Critical appraisal: Diabetes

Università Commerciale Luigi Bocconi

Ludovica Borsoi, Oriana Ciani, Silvia Sommariva, Rosanna Tarricone*

Along with the following Mapping_NCD Consortium members who provided valuable data and analysis for this report: Grant Lewison, Mursheda Begum, Elena Pallari, Francisca Costa, Astrid Grant, Panos Kanavos, John Wright, Erica Visintin

Mapping Chronic Non-Communicable Disease Research Activities and their Impact
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Abbreviations

BMI	Body Mass Index
CARDI	Cardiovascular
CDC	Centers for Disease Control and Prevention
CDRH	Center for Devices and Radiological Health
CE	Conformité Européene
CGM	Continuous Glucose Monitor
CRD	Chronic Respiratory Disease
CVD	Cardiovascular disease
DALY	Disability-adjusted life years
DIAMAP	Road Map for Diabetes Research
DM	Diabetes Mellitus
EASD	European Association for the Study of Diabetes
EC	European Commission
EFSD	European Foundation for the Study of Diabetes
EU	European Union
EUDAMED	European Database on Medical Devices
EURADIA	Alliance for European Diabetes Research
FDA	Food and Drug Administration
FP	Framework Programme
GBD	Global Burden of Disease
GDP	Gross Domestic Product
HTA	Health Technology Assessment
H2020	Horizon 2020
IA	Impact Assessment
ICD	International Classification of Disease
IDF	International Diabetes Federation
MD	Medical device
MRG	Millennium Research Group
OECD	Organization for Economic Co-operation and Development
OTC	Over-the-counter medicines
PMA	Premarket approval
PPI	Patient Public Involvement
PRO	Public Research Organizations
R&D	Research and Development
RFO	Research Funding Organization
SCI	Science for the Science Citation Index
SSCI	Social Sciences Citation Index
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UK	United Kingdom
US	United States
WHO	Word Health Organization
WoS	Web of Science

Executive Summary

According to various sources, diabetes ranks in the top 10 causes of disability worldwide with more than 4.5 million annual deaths. In this report, we describe the results of four different analyses performed as part of the MAPPING_NCD project activities on diabetes: mapping of major past and current research programmes in the field, mapping of private sector investments in diabetes research, interviews with stakeholders' and bibliometric analysis.

The analysis of European research projects has highlighted areas of research where action has been taken to foster knowledge creation and sharing through funding of relevant projects. Diabetes Type I and Type II as classified by ICD-10 are a major focus of funding, which is mirrored by the results of the bibliometric analysis. Cardiovascular complications are most commonly studied in the projects funded by the European programmes, as well as other national and international RFOs. It emerges that major projects tend to focus less on the study of patient-disease management, as well as on the analysis of policies related to diabetes prevention and treatment. A particularly crucial issue in this respect concerns the promotion of effective engagement with the general public to raise awareness on prevention of type II diabetes. Another area where investments are needed is the study of systems to share biological samples through bio-banks, registry data and research findings across Europe.

Over the period 2011-2014, the European pharmaceutical sector has generally increased its R&D expenditures, however with few exceptions. The most substantial increase was registered by smaller pharmaceutical companies. In terms of R&D intensity (a measure that allows to capture the relative importance of R&D among firms in the same industry), current findings suggest that US pharmaceutical companies generally allocate more resources in research and development activities than EU firms. However, when focusing specifically on research pipelines for diabetes, US companies loose their role of leaders, with 26 molecules under development compared to 40 for EU firms. These are mainly aimed at treating type 1 and type 2 diabetes mellitus, with a minority dedicated to diabetes complications. Over the period 2011-2014, the medical device sector commitment to R&D investments has been highly heterogeneous. As regards R&D intensity, US firms generally record higher levels of R&D ratio on sales than EU companies, meaning that US medical devices companies allocate more resources in research and development activities than EU firms. Diabetes medical devices consist of a wide range of products: from insulin pumps to blood glucose meters and infusion sets. Despite being one of the top 10 causes of disability worldwide, few companies in the sector have developed any diabetes relevant medical devices in recent years.

