification of ND in the context of clinical studies in AD and introduced some perspectives on suitable operational frameworks. He observed that stratification is predominantly used for identifying subgroups who share similar rates of decline and proposed that trial designs need to include relevant models for stratification and should be tied to the primary outcome.

His reflections on the benefits and risks together with current and potential approaches to stratification were as follows:

Benefits:

- More homogenous data on decline and therefore potentially larger effect sizes enabling smaller trials
- Provides a better reflection of what ideal clinical practice would be.

Risks:

- Additional stratification may result in high screen failure rates in trials
- Patient strata are too small for companies to justify investment for drug development
- Stratification variables may be expensive/inaccessible to translate to clinical practice

Current and potential stratification:

- Stratified approaches to dementia already adopted (e.g. by APOE genotype)
- International Working Group (IWG-2) has provided advances to improve the specific diagnostic criteria for atypical forms of AD, for mixed AD, and for the preclinical states of AD[8].

Probability Modelling: This can be used to determine an individual's likelihood of decline (signature) and to define groups who will benefit most from individualised interventions. Traditionally a one-dimensional approach was adopted utilising only clinical indicators (e.g. measures of cognitive decline).

Prof. Ritchie suggested that the complexity of AD/ND requires a systems biology approach incorporating complex models involving multiple biomarkers (i.e. adoption of a 2D approach). 3D modelling incorporates the previous two dimensions (clinical indicators, biomarkers) together with risk factors (e.g. age, genotype, lifestyle) to more fully determine an individual's probability of decline. A fourth dimension integrates time, utilising data from longitudinal cohort studies.

A stepped approach to stratification was advocated, which might involve the following steps:

1. Screening population e.g. MCI population
2. Use models created from observational cohorts, add enrichment tests to define groups in strata e.g. fast/slow decliners.
3. Ensure target pathology/pathologies present
    i. Ensure fast decliners have e.g. amyloid
    ii. Anticipate that randomization controls for between group differences in (non-amyloid) factors mediating decline.
4. Enrolment in trial.

To conclude, Prof. Ritchie proposed that the following questions should be considered when designing stratified medicine studies:

- What is the relevant biology?
- How can this be measured in vivo and in clinical populations?
- How does the biomarker relate to clinical improvement?
- How do we intervene and measure success?
- How do we develop probability signatures for individuals? (utilising complex risk models)
- How do we recruit and operate within a collaborative and ethical framework?
- How do we get findings into practice (clinical and public health)?

[8] Dubois B et al, Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13: 614-29.

7. Theme 1: Approaches and data available for the stratification of neurodegenerative diseases

I. Omics technologies

Capability already exists in this area and there is also huge potential for the enrichment of existing data. The group concluded that PM in terms of omics should be about stratifying disease on a mechanistic level. It was agreed that there is a need for harmonisation of quality control including the methods of sample collection, data storage and how data are presented for interoperability. The validation of data against agreed standards was also highlighted as a key area. Additional points made in discussion were as follows:

- Genomics and transcriptomics are becoming more widespread and cost effective
- Genomes may eventually be available for each person
- Genome analytics/system medicine is becoming even more complex
- Proteomics is developing, but not as fast as wanted
- Multi-omics is necessary for patient stratification and thus for clinical studies
- Omics will be a core technology for biomarkers and associated clinical studies.

The following areas remain poorly understood or need attention:

- Gene regulation/dysregulation, role of protein isoforms
- The role of protein modification in disease
- Direct comparisons of longitudinal studies of animals with humans
- Consideration of the time course of omics measurements in study design
- In existing studies, longitudinal monitoring is often missing and incomplete
- Standardization of sample collection and analysis
- Lack of availability of biomedical data scientists
- Currently there is poor or no centralised access to omics data.

The key needs identified were:

- Data scientists need to be embedded in research teams
- Additional measures are required for quality control
- A unified taxonomy of integrated data should be agreed upon
- Robust methodology to interpret omics data is needed including placing it in the context of its spatial origin in tissue.

Priorities for action in the nearer and longer term:

- Identify the best approach for data access for cross-European studies (centralised or decentralised)
- How best to ensure the validation and replication of data
- The inclusion of omics in all future clinical studies
- Standardization of the methods report (metadata reporting)
- Open access data with interoperability of datasets

II. Imaging, cognitive and fluid based markers

In this area it was concluded that there are a good range of modalities available but that further development is necessary.

Benefits to stratification

- Makes it possible to identify a homogenous subgroup
- Easier to predict trajectories
- More targeted treatment of molecular pathology
- More accurate prediction of response to treatment.

Current strengths in this area included:

- Availability of cohorts with serial clinical-biomarker observations
- Better precision of biomarker measurements
- PET/CSF biomarkers are available
- Willingness to share data in the imaging community
- Ability to measure real-time molecular pathology using imaging markers.

Priorities for action in the nearer and longer term:

- Enrichment and expansion of existing cohorts with serial imaging and biomarker assessment
- Tau and PET tracers are still evolving and further research and development would benefit the field.
- Beyond Tau and amyloid there is a need for new markers to broaden the understanding and the time course of accompanying pathological processes. These include markers of inflammation, astrocytosis, microglia activation and synaptic disruption
- Research on the social acceptance of CSF measurements
- Promotion of head to head comparisons of CSF markers/imaging (validate on post mortem tissue, also need to promote brain donation)
- Support the investigation of new biomarkers e.g. retinal imaging, microbiota, electroencephalogram (EEG).

III. Digital technology, environmental and lifestyle measures

This represents a relatively new area of great promise for patient monitoring, risk prediction, diagnosis, clinical trials and treatment. These technologies will enable continuous communication with participants and the ability to capture multimodal parameters longitudinally in large populations including patients in memory clinics and nursing homes. Digital technology devices also tend to be non-intrusive, user-friendly and permit the identification of multiple biomarkers. They can also be used to capture how well patients adopt and accept interventions.

The group concluded that currently there is little experience with digital technologies. Most of these technologies are at the '*proof of concept*' stage with many developments commercially driven and not fully optimized or standardized for medical or research applications.

The key needs identified were:

- Comparison studies are required to identify the most appropriate methods/devices and technology platforms. This should include feasibility/social acceptability and use in large populations
- Need to optimize device parameters for research/clinical use
- Agreement is necessary on technology platforms, taking consideration of the social environment in which they are employed.

Areas with a clear opportunity for research were:

- Identification of the optimal devices for different purposes
- Combination/comparisons to other '*more classical*' biomarkers
- Mapping the natural courses of disease
- Assessment of the feasibility and acceptability of digital technology (e.g electrocardiogram and sleep monitors for EEG)
- Investigating the adaptability of technologies to individuals' abilities (e.g tablet-based Maastricht Electronic Daily Life Observational-tool (MEDLO-tool).
- Taking account of social environment in the use of the device (e.g. chatrooms, QoL[9])
- Legal and ethical considerations regarding data capture
- Uniform data platforms to be developed, especially for patient monitoring.

IV. Disease taxonomy

The following recommendations were made on research opportunities in this area:

- There is further scope to subclassify ND based on variability in disease progression which could lead to the identification of distinct pathological mechanisms e.g identification of rapid and slow progressors in AD using longitudinal approaches could be used as basis to establish disease prognosis and tailor interventions
- Taxonomy should differentiate between non-traditional sub-phenotypes of ND e.g. based on classifications such as neuroinflammation, metabolic, cardiovascular comorbities etc.
- A need to look at variance including the reasons why some people develop dementia and others display resilience
- Linking up parameters of healthy aging and studies of population >85 years to identify factors of resilience. What determines the deviation from healthy ageing?
- Multi-dimensional models are required that integrate lifestyle, personal history and genomic data
- In oncology quantitative models have been employed where personalised patient health data are represented in vectors which can be used to identify subgroups based on tumour progression rates. A similar approach for ND would be valuable in terms of improving clinical predictions and ND taxonomy.

[9] This includes Ecological Momentary Assessment (EMA) that provides methods where a participant can report on symptoms, behaviour and cognition over the course of a study. e.g. mobile assessments such as the PsyMate App.

8. Theme 2: Harnessing the power of 'big data' to advance precision medicine for neurodegenerative disease

I. Clinical trial design, e-technologies

- A framework for implementation of approaches to stratification in PM is needed addressing how infrastructure and e-technologies can support the patient journey from the general population through cohorts and onto recruitment into clinical trials
- Methods are needed to identify patients who are already part of observational cohorts and to provide them with the opportunity to enter into clinical trials without compromising the observational cohort. Support is needed to help cohort organizers to work with trialists
- Extend capacity and ability of existing cohorts and incentivise the enrichment of cohorts for ND studies across Europe
- Data and project information should be accessed using a single collaborative data environment, an online location for collecting, managing and sharing information. Health record linkage should be promoted e.g. electronic medical records.

Lessons learnt (primarily from the oncology field)

- Consent to consent - an expectation exists in oncology that patients are entered into a trial upon diagnosis, a similar culture of engagement would benefit ND research
- A change in attitude/terminology is required where individuals are diagnosed with a particular disease state rather than describing someone as having '*dementia*'
- Similar to common practices in oncology, if major studies in ND were able to focus on younger and more robust patients this will reduce the confounding factors introduced by comorbidities. Findings can then be used to investigate a wider population.
- Incorporation of strata into trial design e.g. using Amyloid Related Imaging Abnormalities (ARIA) or Apolipoprotein E.

II. Access to data - cohorts, biobanks, real world data

The group agreed that a framework for implementation and operationalization was needed for data access particularly to address the difference between the more traditional methods vs. the '*big data*' approach. Recommendations included the establishment of core common data requirements and to lift restrictions on data sharing and use (open-access), which are often complicated by legal issues.

Key infrastructure required in terms of data access

- Take advantage of existing infrastructures and datasets (e.g real world/hospital data) and develop efficent search and indexing systems
- A coordinated strategy is needed to address legal issues, data centralization and preserving anonymity.

Technical and analytical challenges

- Adopt a conceptual framework to validate biomarkers for a PM approach
- Further understanding the difference between ND vs. other areas of medicine and also between network vs. whole organism approach
- A stratified approach could lead to identification of very small groups (concept of ND as a collection of multiple diseases) - this is tackled well in the oncology field.

