Innovative Medicines Initiative

Personalized Therapy in Diabetes

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Personalized medicine and T2DM

Disease

- Complex heterogeneous disorder
- Contribution of multiple genetic and environmental factors
- A ‚silent' disease
- No quantitative determinants for individual, patient-specific progression
- Diagnosis often comes late

Treatment

- Treatment guidelines with few phenotypic selection criteria
- Trial and error approach to find effective drug(s) for individual
- 9 classes of drugs available
- Challenge to position new drug classes in treatment scheme

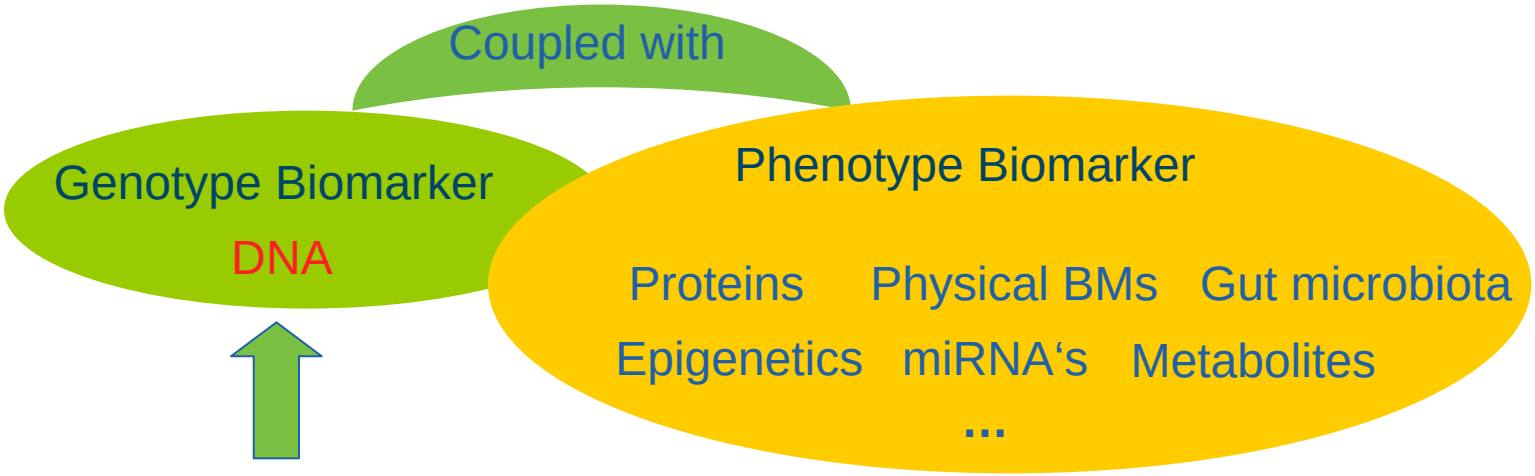
Introduce personalized approaches

- For the benefit of the patient
- For more effective drug development and easier market access

Enabling technologies for personalized medicine

- T2DM has multiple genetic and environmental contributors
- Personalized approaches need to capture both

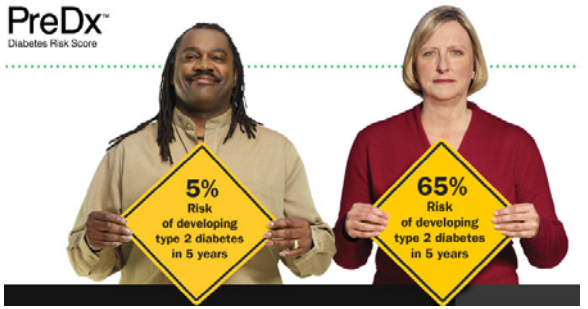
Personalized Medicine = Genetic + phenotypic + environmental traits