The themes emerged from the stakeholders interviews were organized in six major areas: i) challenges in diabetes research, ii) duplication in diabetes research, iii) research gaps, iv) impact of research and priority-setting, v) partnerships and vi) the role of the EU. According to the informants, the challenges faced by researchers and RFOs in diabetes research are financial and organizational. Heterogeneity of funding bodies was perceived to be an opportunity to preserve and develop through structured forms of cooperation. A general broader view on the impact of research as impact on diagnostic and therapeutic practice, patient outcomes and health services was supported. In terms of research gaps or unmet need, informants pointed out the broad area of aetiology (i.e. pathogenesis of hypo/hyperglycaemic events, pathogenesis of chronic complications), prevention

(i.e. genetic factors linked to the adult development of T2DM) or treatment (i.e. adjunct therapies, artificial pancreas, beta-cell transplantation, cell line conversion). Many of these topics were also emerging through the bibliometric and research programs analysis. Similarly, bio-banks development was the most recommended suggestion to speed up genetic-based studies. Another probably unexpected topic suggested for future research was on the social and health related quality of life aspects of people living with the disease, how it is possible to make patients and families more engaged with the treatment and how to get them to use the treatment much more effectively. Finally, and in addition to what can be captured through other methodologies, the role attributed to the EU is one of coordination and leadership, with recommendations on fruitful engagement in discussion with all stakeholders or wider net cast to involve experts in drafting programs calls.

The Bibliometric analysis provides a quantitative methodology to assess the impact of research funding in the field of diabetes in terms of production of scientific publications, as well as level of influence via citation analysis. It has allowed the identification of specific peculiarities related to volume, geography and type of funding institutions. Overall, the volume of diabetes research as a proportion of biomedical scientific production has increased over the years, with geographic heterogeneity across countries in terms of GDP- productivity link. When looking at the burden of disease, countries such as the UK publish more than what prevalence and DALYs of the disease would suggest. There is a tendency for the Northern European countries to devote relatively more attention to Type I diabetes, while the contrary holds true for Southern Europe. Type II diabetes papers are much more numerous and 66% more cited, on average, than Type I diabetes papers. Scandinavian countries display higher number of funders per paper and more private-non-profit sources, especially endowed foundations. For most countries the percentage of internationally-funded papers is quite low and mainly refers to funding from the EU. The European Union is the largest single source of support in terms of the numbers of papers funded, with the second largest being the Danish company Novo Nordisk A/S.

There are numerous discussion points that start to surface by the combined considerations of findings from different analyses in this report. In the next and final evidence synthesis deliverable, we will illustrate the triangulation of the various outputs from the MAPPING_NCD project within each disease categories to contrast, reinforce or discuss emerging directives to guide the future research funding strategies across NCDs around Europe.

1 European Research Programs

This section presents an overview of European research programs funded to study diabetes and enhance the understanding of the disease. The previous "Impact Assessment" deliverable has extensively documented how crucial advancement in this area is needed. Diabetes has, in fact, reached epidemic proportions in the European Union: in 2012, around 32 million people in the EU were living with diabetes. This prevalence translates into considerable expenses for States, as on average 10% of their healthcare resources are devoted to treatment of this pathology and its complications (Nabais, 2013). While new therapies and approaches have improved the prognosis and quality of life for patients affected by diabetes, there is still no complete cure for diabetes and morbidity/increased mortality still represent a challenge: this calls for the need of better research funding strategies, as well as increased funding amounts made available to researchers (Halban & Hills, 2010).

Analyzing the current status quo in terms of type and focus of program funded represents a major step in the development of future funding and promotion strategies at European level in the field of diabetes. For this purposes both national-level and European-level RFOs and their funded projects should be considered in order to highlight relevant work conducted at all governance levels within the European context.

1.1 Methods

1.1.1 Inclusion criteria

We acknowledge the challenges in attempting to provide a comprehensive list of all projects funded in this area across EU31. This work builds upon the findings of the survey on RFOs in Europe conducted and presented in the previous deliverables. Therefore RFOs considered represent only a sample of the actual landscape of organizations that are funding research on diabetes across Europe. For what concerns the objectives of Work Package 4, in the previous work we have mapped two categories of RFOs: those funding research on a range of diseases, including diabetes, and those funding exclusively projects on diabetes. In this section we consider only the latter institutions, as their "narrower" focus on diabetes allows to study their funding strategies on the disease of interest, partially eliminating the potential influence or spillovers from funding strategies for other disease areas. For instance, a RFO supporting projects both in diabetes and cardiovascular pathologies may be drawn to consider more extensively the issue of cardiovascular complications of diabetes rather than other research areas.
Therefore information on specific projects funded was retrieved for those diabetes-specific RFOs identified during the previous survey-phase of the project. As reported in the Impact Assessment report, these RFOs are located in France (n=5), The Netherlands (n=2), Portugal (n=1), United Kingdom (n=3), Ireland (n=1), Norway (n=1) or operate at international level (n=1) (Table 1).