III. Data mining, interpretation and harmonisation

Key points from this discussion group included:

- Models are critical to make sense of data and to make predictions that can be tested in real-life settings. It was recommended to establish modelling workshops/exchange programs to translate knowledge and expertise between fields
- Keeping domain data in the correct area including abstraction and indexing at each site together with a framework for analysis occurring at a central site
- Adopt modern principles e.g Research Description Framework (minimal format)

Recommendations in terms of standardizing of methods and data records

- Need a system and methods for integrating multimodal data
- Adopt standard implementation tools/algorithms to fit ND
- Develop shared semantics, e.g. using the International Classification of Diseases (ICD) codes
- Better access to data from failed clinical trials for retrospective analysis
- Improving the quality of real world data
- Specific institute for medical informatics in Europe to be responsible for quality control of data and analytics and to provide training and curation.

Infrastructure required to support the use of big health data

- Common standards for defining the content and quality of real world data are needed
- Research should be accessible to the public in order to promote engagement and sharing of patient- generated information
- Computer modelling and pattern recognition approach needs to be embedded in the clinic together with the establishment of gold standards and benchmarking.

IV. Data sharing and governance

Key points from this discussion group included:

- A universal definition and consensus criteria for data sharing is needed to clarify accessibility and transparency and to implement quality control checks (e.g. ADNI)
- It will be important to clarify data ownership and patient access to their data
- Large datasets hosted on clouds require descriptors to highlight added value and assist with data standardisation
- Establish working groups to produce guidelines for data standardisation and quality control to enhance and promote the pooling of data

- Greater consideration of the costs and ethical issues associated with data sharing at the European level is needed.

9. General discussion:

Opening remarks:

Participants were asked to provide recommendations based on the previous discussions and to identify tractable goals. One view is that PM in the form of differential diagnosis is not a particularly novel concept; however, with the introduction of new techniques it is an area that has inevitably become more complex.

Other points to consider are that disease taxonomies evolve (e.g. frontotemporal dementia) and that additional stratification is not always appropriate (e.g. in service delivery/care it may be better to group patients). We also need to be cautious in assuming that stratification is the same thing as '*big data*' since the core paradox is that '*the more data that is collected the more hay is added to the haystack and the harder it may be to find the needle'*.

Key points discussed during this session were grouped under the following headings:

Data management and documentation

- Improvements are needed in the management of large data sets to highlight data type and location (metadata). Data managers could be utilised to curate and link up cross-initiative data

- The use of a data and resources catalogue was recommended as a central hub where data, knowledge sources and resources could be indexed and discoverable

- Clear documentation and descriptors of data are required to ensure that it is available for reanalysis including details of the types of analysis that have previously been employed

- Reducing heterogeneity to improve clinical trial design. Researchers should report on sources of heterogeneity to provide added value to the field.

Data Ownership

- The U.S. House of Representatives recently approved a bill[10] permitting genetic screening of employees giving companies the ability to impose financial penalties on the health insurance of those who opt out. It will be important to clarify the European position on the privacy of genetic data.

Areas for further research

- Greater priority should be given to understanding and modelling healthy ageing

[10] Preserving Workplace Wellness Programs Act

- Comorbidities: (e.g. diabetes, vascular health). There is a need to identify the big studies with untapped existing data sets relevant to ND

- Real life cognitive performance measures are needed utilising emerging digital measures e.g. Ecological Momentary Assessment (EMA).

- The lack of translational biomarkers currently limits future progress in terms of a PM based approach to ND

- Creation of virtual patients using *in silico* resources would be a valuable tool enabling virtual global cohorts to be shared across national boundaries

- Further guidance on the stratification of care across health and social systems in Europe needs to be provided

- The approach to PM should not solely be focused on diagnosis - there also needs to be research on how to use PM in prevention and in intervention and management

- There needs to be further work on stratification by gender to take account of sex differences in the development of ND and associated risk profiles.

Data standardisation and quality control

- Standardisation and quality control of pre-analytical work to ensure samples are collected and processed in an acceptable way to enable pooling

- Biomarker stability is a crucial issue. Biomarker stability profiles including the comparison of measurements from frozen and fresh samples should be determined at an early stage to assess suitability for development into robust diagnostic assays. Correspondingly, methods to control stability should also be developed.

- Guidelines are required relating to the basic information and formats needed to pool data. Reproducibility and the use of robust assays are also essential

- Head to head comparisons and benchmarking of assays/methods are needed to validate claims, particularly where proprietary interests are involved.

- IMI have a call under review on the topics of '*Data quality in pre-clinical research and development*' under their '*Research and Innovation Actions*'

Mapping to other initiatives

- Large ND-relevant initiatives (e.g. JPND, IMI, HBP) need to be better connected and consensus should be reached on key ND terminology. Cross collaborative actions are needed to learn from other initiatives e.g. the medical informatics package of HBP is tackling some of the major informatics issues

- A global map of major initiatives and their activities would provide a collective vision of inter-related projects across the ND landscape and a platform for collaboration

    - To provide access to datasets to increase visibility and understanding
    - To learn from approaches used by other harmonised networks e.g. ADNI
    - Joint conferences and workshops recommended to map the landscape and to identify gaps and new developments

- The knowledge gap between clinical and computational sectors needs to be bridged. In particular, interactions between the clinical sector and digital technologies are limited. Exchange programs or scholarships may help to cross link these disciplines

- Connections between cohorts and clinical trials need to be improved which aligns closely with the objectives and infrastructure setup by EPAD e.g. 27 linked European cohorts.

Educational/policy needs identified

- The concept of PM in terms of ND research needs to be defined including its role in understanding disease mechanisms and identifying responders to treatment

- The culture of '*diagnosing dementia*' needs rethinking and replacement by more refined terminology for education and future policies

- It is important to have consent models and to understand patient perception in relation to stratification. In 2015, JPND produced guidelines on Patient and Public Involvement (PPI) including issues on data sharing, secondary use of data and consent models (Link to PPI in JPND Research). These guidelines may have to be developed further

- Greater focus should be directed at education and the public understanding of ND including family perceptions, which are known to modify patient symptoms

- There is currently a lack of bio-informaticians and data component scientists/medical professionals and there is a requirement for more training needs in this area

- Economic health modelling is needed to determine the cost effectiveness/viability of further stratification under a PM based approach to ND.

10. Summary and conclusions

It was concluded that a precision medicine approach could be taken across the full remit of JPND research, which may need to be reflected in the SRIA.

Common themes emerged during the workshop, including:

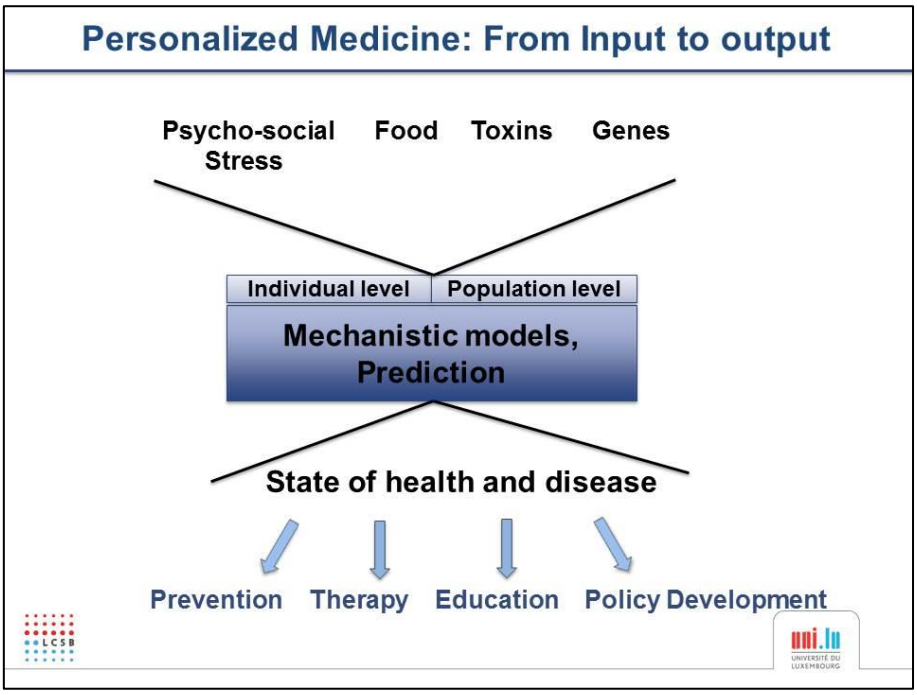
- The importance of data standardisation and maintaining quality control to promote reproducibility and permit the pooling of data
- Improving guidelines for data access and management to promote cross initiative data exchange
- Establishment of core common data requirements for data sharing and to alleviate current restrictions on data access
- Promoting head to head assessments to validate new biomarkers including comparisons against gold standards
- Integrating digital technologies within ND research which should include optimising/standardising these for medical and clinical use
- Better utilisation of real world data and agreeing common standards for the content and quality of this data type
- Establishing better connections between long term observational cohorts and clinical trials
- PPI aspects and health & social care elements of a PM approach are important and relatively neglected research areas, particularly the care-related aspects
- Promoting the linking up of major global ND initiatives to map the research landscape and provide a platform for collaboration
- A PM-approach to ND requires the availability of trained data competent scientists and the integration of data modelling to construct valid predictions.