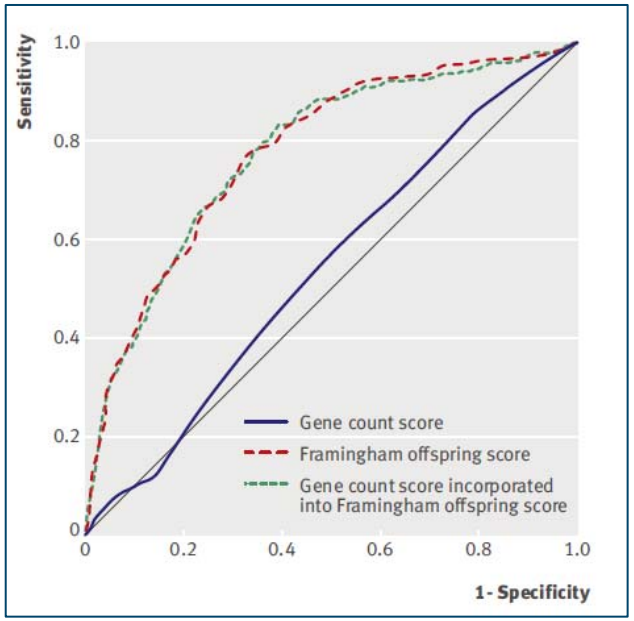


Today, we only handle this

Today: Poor performance of currently known risk genes as predisposition markers of T2D

- **Compare: Genetic risk markers with classical markers (BMI, age, fasting glucose, etc.)**
  - a) Talmud et al, *BMJ* 2010, 340:b4838; b) van Hoek et al, *Diabetes* 2008, 57, 3122; c) Lango et al, *Diabetes* 2008, 57, 3129.
- **So far: Poor performance of genes for risk assessment in most studies**
  - No or little added value to established phenotype scores
  - Conclusion: „The major translational application…is likely to come from the insight … on causes of disease and potential therapeutic targets (Talmud et al).”





Tethys risk score (protein-based)