Table 1 RFOs funding exclusively research in the field of diabetes

France
▪ Association Française des Diabétiques ▪ Association pour la Recherche sur le Diabète ▪ Fondation Francophone pour la Recherche sur le Diabète ▪ Fondation Josette-Solvay - Lutter contre le diabète et les maladies renales ▪ Fondation Orange
The Netherlands
▪ Dutch Diabetes Research Foundation ▪ Diabetes Fonds
Portugal
▪ Association of diabetics of Portugal / Associacao protectora dos diabeticos de Portugal
United Kingdom
▪ Diabetes UK ▪ The Diabetes Research & Wellness Foundation ▪ Independent Diabetes Trust

Ireland
▪ Diabetes Ireland Research Alliance (+HRB/MRCG)
Norway
▪ Norwegian Diabetes Association
International
▪ Juvenile Diabetes Research Foundation

Given that the European Union is a major active funder of health research, particularly through its framework programmes, a list of projects funded by the European Commission under EU FP-6 and FP-7 relevant to diabetes research was retrieved. Also the list of H2020 projects was consulted.
The general criteria for inclusion of projects were: i) timeframe 2006-13 to include projects under FP-6 and FP-7[1]; ii) projects funded by diabetes-specific RFOs identified during the previous phase of the MAPPING_NCD project, that is RFOs that responded to the survey or for which funding data was available; iii) projects in the diabetes-related categories (e.g. Type I and type2) as classified by the International Statistical Classification of Diseases and Related Health Problems 10th Revision[2]. The resulting lists of projects are reported in Appendix 1,2 and 3.

1.1.2 Search of relevant projects

Research on specific projects funded by the identified list of RFOs was conducted on institutional websites and websites of national associations on diabetes. Out of 14 diabetes-specific RFOs, detailed information on type of projects funded was found for 6 RFOs.

Table 2 provides a summary of the organizations and of projects funded (full list in Annex 1). The list may not be exhaustive, given that not all RFOs report information on currently or recently funded projects.

Table 2 Diabetes-specific RFOs, projects funded

RFO name	Projects funded
Diabetes UK	82 projects
Dutch Diabetes Research Foundation	33 current projects, 103 completed projects
The Diabetes Research & Wellness Foundation	88 projects, of which 41 in the period 2006-2013

[1] To feed the discussion on future research trends a list of H2020 projects is also reported.
[2] Research investment in diabetes was defined as “research into causation, occurrence, prevention, diagnosis, pathophysiology and treatment of diabetes mellitus and its long-term consequences". Four the purposes of this work two major ICD-10 categories for diabetes, namely Type I diabetes mellitus (T1DM) and Type II diabetes mellitus (T2DM), are identified.

Diabetes Ireland Research Alliance	7 projects from 2009 to 2014
Juvenile Diabetes Research Fund	313 in major EU countries
Association Française des Diabétiques	16 projects from 2010 to 2013

The list of projects funded by the European Commission under the Framework Programmes Sixth and Seventh (and Horizon 2020) was drawn from a key word search on the CORDIS (Community Research and Development Information Service) platform.
To retrieve EC-funded projects we originally conducted a search in the CORDIS database using a search string comprising the keywords "diabetes mellitus" (given the relevant ICDs identified, see footnote in previous page) produced 117 results, of which 64 belonging to the relevant time period. We noticed however that some big research projects (e.g. MAPPING_NCD itself) were left out so we conducted the same research using the more general keyword "diabetes", with a filter for FP7 and FP6 programmes. The results show 446 projects relevant to the time period 2006-2013. Of these, 327 were FP7 projects, while 119 were funded through the FP6 program. A further selection was carried out, searching the 446 by keywords in the fields "title" or "content" ("diabetes", "diabetic", "insulin") to single out projects specifically related to diabetes (rather than for instance chronic diseases in general): 139 projects were selected of which 36 F6 and 103 FP7 (Annex 2). A search conducted in the database for Horizon 2020[3], using the same keywords found 52 relevant projects (Annex 3).