Annex 1 - Abbreviations

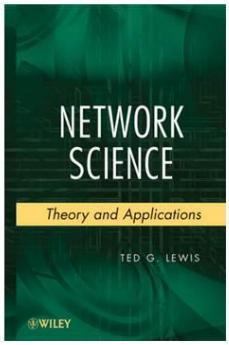
ADNI	Alzheimer's Disease Neuroimaging Initiative
ARIA	Amyloid Related Imaging Abnormalities
BBMRI	Biobanking and BioMolecular resources Research Infrastructure
CORBEL	Coordinated Research Infrastructures Building Enduring Life-science
EATRIS	European Infrastructure for Translational Medicine
ECRIN	European Clinical Research Infrastructure Network
EEG	electroencephalogram
ELIXIR	European Distributed Infrastructure for life-- science information
EMA	Ecological Momentary Assessment
EMBRC	European Marine Biological Resource Centre
EMIF-AD	European Medical Information Framework – Alzheimer's disease
EPAD	European Prevention of Alzheimer's Dementia (Longitudinal Cohort Study)
EU-OPENSCREEN	European Infrastructure of Open Screening Platforms for Chemical Biology
Euro-BioImaging	European Research Infrastructure for Biological Imaging
HBP	Human Brain Project
ICD	International Classification of Diseases
IMI	Innovative Medicines Initiative
Infrafrontier	Infrastructure for mouse disease models and phenotype data
Instruct	Integrated Structural Biology unlocking the Secrets of Life
ISBE	Infrastructure for Systems Biology Europe
JPND	Joint Programme for Neurodegenerative Disease
LBD	Lewy body dementia
MIRRI	Microbial Resource Research Infrastructure
ND	Neurodegenerative Disease
PM	Precision Medicine
PPI	Patient and Public Involvement

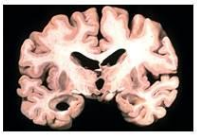
Annex 2 - Presentation Slides

Precision medicine of neurodegenerative Disease - What needs to be done?
(*R.Balling, University of Luxembourg*)

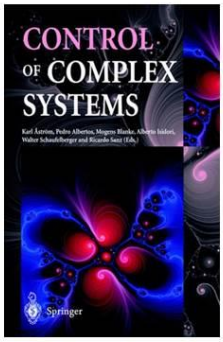


Neurodegenerative diseases: The next decade

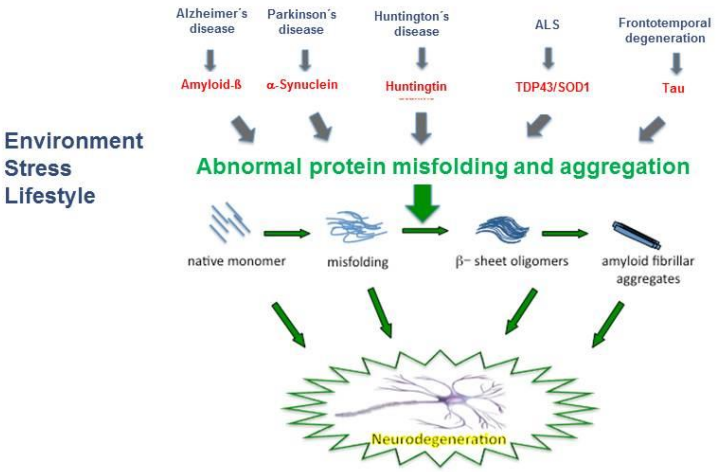




Alzheimer
Parkinson
Huntington
ALS
Multiple Sclerosis



What´s true for AD, is true for PD, is true for HD...



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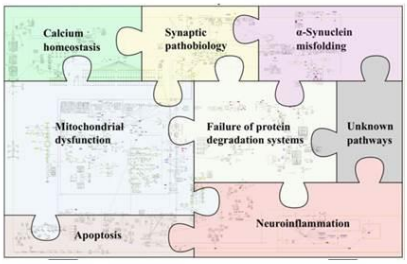
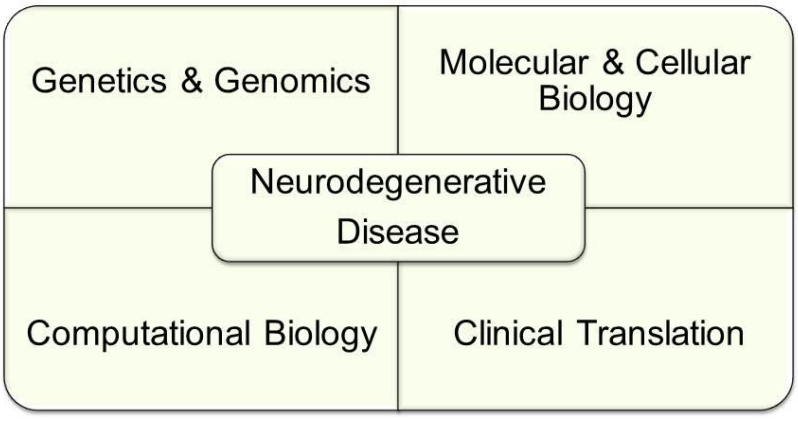
Cause or consequence?



Precision Medicine of Neurodegenerative disease

Is there something we can learn from cancer?



Will it be the heydays of cell biology?

Science **353** (6302), 872-873. [doi: 10.1126/science.aai7622]

NEUROSCIENCE

A path toward understanding neurodegeneration

A focus on cell biology may accelerate progress in disease prevention and cures

By **K. S. Kosik,[1] T. J. Sejnowski,[2,3] M. E. Raichle,[4] A. Ciechanover,[5] D. Baltimore[6]**

Personalized Medicine will become "Data driven"


Experimental Biology


Clinical Research


Bioinformatics Computational Biology

METHODS

Human Mutation

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY

Use of Support Vector Machines for Disease Risk Prediction in Genome-Wide Association Studies: Concerns and Opportunities

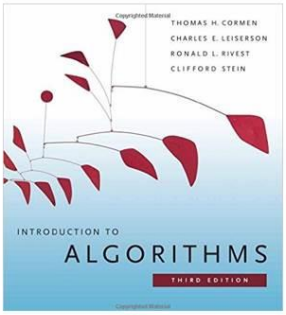
Florian Mittag,[1] Finja Büchel,[1] Mohamad Saad,[2,3] Andreas Jahn,[1] Claudia Schulte,[4] Zoltan Bochdanovits,[5] Javier Simón-Sánchez,[5] Mike A. Nalls,[6] Margaux Keller,[6,7] Dena G. Hernandez,[6,8] J. Raphael Gibbs,[6,8] Suzanne Lesage,[9,11,12] Alexis Brice,[9,10,11,12] Peter Heutink,[3] Maria Martinez,[2,3] Nicholas W Wood,[4] John Hardy,[5] Andrew B. Singleton,[6] Andreas Zell,[1] Thomas Gasser,[1] and Manu Sharma[1] for the International Parkinson's Disease Genomics Consortium (IPDGC)

nature INSIGHT
MACHINE INTELLIGENCE
28 May 2015 / Vol 521 / Issue No 7553

Deep learning
Yann LeCun[1,2], Yoshua Bengio[3] & Geoffrey Hinton[4,5]

Probabilistic machine learning and artificial intelligence
Zoubin Ghahramani[1]

Reinforcement learning improves behaviour from evaluative feedback
Michael L. Littman[1]



Partner or threat?

Google

amazon web services

LCSB

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What do we need?

Neurodegeneration Research Community

Neurodegeneration Healthcare Providers and Patients

Infrastructure

Neurodegeneration Research Community

EATRIS

ECRIN

ELIXIR

EU-OPENSCREEN

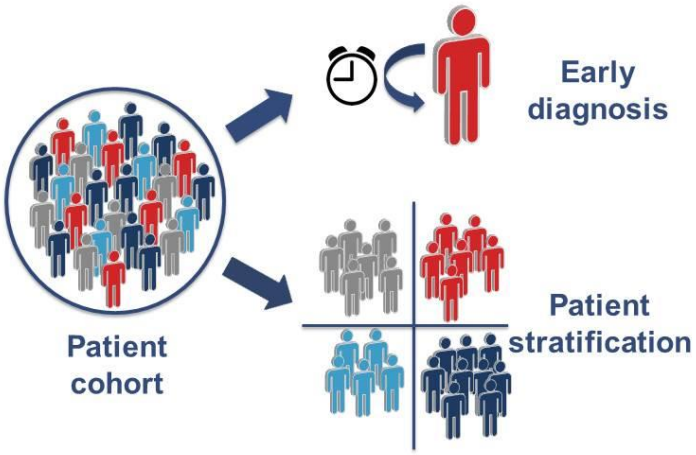
Euro-BioImaging

Instruct

ISBE

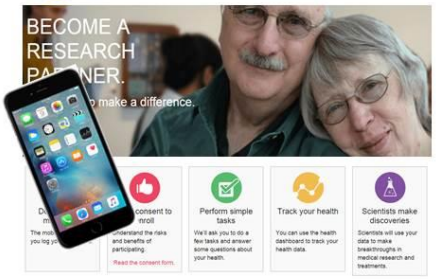
MIRRI

Deeply phenotyped ND-Cohorts



Deep comprehensive clinical and molecular assessment

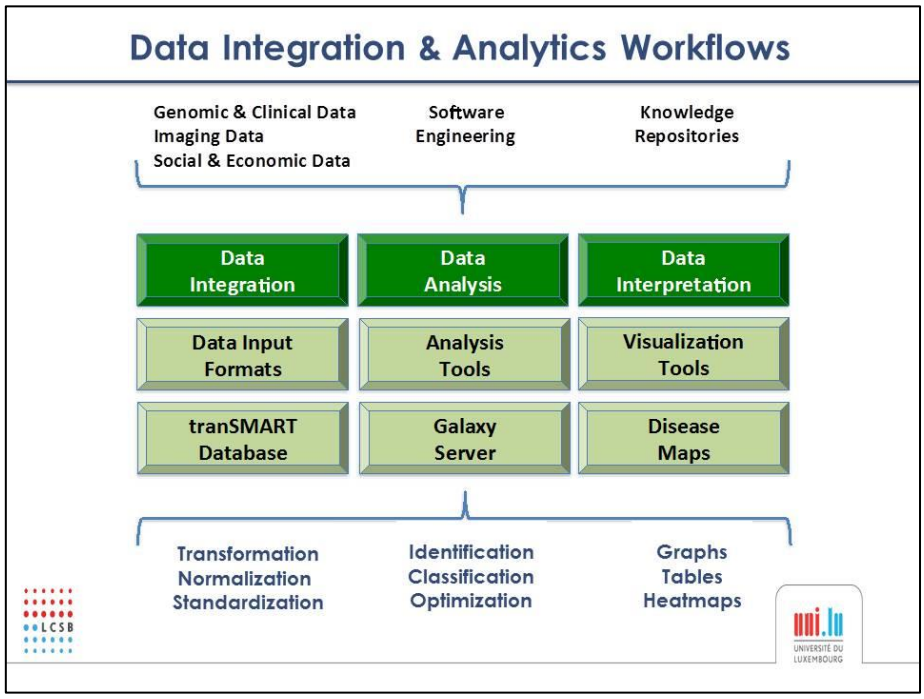
mPower: Mobile Parkinson Disease Study



npj | Parkinson's Disease

EDITORIAL OPEN

Smartphones as new tools in the management and understanding of Parkinson's disease