PJ Talmud et al, BMJ 2010

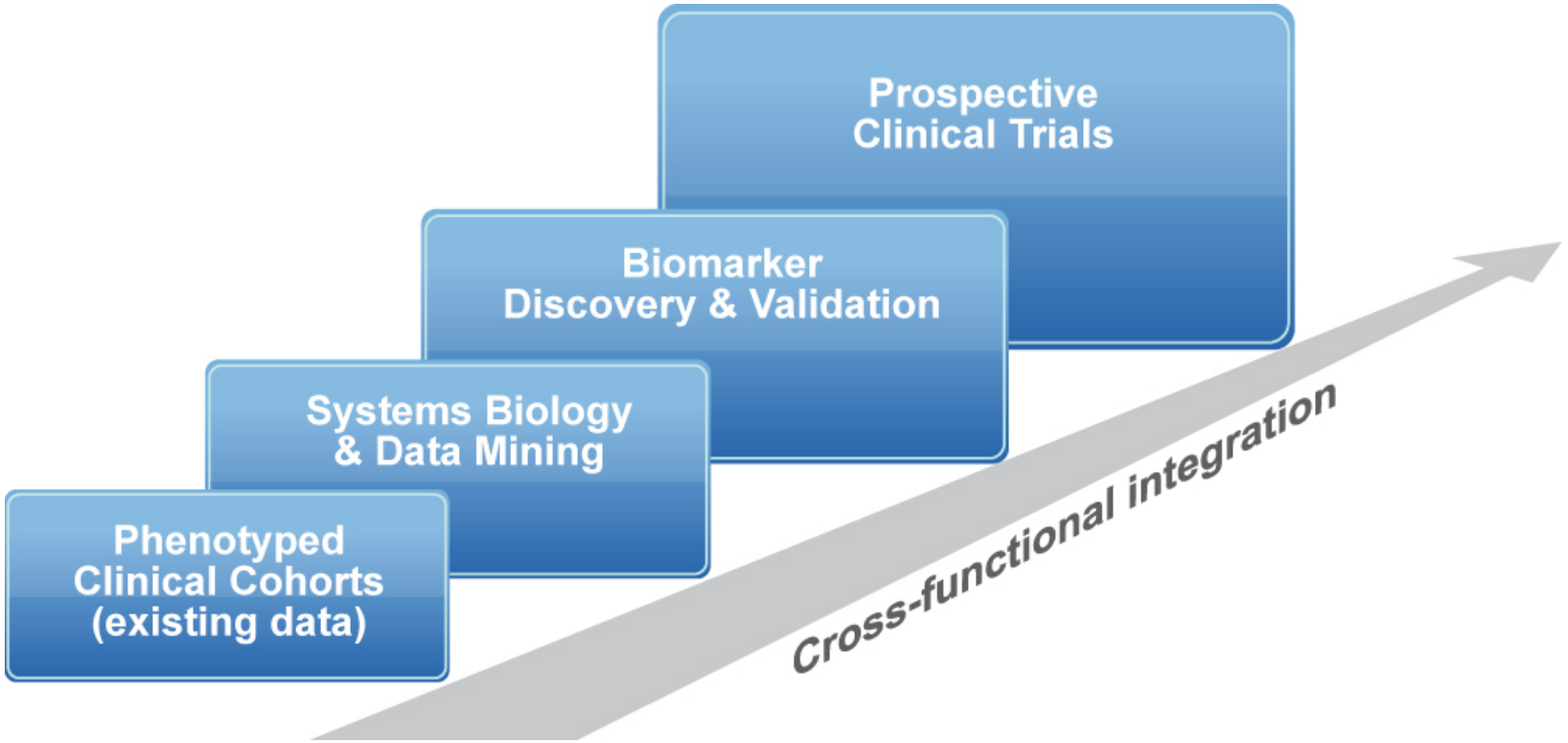
Need for public-private collaboration

- To build a large accessible data collection from well described phenotypes (patients with ‘early’ or ‘pre-diabetes’ or at risk diabetes progression to end-organ manifestation)
- To collect patient samples from academia and industry in a large data set for system biology, development of new diagnostic tools for patient stratification and response to treatment
- To access to different data mining tools
- To use broad knowledge from academia, SME and industry to process large data banks from well phenotyped patients.
- To enable clinical evaluation & testing of biomarkers and corresponding diagnostic tests in close interaction with the relevant regulatory agencies to gain acceptance for these newly derived methods and stratification strategies.

Objectives

- Development of robust disease stratification and response tools for drug development
- Improvement of patient care through a personalized therapeutic strategies (increase efficacy and less side effects) in well-defined sub-populations.
- **PART 1:**
  - Use available resources, technologies, infrastructure and knowledge management tools & technologies to enhance understanding of the disease and to generate new disease hypothesis based on data from well phenotyped patients.
  - Harmonisation of data mining across academia and industry
  - Standardisation of protocols for basic (e.g. Hb1Ac, FPG, OGTT, etc.) and deep/specific (e.g. MRI, PET, clamp, etc.) phenotyping.
- **PART2** (provided a new disease hypothesis will be identified in PART1)
  - Conduct prospective clinical trials to qualify new disease hypothesis

Translation of bottlenecks into IMI Projects: Personalized Therapy in Diabetes



Expected impact on the R&D process

- Better definition of patient subpopulations based on biomarker for early proof of concept studies.
- Enabling to design specific clinical studies for early proof of efficacy and safety for new treatment modalities. Cost reduction in clinical development.
- Common basis across academia and industry for patient stratification.
- The systems biology description of early type II diabetes will increase the understanding of the pathophysiology of the disease (provided by a single data repository).
- Potential delivery of new drug targets
- Potential translation of new biomarker(s) from preclinical animal models to proof of concept in patients.

Suggested architecture* of the project

- **Overall**
  - **WP1: Project Management**
    - Focus: management, project management and support.
  - **WP10: Statistical Analysis**
    - Focus: Evaluation of novel statistical and clinical trial design concepts and methods for the clinical evaluation of biomarker tools.
- **Part 1**
  - **WP2: Database Establishment + Retrospective Hypotheses Testing**
    - Focus: Merging of existing data from small/individual cohorts into a large, high quality European data bank for data mining
  - **WP3: Phenotype Data Generation:**
    - Focus: To consolidate / generate a broad data set for individual patients (in line with corresponding legal and ethical guidelines) using highly disease relevant technologies (for example clamp, MRI, PET, etc.).
  - **WP4: Systems biology**
    - Focus: Systems biology platform to be established by integrating clinical data, biological data, genomics, metabonomics and other relevant data.
  - **WP5: Data mining**
    - Focus: Application and development of novel data mining tools and algorithms to generate stratification and response biomarker candidates (i) describing patients at risk of diabetes and at risk for disease progression, (ii) to derive a personalized treatment strategy and (iii) potentially identify new drug development targets.