1.1.3 Definition of a purposive sample

From the lists of projects reported above (cfr. Annex 1,2,3), a set of particularly relevant project is presented in the tables below, organized by ICD. Projects were selected on the basis of total funding received (>1 million Euros), where such selection was possible. This serves the purpose of identifying the key areas where RFOs have been willing to invest large amounts of money.
With the exception of EC programs, RFOs did not report funding amounts by project (at least not in an organized and searchable fashion), therefore such projects could not be classified in the tables below; their content however is presented in a descriptive manner in the following paragraphs. Horizon 2020 projects were also considered to show current or foreseeable future relevant research conducted in the field. The details of the sample of selected projects are reported in Table 3 and Table 4.

[3] Accessible from https://open-data.europa.eu/en/data/dataset/cordis-eu-research-projects-under-horizon-2020-2014-2020

1.2 Results of European projects receiving funding

The following tables report details of the activities funded in ICD E10 and E11 where amounts provided to the research were greater than one million Euros. Figure 1 and Figure 2 provide some descriptive information on the sample.

Table 3 Research Programs for *Type I diabetes mellitus* (E10) 2006-2013, selected projects

Funder	Recipient	Level of Collaboration	Partner Countries	Project Title	Research Area (focus)	Project (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding[4]
EU (FP6) RCN 75288	HANNOVER MEDICAL SCHOOL	European	UK, Italy, Belgium, Sweden, Germany, Denmark, Ireland, Finland, Netherlands, France	Coordination Action on the Aetiology, pathology and prediction of Type I diabetes in Europe	Aetiology, the causes and origins of the disease	2004-2008	Elucidation of the cellular and molecular mechanisms responsible for T1DM through	Detect the underlying causes of T1DM with the aim of identifying targets for prevention, diagnosis and treatment	EUR 1 000 000
EU (FP6) RCN 74396	CENTRE EUROPEEN D'ETUDES DU DIABETE	European	France, Germany, Portugal, Italy, Belgium	Development of a bioartificial pancreas for type I diabetes therapy	Development and evaluation of treatments and therapeutic interventions	2004-2006	Develop, improve and validate an efficient reliable bioartificial pancreas for human application	The BARP+ device demonstrated a promising approach for providing insulin-secreting islets in an encapsulated supportive environment	EUR 2 495 600
EU (FP7)	CENTRE EUROPEEN	European	UK, France,	A bioartificial pancreas to treat	Development	2013-2015	Bring the MAILPAN (MAcroencapsulation	Improve the bioartificial pancreas,	EUR 5 469 603

[4] For EU funded projects, the amount refers to EU contribution

RCN 106271	D'ETUDE DU DIABETE		Belgium	Type I diabetes: optimization of cell survival and function in preclinical and clinical phases	and evaluation of treatments and therapeutic interventions		of PANcreatic Islets) prototype to the pre-clinical and clinical phases necessary to the ensuing commercialization	eg. to enhance cells survival inside the device, to further lower the rejection risk, to test the prototype in primates, and to validate its further use in humans.	
EU (FP7) RCN 105252	CARDIFF UNIVERSITY	International	France, UK, Israel, Netherlands, Sweden	Beta cell preservation via antigen-specific immunotherapy in Type I Diabetes: Enhanced Epidermal Antigen Delivery Systems	Development and evaluation of treatments and therapeutic interventions	2012-2016	Development of novel approaches to deliver effective Antigen specific immunotherapy (ASI)	The Enhanced Epidermal – Antigen Specific Immunotherapy (EE-ASI) system represents an innovative approach to ASI	EUR 5 983 871
EU (FP7) RCN 188654	UNIVERSITE DE GENEVE	National	Switzerland	Metabolic actions of brain leptin receptors signaling in Type I diabetes	Development and evaluation of treatments and therapeutic interventions	2014-2019	Identifying the critical cellular and molecular components underlying the beneficial effects of leptin in the context of insulin deficiency	Manipulation of these components has the potential to improve life-expectancy and -quality of the millions affected by insulin deficiency (e.g.: T1DM and also some late-stage Type II diabetics).	EUR 1 999 500
EU (FP7)	UNIVERSITE	European	Belgium, UK, Italy,	Macroencapsulated	Aetiolog	2013-2016	Evaluate in vitro the	A pilot study for safety	EUR 5 037 148