Data Integration & Analytics Workflows
Genomic & Clinical Data
Imaging Data
Social & Economic Data
Software Engineering
Knowledge Repositories
Data Integration
Data Analysis
Data Interpretation
Data Input Formats
Analysis Tools
Visualization Tools
tranSMART Database
Galaxy Server
Disease Maps
Transformation
Normalization
Standardization
Identification
Classification
Optimization
Graphs
Tables
Heatmaps
LCSB
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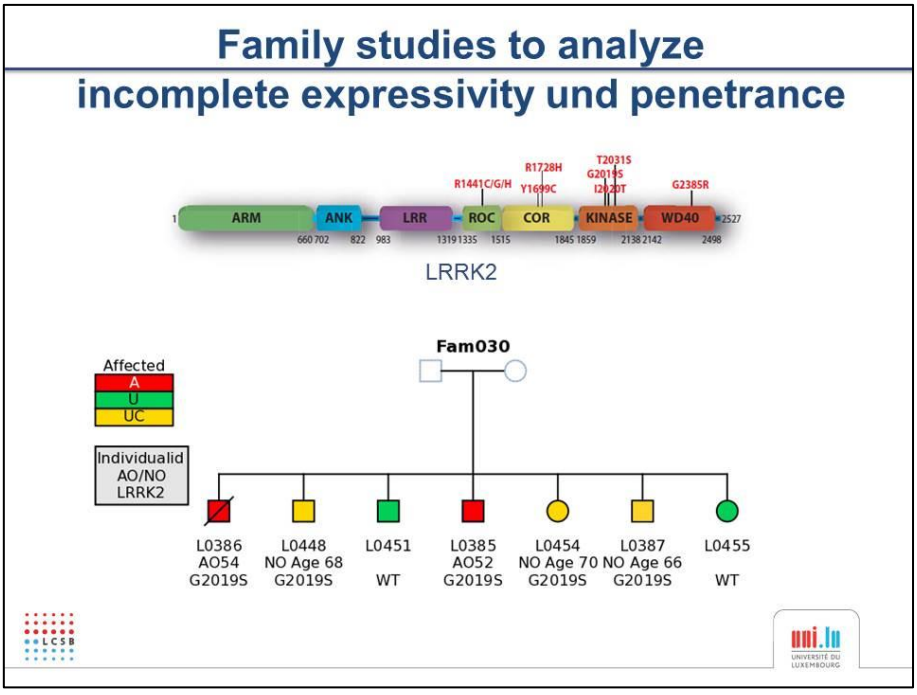
Family studies to analyze incomplete expressivity und penetrance
R1728H
T2031S
G2019S
R1441C/G/H
Y1699C
I2020T
G2385R
ARM
ANK
LRR
ROC
COR
KINASE
WD40
1
660 702
822
983
1319 1335
1515
1845 1859
2138 2142
2498
2527
LRRK2
Fam030
Affected
A
U
UC
Individualid
AO/NO
LRRK2
L0386
AO54
G2019S
L0448
NO Age 68
G2019S
L0451
WT
L0385
AO52
G2019S
L0454
NO Age 70
G2019S
L0387
NO Age 66
G2019S
L0455
WT
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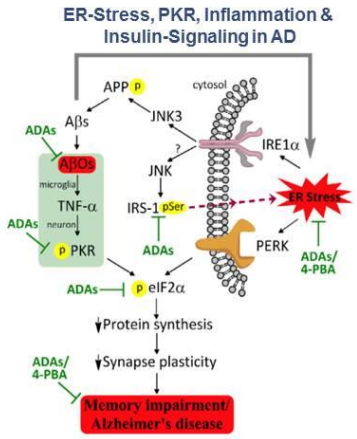
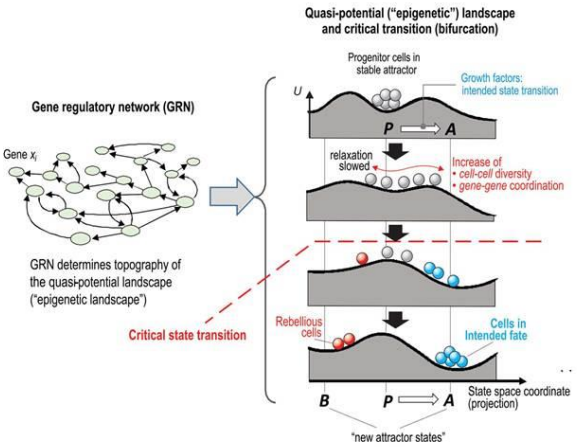
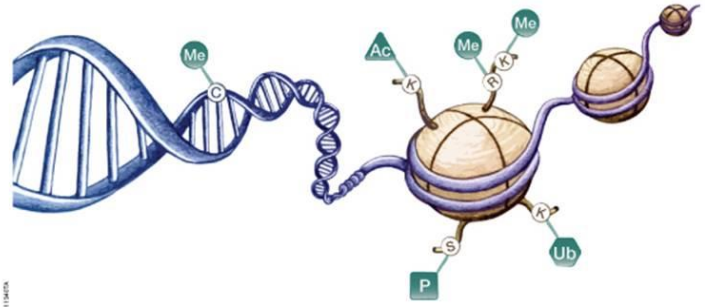
Comorbidities:
Lets talk to the Diabetes-community



Rethinking Biomarkers:
Critical transitions and early warning signals

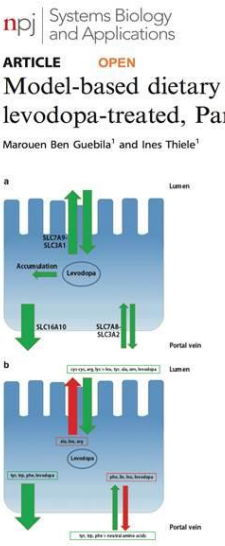


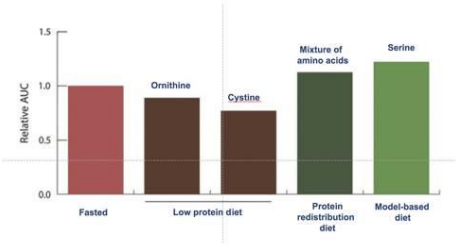
Integration of Environmental factors
Epigenetic signatures have great potential



Understanding the microbiome and disease pathogenesis

Personalized nutrition on the basis of the microbiome





npj | Systems Biology and Applications

ARTICLE OPEN

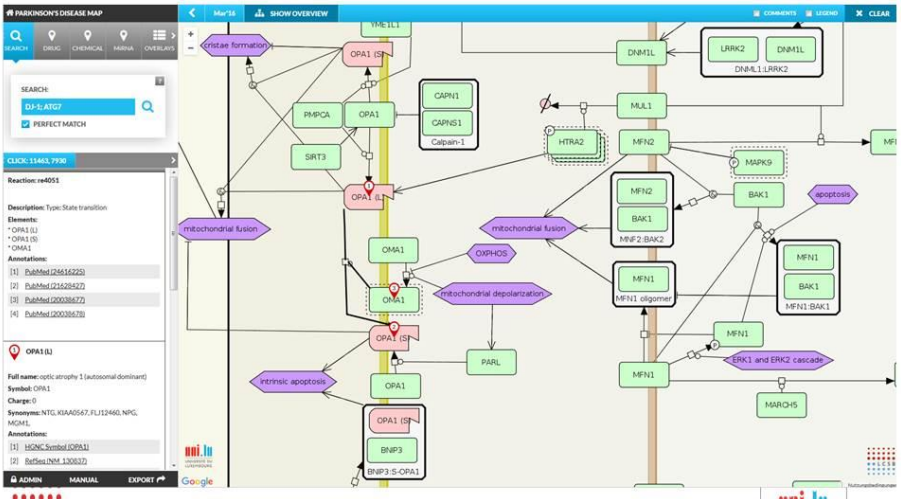
Model-based dietary optimization for late-stage, levodopa-treated, Parkinson's disease patients

Marouen Ben Guebila[1] and Ines Thiele[1]

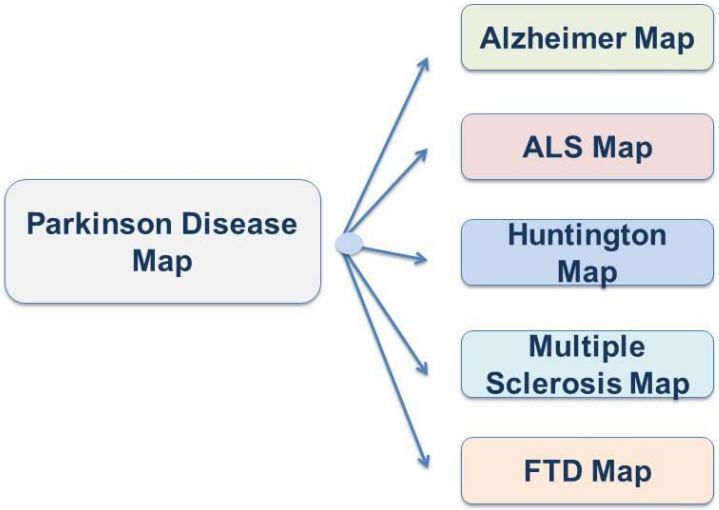
Combining PBPK- and COBRA-modeling

PBPK - Physiologically Based Pharmacokinetics
COBRA - Constraint Based Reconstruction and Analysis