** different innovative project designs are welcome, if properly justified.*

Suggested architecture of the project

- **Part 1 (continued)**
  - **WP6: Biomarker assay development**
    - Focus: : “Industrialized” confirmation and qualification of new or already known biomarkers for personalized therapy in well defined sub-populations (Part 1: application in retrospective trials; Part 2: support exploring novel clinical design strategies, e.g. adaptive clinical trial designs). Quantification of patient metabolism and target variability.
- **Part 2**
  - **WP7: Design of prospective clinical trial(s)**
    - Focus: Design of prospective clinical trials for Validation of biomarker candidates. Potential scenarios depending on the Biomarker Candidate types to be tested (follow-up of 5-7 years; example 1: deep phenotyping, e.g. PET, MRI, clamp in ~ 500 patients; example 2: basic phenotyping in ~ 3000 patients). Assessment of the response (or lack of response) to established therapies (targeting extensively characterized mechanisms, for instance incretin pathway) in well defined sub-populations.
  - **WP8/9: Execution of prospective clinical trial(s) and interpretation of results**
    - Focus: Execution of trials (examples see WP7)

Expected contributions of the applicants

The Applicant Consortium is expected to provide both pre clinical and clinical expertise and ability for interdisciplinary and inter-sectorial work in order to:

- build a large high quality EU database from phenotyped patients
- develop a diabetes specific systems biology platform.
- indentify, evaluate and qualify biomarker candidates
- perform phenotyping, genetic and metabolic assays.
- develop and validate new biomarker tools and corresponding predictive biomarker assays
- have experience in conducting (small and/or large land mark) clinical trials.
- provide and develop novel clinical trial design concepts (adaptive clinical trial designs).

Expected (in kind) contributions of EFPIA members

- **Overall**
  - Project Management
  - Statistical Analysis
- **PART1:**
  - Database Establishment + Retrospective Hypotheses Testing (samples and data from clinical trials, which may also come from outside EU/FP7)
  - Phenotypic data generation
  - Systems Biology Platform (expertise and know how)
  - Data Mining (expertise and tools)
  - Biomarker Assay Development (expertise and application support.)
- **PART2:**
  - Design of prospective clinical trial(s): resources and expertise for trial design,
  - Execution of prospective clinical trial(s) and interpretation of results: resources and expertise to conduct multi-centre clinical trials (monitoring, data management, etc.)

Key deliverables of full project

Part 1

- Patient samples and data: generation of a high quality European data bank to generate relevant phenotypical data sets.
- Systems Biology Platform: Integrating clinical data, biological data, genomics, metabonomics and other relevant data.
- Data Mining: Application and development of novel data mining tools and algorithms to generate stratification and response biomarker candidates (i) describing patients at risk of diabetes and at risk for disease progression, (ii) to derive a personalized treatment strategy and (iii) potentially identify new drug development targets.
- Development of Biomarker Assays: “Industrialized” confirmation and qualification of new or already known biomarkers for personalized therapy in well defined sub-populations.