RCN 108766	CATHOLIQUE DE LOUVAIN		Hungary	Porcine Pancreatic Islets to cure Diabetes Mellitus Type I/2	y, the causes and origins of the disease		effect of GLP1 transgene expression in pig islets after hyperglycaemic challenge	will be achived whether all the prerequisite are achieved within the third year."	
EU (FP7) RCN 105311	ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS	European	France, UK, Switzerland, Germany	Ultra-low dose of IL-2 for the treatment of recently diagnosed Type I diabetes	Development and evaluation of treatments and therapeutic interventions	2012-2016	a double-blind randomised placebo-controlled age-stratified (7-35 year) multicentre European trial assessing efficacy and safety of uld-IL2 (5x10e5 IU/m2/day) in 200 recently-diagnosed T1D patient	If successful, this trial will have profound impacts for the management of patients with recently-diagnosed T1D, their families and EU economy. It will be a milestone towards preventing T1D in people at risk of this increasingly common childhood disease	EUR 5 900 000
EU (FP7) RCN 92853	KATHOLIEKE UNIVERSITEIT LEUVEN	European	Belgium, Germany, UK, Portugal, Italy, Netherlands, Denmark	Novel immunotherapies for Type I diabetes	Development and evaluation of treatments and therapeutic interventions	2009-2015	Pioneer the concept of tailored interventions with minimal immune system interference in new onset T1DM, leading to beta-cell protection and restoration, based on a solid understanding of the disease pathogenesis	Developing novel technologies allowing translation of basic research results towards clinical applications	EUR 10 920 800

EU (FP7) RCN 100711	DEUTSCHES FORSCHUNGS ZENTRUM FUER KUENSTLICHE INTELLIGENZ GMBH	European	Germany, Switzerland, Netherlands, UK, France, Poland, Slovenia	Continuous Multi-parametric and Multi-layered analysis Of Diabetes Type I & 2	Disease/ patient manage ment	2011-2014	exploit multi-parametric data to provide healthcare workers and patients, with clinical indicators for the treatment of diabetes Type I and 2.	curb diabetes hospitalisation costs and to curb the percentage of diabetic patients experiencing cardiovascular complications	EUR 4 051 000

Table 4 Research Programs for Type II diabetes mellitus (E11) 2006-2013 and H2020

Funder	Recipient Type	Level of Collaboration	Partner Countries	Project Title	Research Area (focus)	Project (years)	Summary Description (Project aim)	Achieved/ Anticipated Outcomes	Amount of Funding
EU (FP7) RCN 108766	UNIVERSIT E CATHOLIQ UE DE LOUVAIN	European	Belgium, UK, Italy, Hungary	Macroencapsulated Porcine Pancreatic Islets to cure Diabetes Mellitus Type I/2	Aetiology, the causes and origins of the disease	2013-2016	Evaluate in vitro the effect of GLP1 transgene expression in pig islets after hyperglycaemic challenge	A pilot study for safety will be achived whether all the prerequisite are achieved within the third year."	EUR 5 037 148
EU (FP7) RCN 100711	DEUTSCHES FORSCHUNG ZENTRUM FUER KUENSTLICH INTELLIGENZ GMBH	European	Germany, Switzerland, Netherlands, UK, France, Poland, Slovenia	Continuous Multi-parametric and Multi-layered analysis Of Diabetes Type I & 2	Disease/ patient managemen t	2011-2014	Y12 system will exploit multi-parametric data to provide healthcare workers and patients, with clinical indicators for the treatment of diabetes Type I and	to curb diabetes hospitalisation costs and to curb the percentage of diabetic patients experiencing cardiovascular complications	EUR 4 051 000

							2.		
EU (FP6) RCN 84940	MEDICAL RESEARCH COUNCIL	International	UK, Netherlands, Finland, France, Italy, Denmark, Sweden, Germany, Spain, India	An examination of the interaction of genetic and lifestyle factors on the incidence of Type II diabetes	Aetiology, the causes and origins of the disease	2006-2011	Observational and trial data to investigate interaction between genetic and lifestyle behaviour factors and explore the implications of these discoveries for preventive action	Describe the association of dietary and nutritional factors with Type II diabetes, and describe the association of physical activity with future risk and the ways that these factors interact with obesity	EUR 10 000 000
EU (FP6) RCN 78694	GÖTEBORG UNIVERSITY	European	Sweden, Denmark, UK, Spain, Germany, France, Hungary, Ireland, Italy	Novel molecular drug targets for obesity and Type II diabetes	Development and evaluation of treatments and therapeutic interventions	2004-2008	Seek novel drug targets to combat obesity and Type II diabetes	Demonstrated the role of the hypothalamus in the control of appetite and energy balance, highlighted the importance of discrete nerve cell populations, specific genes and specific mechanisms regulating those genes. Novel targets emerged from this study and led to the development of new drugs for treatment of these diseases.	EUR 11 601 083
EU (FP6) RCN 74073	GOTEBORG UNIVERSIT	European	Sweden, Finland, Italy, UK, Denmark, Germany, Spain,	European network on functional genomics of Type II	Aetiology, the causes and origins	2004-2009	Unravel the complex pathogenesis of Type II diabetes and the	Novel reagents, antibodies and protocols were	EUR 8 000 000