Knowledge-Management and visualization tools

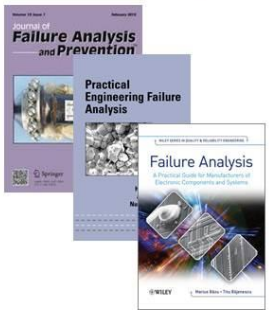


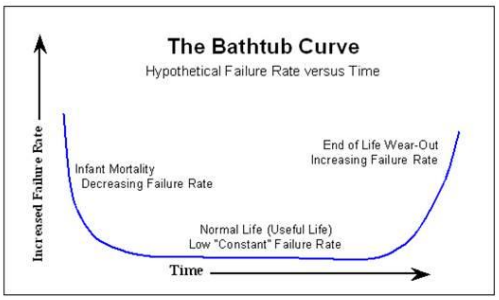
The concept of Disease maps



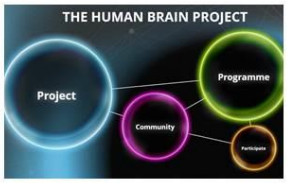
Learn from failures





"Use-cases" for the HBP



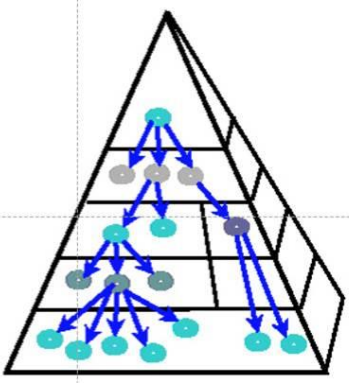
Needs

Features

Use Cases

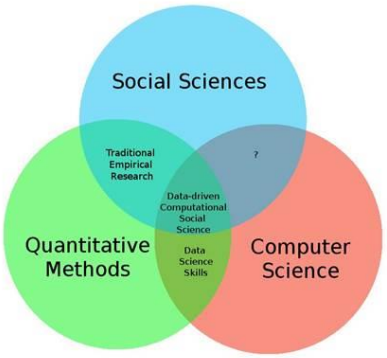
Scenarios

Test Cases



A „Testbed" for neurodegenerative diseases

- Alzheimer
- Parkinson
- Huntington
- ALS
- Multiple Sclerosis



A common vision

in silico
Clinical Trials:

How Computer Simulation will Transform the Biomedical Industry

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UNIVERSITÉ DU LUXEMBOURG

Community projects

commentary

Social engineering for virtual 'big science' in systems biology

Hiroaki Kitano, Samik Ghosh & Yukiko Matsuoka

A new type of big science is emerging that involves knowledge integration and collaboration among small sciences. Because open collaboration involves participants with diverse motivations and interests, social dynamics have a critical role in making the project successful. Thus, proper 'social engineering' will have greater role in scientific project planning and management in the future.

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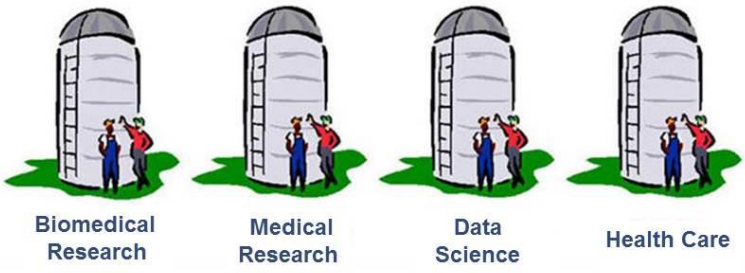
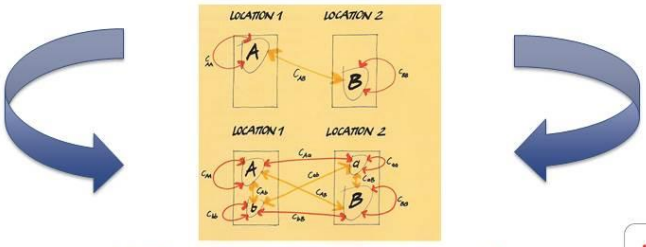
Best practice community projects

ParkinsonNet

A break down of the silo´s

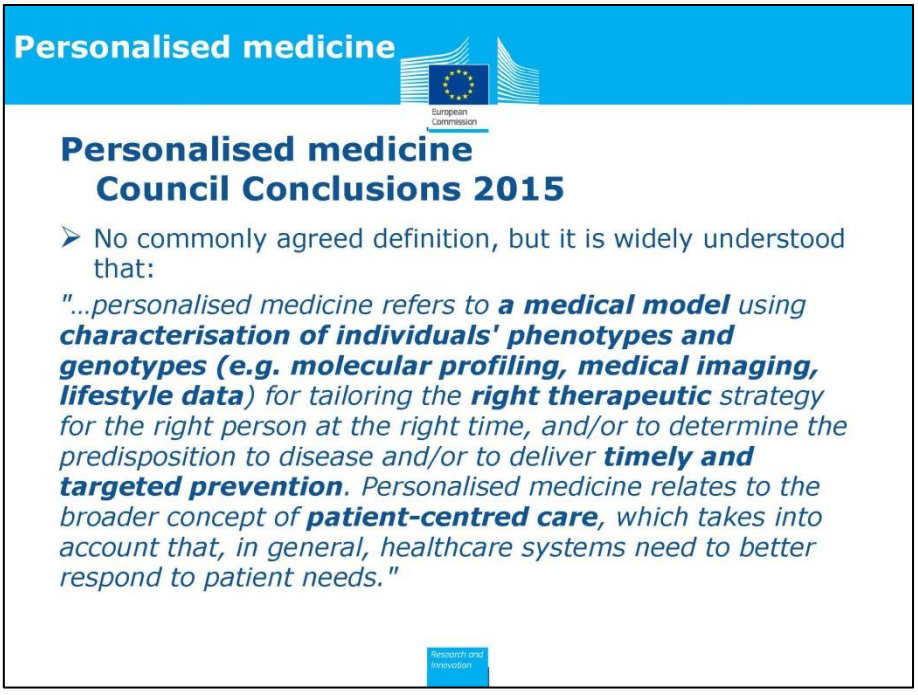




Little a to large B - little b to large A

Henn & Allen: The architecture of innovation

2. **Developing personalised medicine at EU level: Opportunities & challenges** *(L.Passante, European Commission)*



Personalised medicine

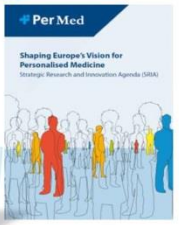
Developing personalised medicine at EU level

- Personalised medicine drives innovation and contributes to sustainable healthcare by better prevention, prediction and disease management strategies
- EC was an early mover in Personalised medicine with workshops 2010 and first conference 2011.
- Personalised Medicine Conference June 2016 launched IC PerMed

Personalised medicine
Setting the framework

Personalised medicine at activities at EU level

2010: Preparatory workshops
2011: European Perspectives conference
2013: Commission Staff Working Document on "use of '-omics' technologies in the development of personalised medicine"
2015: Council conclusions on Personalised Medicine
2015: Strategic Research and Innovation Agenda of PerMed
2016: Personalised Medicine Conference
2016: Launch of International Consortium of Personalised Medicine



Research areas

- Large scale data gathering and "-or
- Technology development
- Statistics
- Diagnostics
- Biomarkers
- Clinical trial methodologies
- Pre-clinical and clinical research
- Rare diseases: small patient populations
- Omics for health promotion and disease prevention
- Piloting personalised medicine in healthcar

EU funding - over 2 billion EUR to top research

Personalised medicine
Setting the framework

European Commission

PerMed
Shaping Europe's Vision for Personalised Medicine
Strategic Research and Innovation Agenda (SRIA)

PerMed (2013-2015)
Strategic Research & Innovation Agenda

- Challenge 1 – Developing Awareness and Empowerment
- Challenge 2 – Integrating Big Data and ICT Solutions
- Challenge 3 – Translating Basic to Clinical Research and Beyond
- Challenge 4 – Bringing Innovation to the Market
- Challenge 5 – Shaping Sustainable Healthcare

Research and Innovation

Personalised medicine
International consortium

European Commission

ICPerMed
INTERNATIONAL CONSORTIUM

International Consortium for Personalised Medicine (2016-2020)

WHAT

Collaboration of research funders and policy makers from EU Member States and beyond

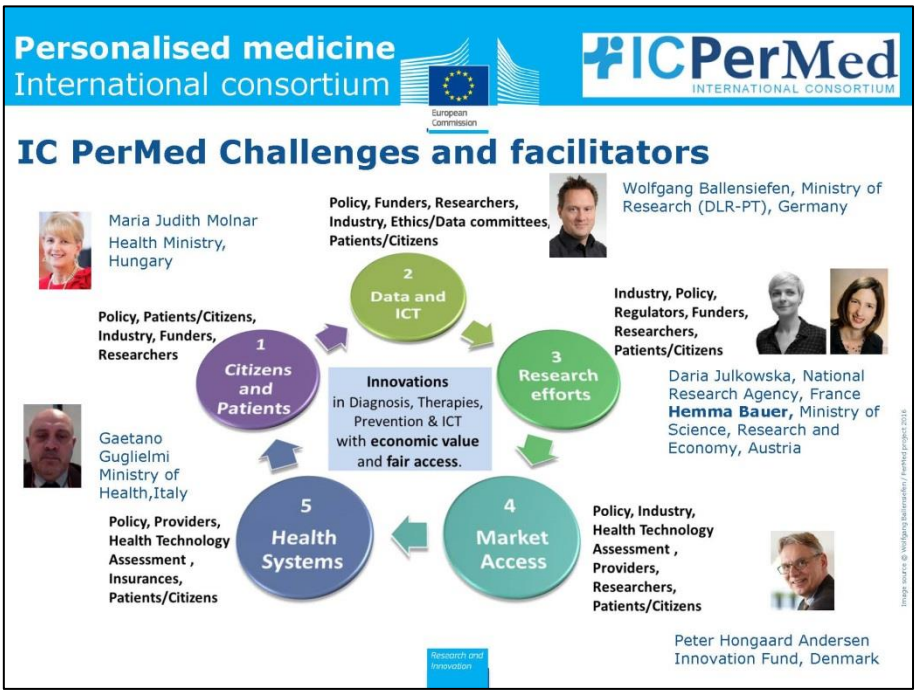
WHY

- Establish Europe as a global leader in PM research
- Support the PM science base through a coordinated approach to research
- Provide evidence to demonstrate the benefit of PM to citizens and healthcare systems
- Pave the way for PM approaches for citizens