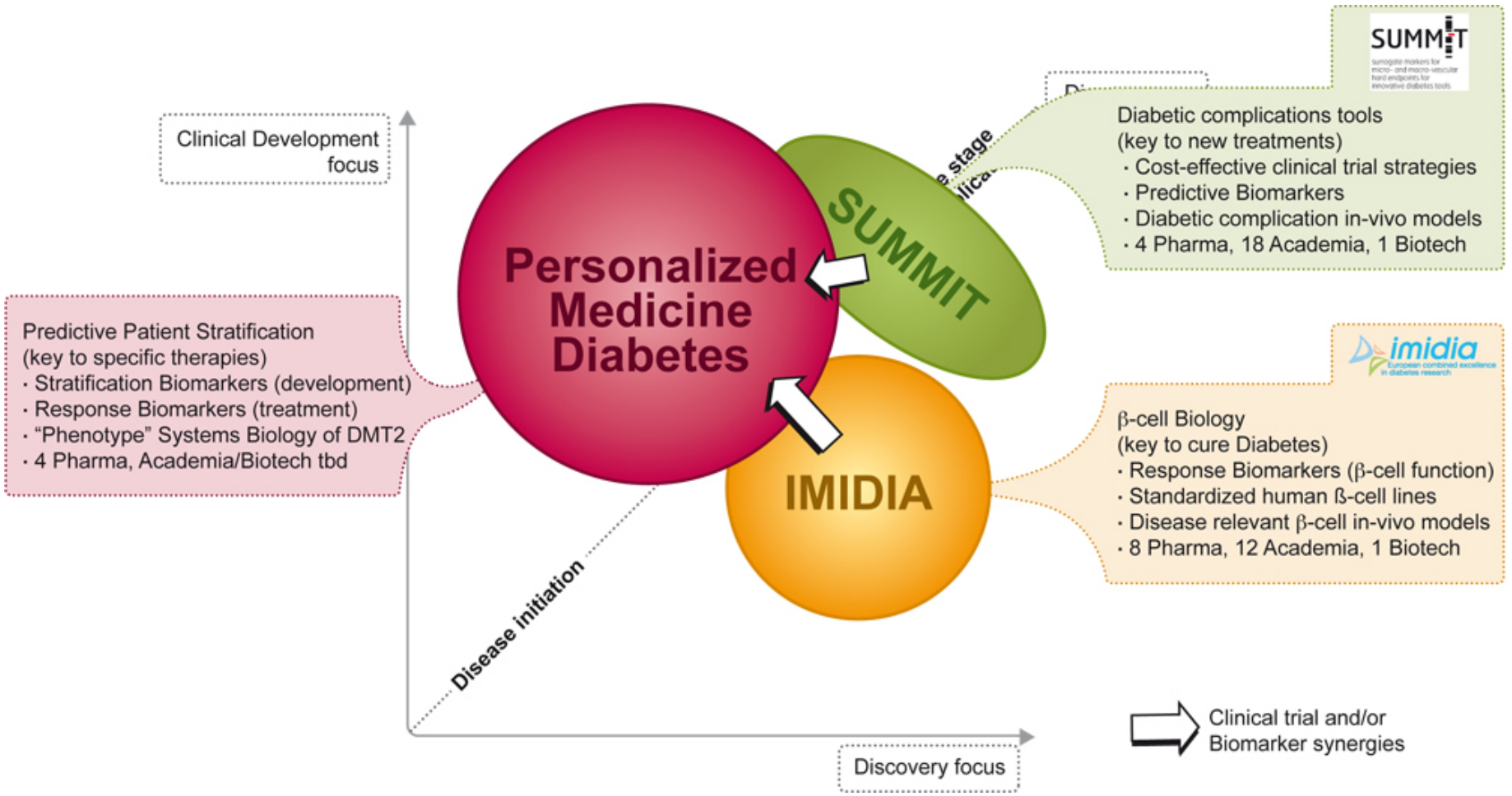
Key deliverables of full project

PART 2

(only if Part 1 delivered new disease hypothesis worth while to be validated)

- (based on PART 1 delivering new stratification and/or response biomarker candidates; which will determine the details of the prospective clinical trials of PART 2)
- Prospective Clinical Trials: Validation of biomarker candidates in prospective clinical trials (potential scenarios depending on the Biomarker Candidate types to be tested; follow-up of 5-7 years):
- Assessment of the response (or lack of response) to established therapies (targeting extensively characterized mechanisms, for instance incretin pathway) in well defined sub-populations.

IMI Diabetes Platform - Complementarities



For questions, please contact the IMI Executive office:

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