	Y		France	diabetes (Eugene2)	of the disease		specific role of the skeletal muscle, fat and the liver	developed and made accessible to the network partners. spread, application and validation of these novel reagents by Eugene2 experts made them attractive to biotech companies in Europe.	
EU (FP6) RCN 84717	MEDIZINISCHE HOCHSCHULE HANNOVER	International	Germany, France, Italy, Spain, Switzerland, Sweden, Belgium, UK, Israel	Functional genomics of pancreatic beta cells and of tissues involved in control of the endocrine pancreas for prevention and treatment of Type II diabetes	Prevention of disease and conditions	2006-2010	Understanding of the factors influencing the maintenance (and loss) of normal beta cell functional capacity	Develop a strong understanding of beta cell molecular physiology and pathophysiology to pave the way for improved health in Europe	EUR 9 150 000
EU (FP6) RCN 81753	DEUTSCHES KREBSFORSCHUNGSZENTRUM	National	Germany	Control of insulin sensitivity through transcriptional co-factors: implications for type II diabetes therapy	Development and evaluation of treatments and therapeutic interventions	2005-2009	identify RIP140 target gene networks in muscle and and to establish nuclear RIP140-interacting proteins as novel targets for therapeutic synthetic compounds	Identified novel transcriptional co-factor complexes as integrative sites for dietary, inflammatory, and hormonal pathways, thereby impacting both pro-inflammatory and metabolic programs in critical target tissues and determining systemic energy	EUR 1 756 245

								homeostasis.	
EU (FP7) RCN 101811	Steno Diabetes Center A/S	International	Denmark, Ireland, Spain, Finland, USA, UK	Mechanisms of prevention of Type II diabetes by lifestyle intervention in subjects with pre-diabetes or at high-risk for progression	Prevention of disease and conditions	2012-2015	DEXLIFE will identify novel diagnostic and predictive biomarkers (i) to detect the progression toward diabetes in high risk individuals and (ii) that are responsive to lifestyle interventions known to be effective in diabetes prevention.	strong translational focus to this proposal, by setting the main intervention in the real-life context of a major health insurance system	EUR 5 486 631
EU (FP7) RCN 102211	SERVICIO MADRILEÑO DE SALUD	European	Spain, UK, France, Italy, Germany, Belgium, Czech Republic	A RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFECTIVENESS OF A MULTI-MODAL INTERVENTION IN OLDER PEOPLE WITH TYPE II DIABETES ON FRAILTY AND QUALITY OF LIFE: THE MID-FRAIL STUDY	Disease/ patient management	2012-2016	Phase IIb open randomized clinical trial to evaluate the effectiveness of a multi-modal intervention (optimizing medical management, resistance-based exercise program and educational/nutritional intervention) in 1,704 frail or pre-frail subjects ≥ 70 years with T2D to prevent functional decline and maintain or improve quality of life and its associated	to demonstrate a reduction of 20% in that risk, which will mean an annual prevention of around 700,000 incident cases of some disability in old people, with a major impact on global quality of life and financial costs.	EUR 5 975 821

							costs.		
EU (FP7) RCN 110407	UNIVERSITE CATHOLIQUE DE LOUVAIN	National	Belgium	Gut microbiota, innate immunity and endocannabinoid system interactions link metabolic inflammation with the hallmarks of obesity and Type II diabetes	Aetiology, the causes and origins of the disease	2013-2018	elucidate what could be one of the most fundamental processes shared by different key hallmarks of obesity and related diseases.	provide different perspectives about disease pathogenesis and knowledge-based evidence of new therapeutic options for obesity and associated metabolic disorders in the future	EUR 1 494 640
EU (FP7) RCN 105825	IMPERIAL COLLEGE OF SCIENCE, TECHNOLOGY AND MEDICINE	European	UK, France	Genetics and epigenetics of Type II Diabetes physiology	Aetiology, the causes and origins of the disease	2012-2017	identify novel genetic causes of familial T2D and identify DNA methylation variation associated with T2D	identify genome-wide methylation patterns that are cell and tissue-specific and disease-specific for five main tissues important in T2D	EUR 2 476 324,99
EU (FP7) RCN 101813	Steno Diabetes Center A/S	European	Denmark, Germany, Netherlands, UK, Italy, Checz Republic, Spain, France, Switzerland, Macedonia	Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention of early diabetic nephropathy In Type II diabetic patients with normoalbuminuria	Development and evaluation of treatments and therapeutic interventions	2012-2017	to assess the potential of this technology to identify normoalbuminuric patients at risk and to target therapy with an aldosterone receptor antagonist (spironolactone) as add-on to recommended therapy including angiotensin	first biomarker-directed therapy trial for primary prevention of diabetic kidney disease	EUR 5 980 500