HOW

Implementation of a Roadmap based on PerMed Strategic Research Agenda (SRIA)

Research and Innovation


Personalised medicine
International consortium
European Commission
ICPerMed
INTERNATIONAL CONSORTIUM
IC PerMed Challenges and facilitators
Maria Judith Molnar
Health Ministry,
Hungary
Policy, Funders, Researchers,
Industry, Ethics/Data committees,
Patients/Citizens
Wolfgang Ballensiefen, Ministry of
Research (DLR-PT), Germany
2
Data and
ICT
Industry, Policy,
Regulators, Funders,
Researchers,
Patients/Citizens
Policy, Patients/Citizens,
Industry, Funders,
Researchers
1
Citizens
and
Patients
Innovations
in Diagnosis, Therapies,
Prevention & ICT
with economic value
and fair access.
3
Research
efforts
Daria Julkowska, National
Research Agency, France
Hemma Bauer, Ministry of
Science, Research and
Economy, Austria
Gaetano
Guglielmi
Ministry of
Health,Italy
Policy, Providers,
Health Technology
Assessment ,
Insurances,
Patients/Citizens
5
Health
Systems
4
Market
Access
Policy, Industry,
Health Technology
Assessment ,
Providers,
Researchers,
Patients/Citizens
Peter Hongaard Andersen
Innovation Fund, Denmark
Research and Innovation


Personalised medicine
International consortium
European Commission
ICPerMed
INTERNATIONAL CONSORTIUM
IC PerMed Secretariat
A Coordination and Support action (CSA)
Financed by the European Union's Horizon 2020 research and innovation programme.
Budget: ≈ 2 Million Euro
Duration: 4 years, November 2016 – October 2020
Main Goal: Support International Consortium for Personalised Medicine (ICPerMed)
The ICPerMed Secretariat partners are:
DLR
Project management agency of the German Aerospace Center (DLR, Germany),
French National Research Agency (ANR, France),
ANR
National Institute of Health Carlos III (ISCIII, Spain) and the
Instituto de Salud Carlos III
Italian Ministry of Health (IT-MoH).
Ministero della Salute
8
Research and Innovation

Horizon 2020
Research developments

European Commission

Our priorities
Health collaborative research 2014-2017

Call 2014-15: EUR 1.3 B

Call 2016-17: EUR 1.4 B

Personalised medicine

Healthy ageing
(2014-2017)

Health ICT
(2014-2017)

Human biomonitoring
(2016-2017)

Research and Innovation

Maternal and child health
(2016-2017)

Horizon 2020
Research developments

European Commission

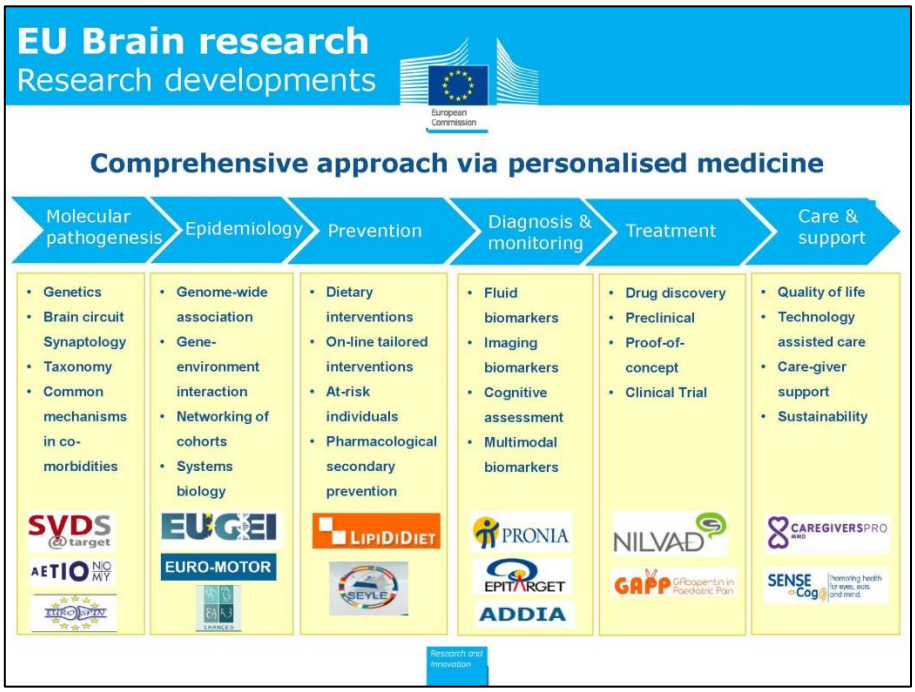
Ubiquitous Pharmacogenomics: Making actionable pharmacogenomic data and effective treatment optimisation accessible to every European citizen

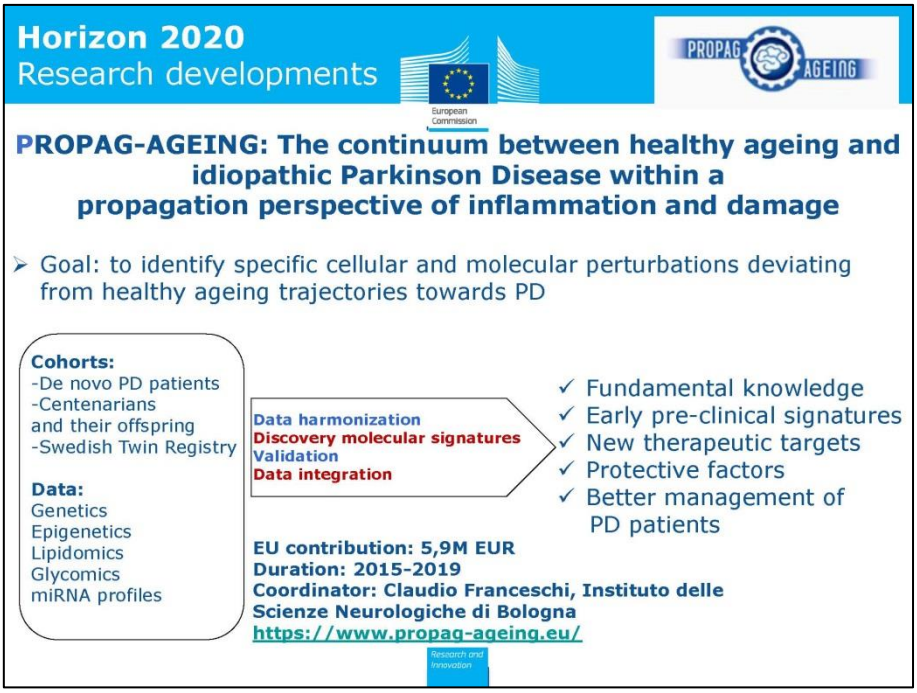
- Pre-emptive genotyping of multiple important pharmacogenes
- Data collected prospectively and embedded into the electronic records of patients in NL, ES, UK, IT, AT, GR and SL
- Prescribers and pharmacists alerted through electronic clinical decision support systems when a drug is ordered or dispensed for a patient with an at-risk genotype
- Analysis of cost-effectiveness and health outcomes

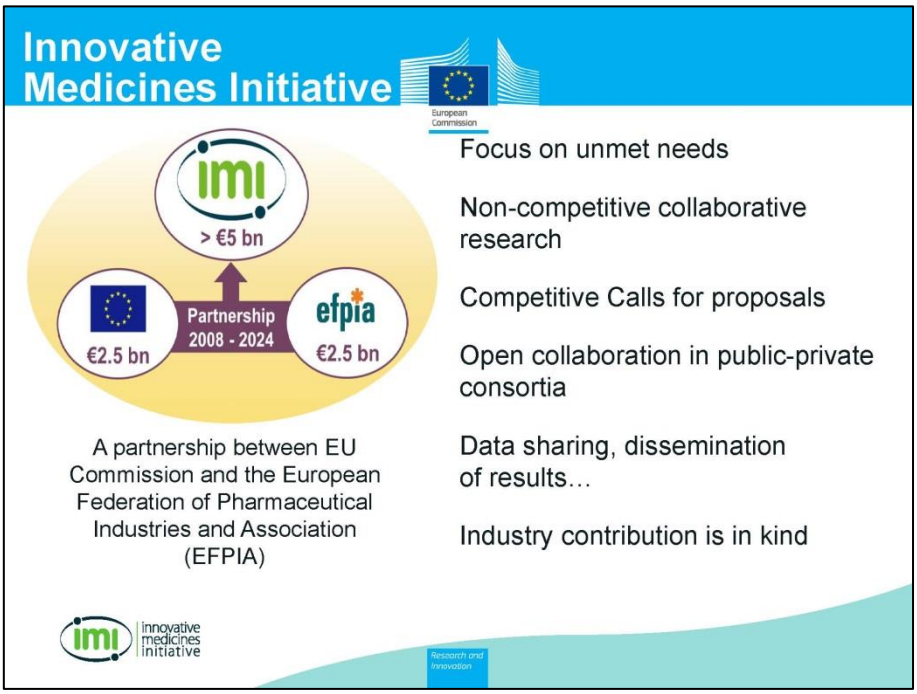
EU contribution: 15M EUR
Duration: 2016-2020
Coordinator: HJ Guchelaar, UMC Leiden
http://upgx.eu/