							converting enzyme (ACE) inhibition or angiotensin II receptor blockers (ARBs)		
EU (FP7) RCN 98878	LUNDS UNIVERSITET	National	Sweden	General and targeted approaches to unravel the molecular causes of Type II diabetes	Aetiology, the causes and origins of the disease	2011-2016	explore the molecular mechanisms by which TCF7L2, the strongest T2D gene, causes T2D	these general and targeted approaches are expected not only to provide new insights into the causes of T2D but also contribute with vital information for development of new treatments for T2D	EUR 2 499 796
EU (FP7) RCN 89155	KAROLINSKA INSTITUTET	National	Sweden	Discovery of Type II Diabetes Targets	Aetiology, the causes and origins of the disease	2009-2013	target identification platforms including microarray, proteomics and bioinformatics to identify dysregulated genes in normal glucose tolerant versus T2DM subjects or genetically modified model systems; functional genomics to assign a physiological role of the identified targets in Aim 1 using cellular and whole-	identification and biological validation of the metabolic pathways and key regulatory genes that control insulin sensitivity in Type II diabetes mellitus (T2DM)	EUR 2 500 000

							body approaches		
EU (FP7) RCN 87463	EIDGENOESSISCHE TECHNISCHE HOCHSCHULE ZUERICH	National	Switzerland	Adipocyte Differentiation and Metabolic Functions in Obesity and Type II Diabetes	Aetiology, the causes and origins of the disease	2008-2013	facilitate development of novel therapeutic approaches for the treatment of obesity and associated metabolic disorders	elucidate molecular mechanisms underlying the altered adipocyte differentiation and maturation in different models of obesity associated metabolic disorders	EUR 1 607 105
EU (FP7) RCN 108366	CONSIGLIO NAZIONALE DELLE RICERCHE	European	Italy, Germany, Netherlands, UK	Multiscale Immune System Simulator for the onset of Type II Diabetes integrating genetic, metabolic and nutritional data	Prevention of disease and conditions	2013-2016	developing and validating an integrated, multilevel patient-specific model for the simulation and prediction of metabolic and inflammatory processes in the onset and progress of the Type II diabetes (T2D)	nderstand the complex mechanisms underpinning the onset of T2D and to identify early diagnostic parameters and related inflammatory indicators, by following a personalized medicine approach.	EUR 2 310 000
EU H2020 RCN 194100	IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE	International	UK, India, Sri Lanka, Netherlands, Finland, Pakistan	Family-based intervention to improve healthy lifestyle and prevent Type II Diabetes amongst South Asians with central obesity and prediabetes	Prevention of disease and conditions	2015-2020	determine whether screening by waist circumference and/or HbA1c, coupled with intervention by family-based lifestyle modification, is an efficient, effective	complete a cluster-randomised clinical trial at 120 locations across India, Pakistan, Sri Lanka and the UK	EUR 3 614 084

							and equitable strategy for prevention of T2D in South Asians		
EU H2020 RCN 194091	KAROLINSKA INSTITUTET	International	Sweden, Belgium, Finland, Uganda, South Africa	A people-centred approach through Self-Management and Reciprocal learning for the prevention and management of Type-2-Diabetes	Disease/ patient management	2015-2019	empower patients, their families and communities through the self-management approach	strengthen capacity for T2DM care including prevention in high-risk population, through proven strategies like task shifting to community health workers, and expanding care networks through community-based peer support groups.	EUR 3 344 979

Figure 1 Number of projects by disease (n=27)