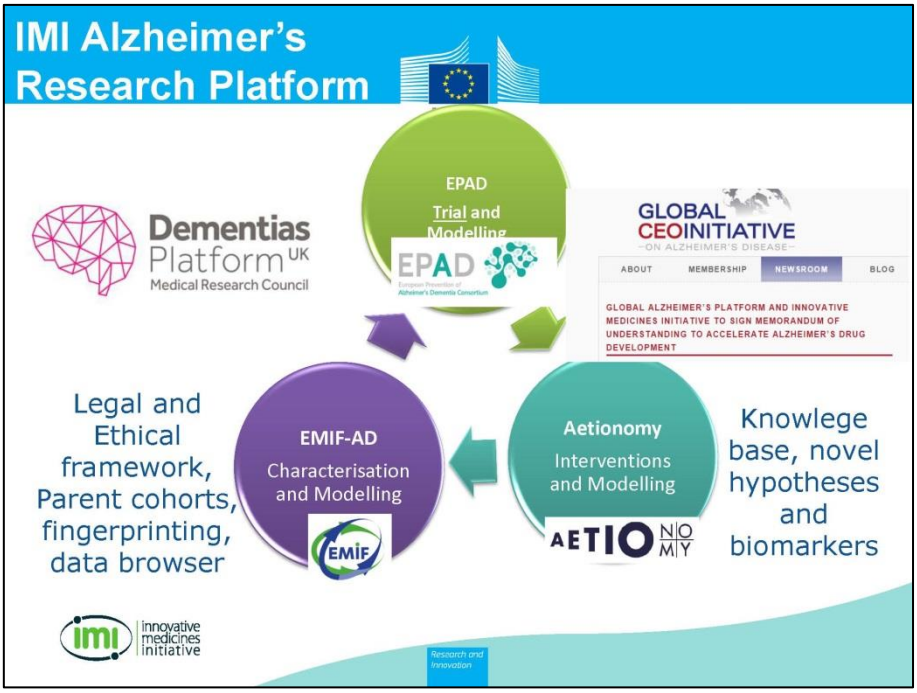
10

Research and Innovation


EU Brain research
Research developments
European Commission
Comprehensive approach via personalised medicine
Molecular pathogenesis
Epidemiology
Prevention
Diagnosis & monitoring
Treatment
Care & support
• Genetics
• Brain circuit Synaptology
• Taxonomy
• Common mechanisms in co-morbidities
• Genome-wide association
• Gene-environment interaction
• Networking of cohorts
• Systems biology
• Dietary interventions
• On-line tailored interventions
• At-risk individuals
• Pharmacological secondary prevention
• Fluid biomarkers
• Imaging biomarkers
• Cognitive assessment
• Multimodal biomarkers
• Drug discovery
• Preclinical
• Proof-of-concept
• Clinical Trial
• Quality of life
• Technology assisted care
• Care-giver support
• Sustainability
SVDS
AETIONOMY
EUROSPIN
EUGEI
EURO-MOTOR
LIPIDIDIET
SEYLE
PRONIA
EPITARGET
ADDIA
NILVAD
GAPP
CAREGIVERSPRO
SENSE-Cog
Research and Innovation


Horizon 2020
Research developments
European Commission
PROPAG AGEING
PROPAG-AGEING: The continuum between healthy ageing and idiopathic Parkinson Disease within a propagation perspective of inflammation and damage
➢ Goal: to identify specific cellular and molecular perturbations deviating from healthy ageing trajectories towards PD
Cohorts:
-De novo PD patients
-Centenarians and their offspring
-Swedish Twin Registry
Data:
Genetics
Epigenetics
Lipidomics
Glycomics
miRNA profiles
Data harmonization
Discovery molecular signatures
Validation
Data integration
✓ Fundamental knowledge
✓ Early pre-clinical signatures
✓ New therapeutic targets
✓ Protective factors
✓ Better management of PD patients
EU contribution: 5,9M EUR
Duration: 2015-2019
Coordinator: Claudio Franceschi, Instituto delle Scienze Neurologiche di Bologna
https://www.propag-ageing.eu/
Research and Innovation


Innovative Medicines Initiative
European Commission
imi
> €5 bn
€2.5 bn
Partnership 2008 - 2024
efpia
€2.5 bn
A partnership between EU Commission and the European Federation of Pharmaceutical Industries and Association (EFPIA)
Focus on unmet needs
Non-competitive collaborative research
Competitive Calls for proposals
Open collaboration in public-private consortia
Data sharing, dissemination of results…
Industry contribution is in kind
imi innovative medicines initiative
Research and Innovation


IMI Alzheimer's Research Platform
Dementias Platform UK
Medical Research Council
EPAD
Trial and Modelling
EPAD
GLOBAL CEOINITIATIVE
ON ALZHEIMER'S DISEASE
ABOUT
MEMBERSHIP
NEWSROOM
BLOG
GLOBAL ALZHEIMER'S PLATFORM AND INNOVATIVE MEDICINES INITIATIVE TO SIGN MEMORANDUM OF UNDERSTANDING TO ACCELERATE ALZHEIMER'S DRUG DEVELOPMENT
Legal and Ethical framework, Parent cohorts, fingerprinting, data browser
EMIF-AD
Characterisation and Modelling
EMIF
Aetionomy
Interventions and Modelling
AETIONOMY
Knowlege base, novel hypotheses and biomarkers
imi innovative medicines initiative
Research and Innovation

Personalised Medicine
The case of rare diseases

Need for a coherent strategy – from bench to bedside

- Programme to implement a research and innovation pipeline, from bench to bedside
- Integrative programme linking major EU and national initiatives including intra-mural activities
- Links to ERNs to help implementing research results and taking lessons learned from the clinic back to the bench

https://ec.europa.eu/health/ern/networks_en

Personalised Medicine
Available resources

- **European reference networks** (ERNs) for rare diseases: research and knowledge centres, contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities

- **The Human Brain Project** (HBP): ICT infrastructure for neuroscience, medicine and computing to catalyse collaborative efforts to better understand the brain and its diseases

https://www.humanbrainproject.eu

- **ELIXIR: distributed infrastructure** for life-science information that brings together life science resources from across Europe. Includes databases, software tools, training materials, cloud storage and supercomputers

https://www.elixir-europe.org/

- **Biobanking and BioMolecular Resources Research Infrastructure** (BBMRI-ERIC): is dedicated to establish, operate, and develop a pan-European distributed research infrastr and biomolecular resources

www.bbmri-eric.eu/

Horizon 2020
Current opportunities

SC1-HCO-03-2017-Implementing the Strategic Research Agenda on Personalised Medicine (closes on 11 April)

"…Today, **development is uneven** across and within sectors, regions and Member States due to fragmented activities, insufficient communication and lack of commonly accepted solutions and standards."

"Proposals should pool the necessary financial resources from the participating national (or regional) research programmes with a view to **implementing a joint call for proposals** resulting in grants to third parties with co-funding in this area."

"This call should aim at implementing a **key area of the PerMed Strategic Research Agenda**"

http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/sc1-hco-03-2017.html

The Council of the European Union invited:

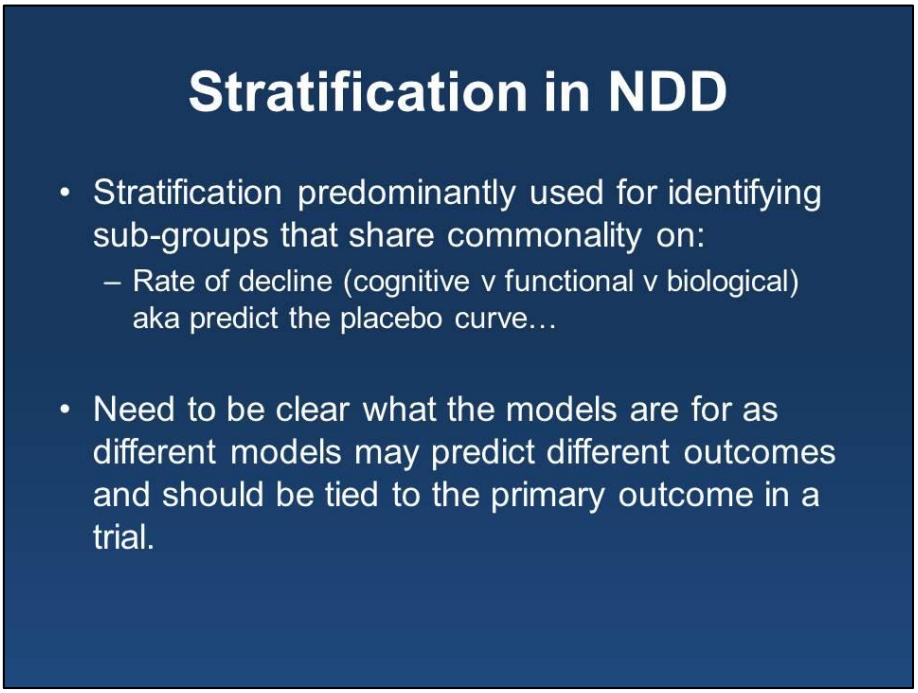
The Member States to:

- Foster cooperation in the collection, sharing, management and appropriate standardisation of data necessary for effective research
- Support the standardisation and networking of biobanks to combine and share resources, Consider exchange of information and best practices
- Promote cross-disciplinary interaction
- Put in place information and awareness strategies for patients

The Member States and the Commission to:

- Promote the interoperability of electronic health records
- Develop common principles on data collection based on standards and a sound legal framework

3. **Early ideas on stratification in ND** *(Craig Ritchie, University of Edinburgh)*



Risks and Benefits of Stratification

- The more 'stratified' a sample:
- Up side
  - More homogenous decline and larger effect sizes = smaller trials
  - Reflects better what ideal clinical practice would be.
- Down side
  - High screen failure rate in trials
  - Too small a market to justify development
  - Stratification variables may be very expensive/inaccessible

Current and Potential Stratification

- IWG2
  - Incorporate a biomarker in amnestic
  - Probably pretty poor specificity and tethered to incident dementia.
- Future stratification
  - Incorporate risks and changes over time
    - Neuropsychiatric features predict decline better that many biomarkers
    - How to handle comorbidities
  - Individual risk score v stratification/segmentation

Current Understanding

[Current] Research Diagnostic Criteria for Prodromal Alzheimer's dementia.

- Note reliance on amnestic symptoms
- Analysis tethered to predictive value for a dementia diagnosis
- No empirical division between prodromal and dementia phase of Alzheimer's disease
- Selective use of a small number of small cohorts (ADNI, DESCRIPA and Swedish Brain Power)

DuBois et al. *Lancet Neurol* 2014; 13: 614–29

Panel 1: **IWG-2 criteria for typical AD (A plus B at any stage)**

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

B In-vivo evidence of Alzheimer's pathology (one of the following)

- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Exclusion criteria† for typical AD

History

- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, major and prevalent behavioural changes

Clinical features

- Focal neurological features
- Early extrapyramidal signs
- Early hallucinations
- Cognitive fluctuations

Other medical conditions severe enough to account for memory and related symptoms

- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic, inflammatory, and metabolic disorders, all of which may require specific investigations
- MRI FLAIR or T2 signal changes in the medial temporal lobe that are consistent with infectious or vascular insults

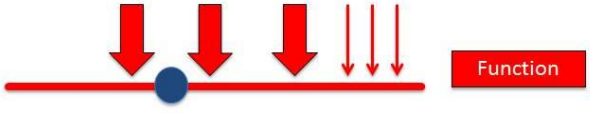
PROBABILITY MODELLING

One Dimensional Approach

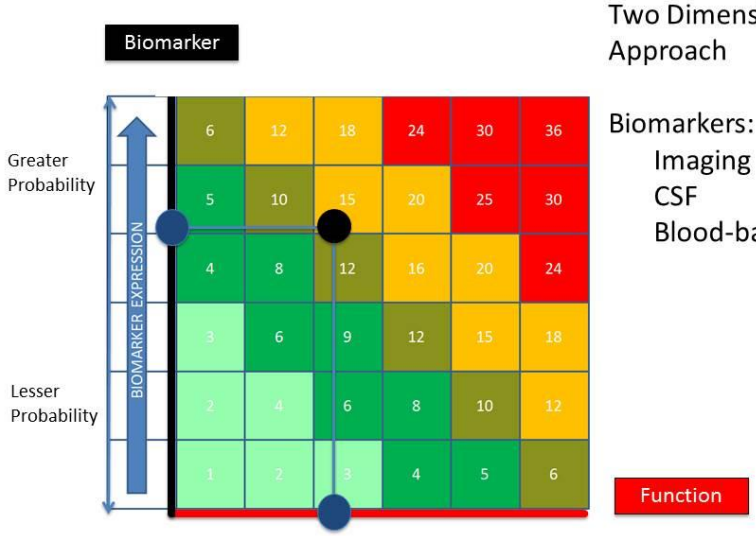
Function:
- Cognitive
- Activities of Daily Living

Thresholds:

Subjective Cognitive Impairment	X% probability decline
Mild Cognitive Impairment	2-15% probability
Dementia	99% probability



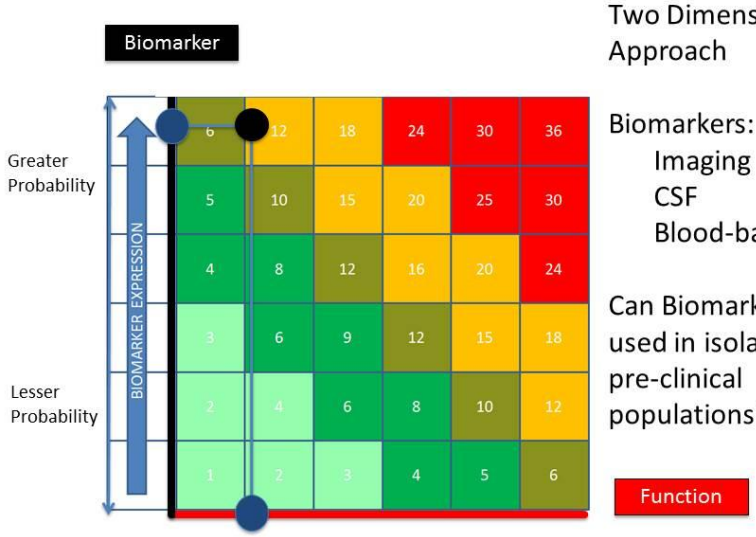
PROBABILITY MODELLING



Two Dimensional Approach

Biomarkers:
- Imaging
- CSF
- Blood-based

PROBABILITY MODELLING

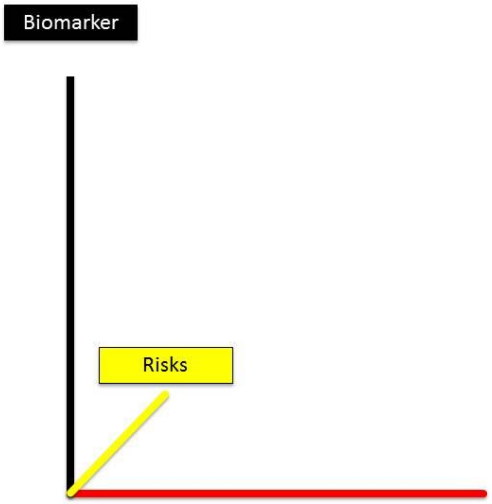


Two Dimensional Approach

Biomarkers:
- Imaging
- CSF
- Blood-based

Can Biomarkers be used in isolation in pre-clinical populations?

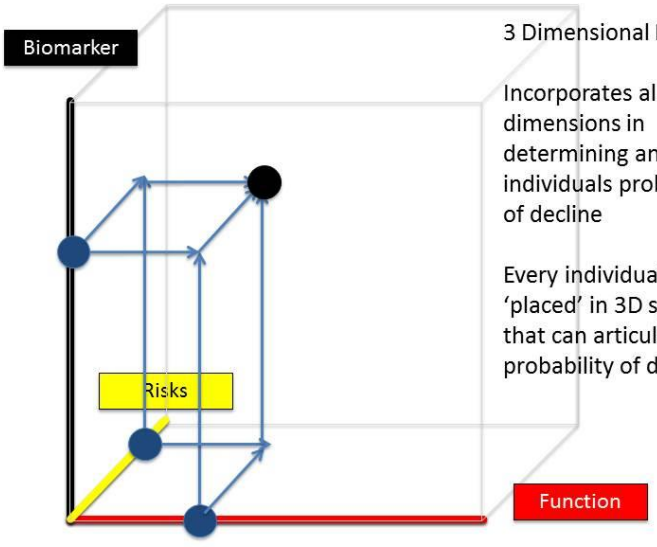
PROBABILITY MODELLING



Three Dimensional Approach

Risk Factors:
- Age
- Genotype
- Head Injury
- Diabetes
- Depression
- Lifestyle

PROBABILITY MODELLING

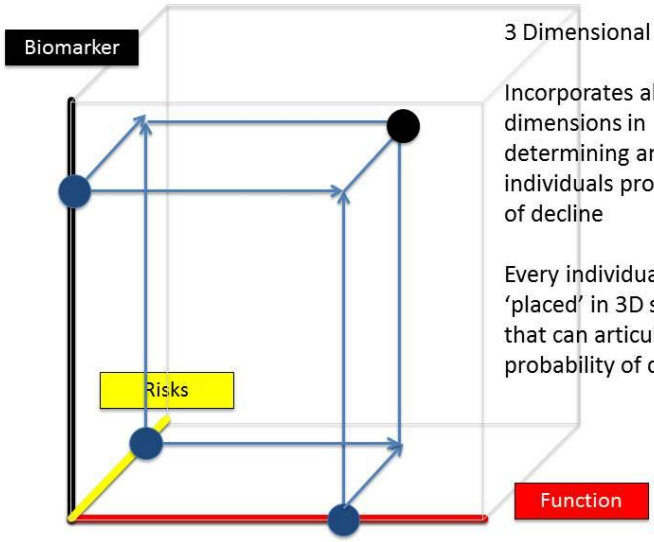


3 Dimensional Model

Incorporates all 3 dimensions in determining an individuals probability of decline

Every individual can be 'placed' in 3D space that can articulate a probability of decline

PROBABILITY MODELLING

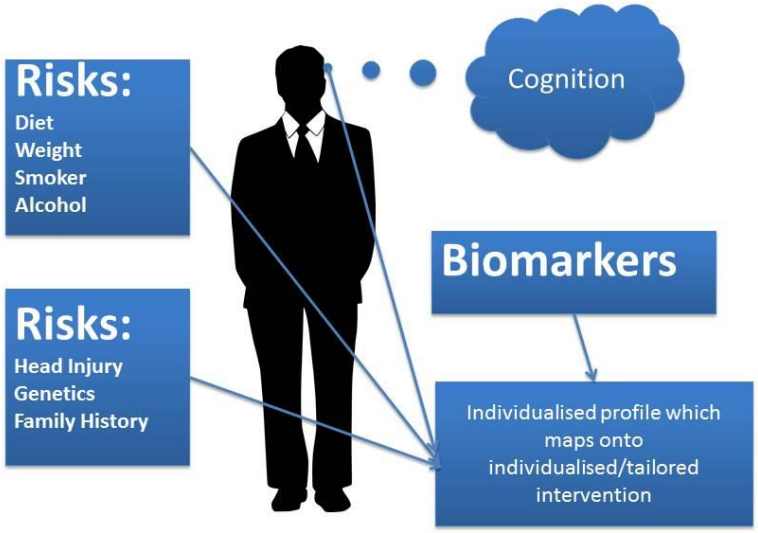


3 Dimensional Model

Incorporates all 3 dimensions in determining an individuals probability of decline

Every individual can be 'placed' in 3D space that can articulate a probability of decline

We can find the people who will benefit most



Stepped approach

- Screening population e.g. MCI population in a memory clinic.
- Add enrichment tests to create desired strata
  - Define fast decliners
- Ensure target pathology/pathologies present
  - Ensure fast decliners have e.g. amyloid
  - Hope randomisation manages between group differences in (non-amyloid) factors mediating decline.
- Enroll in trial

Accepted Uncertainties or Knowledge Gaps:

- What is the relevant biology?
- How can this be measured *in vivo?*
- What is the associated clinical phenotype?
- How do we intervene and measure success?
- How do we develop 'probability' signatures for individuals?

- How do we recruit and operate within a collaborative and ethical framework?
- How do we get findings into practice (clinical and public health)