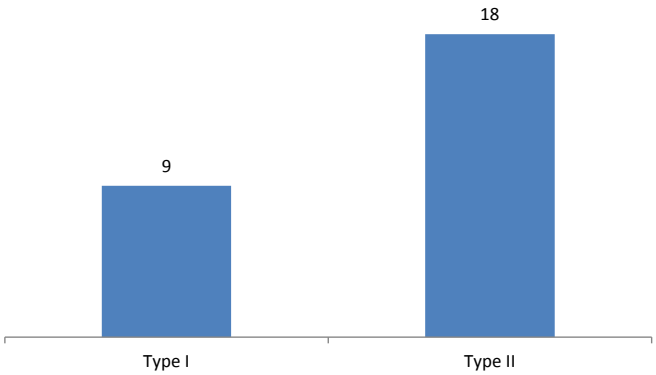
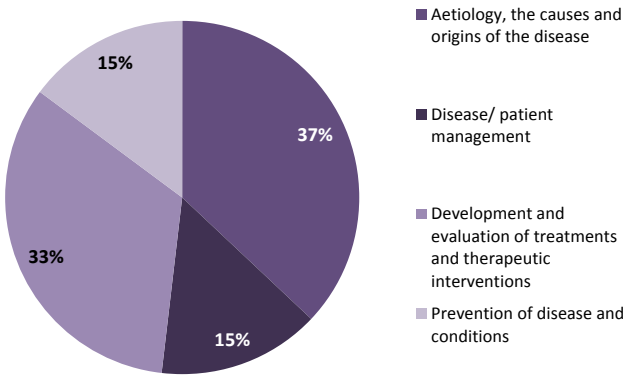


Figure 2 Research Area Focus (n=27)



1.2.1 Type I diabetes

Table 3 includes 9 projects, of which 7 involve European level cooperation, one is a national project and one is run on a global scale. Two projects deal with research on aetiology and origin of the disease, 6 projects study the development of new drugs or therapies and 1 project is related to disease/patient management. On average the duration of projects is 3.5 years.

1.2.2 Type II diabetes

Table 4 includes 18 projects[5], of which 8 are conducted with collaboration of different European countries, five projects (including both H2020 projects) and the remaining are conducted on a global scale. Eight projects deal with research on aetiology and origin of the disease, 3 studies refer to the development and evaluation of treatments and therapeutic interventions, 4 projects are conducted on disease prevention and three are related to disease/patient management. On average the duration of projects is 4 years.

[5] Including two projects funded under H2020

1.3 Discussion and conclusion

A vast range of European projects, each receiving over one million Euros of funding, target diabetes and its complications, with a major focus on aetiology and origin of the disease or development and evaluation of new therapeutic interventions. Fewer projects relate to patient or disease management. Four projects aim at improving prevention strategies for Type II diabetes and, unsurprisingly, no projects among those presented in Table 3 and Table 4 target the issue of prevention of Type I diabetes. However, the development of novel prevention strategies for Type I diabetes was identified as a priority of research in diabetes (DIAMAP project, 2010). The considerable improvement in understanding the genetic basis of this pathology needs to be complemented with a more advanced understanding of the environmental factors that play a key role in the rise of the disease. The rapid increase in the incidence of Type I diabetes in genetically stable populations implies an important role for environmental factors (Knip, 2005). Some national RFOs have funded narrower projects in this field. For instance, the Dutch Diabetes Research Foundation has funded a study on "Prevention and treatment of ketoacidosis in Type I diabetes via the inhibition of hepatic beta-oxydation" (see Annex 1). The Juvenile Diabetes Research Fund promoted a project on Type I prevention by induction of dermal tolerogenic dendritic cells and another study on Prevention of Type I diabetes by Treg vaccination with an insulin mimetope.

Preventive efforts on Type II diabetes currently tend to focus on high-risk patients. An example is the EU (FP7) project RCN 101811 (2012-2015), led by the Steno Diabetes Center, which aims at identifying novel diagnostic and predictive biomarkers (i) to detect the progression toward diabetes in high- risk individuals and (ii) that are responsive to lifestyle interventions known to be effective in diabetes prevention. The project has a strong translational focus, by setting the main intervention in the real-life context of a major health insurance system. While individual approaches in specific sub-groups are effective, future research should aim at tackling the problem at population-level (DIAMAP project, 2010; Rosella, 2011).

Another area that should be further expanded is the study of preventive and treatment measures for complications, given the impact of complications (such as vascular complications) on the social and economic burden for patients and society (Van Dieren, 2010). Randomised controlled trials testing therapies for people with Type II diabetes have demonstrated that many of the complications of diabetes are preventable (DIAMAP project 2010). Most recent research focuses on the role of diabetes in determining micro- and macrovascular disease (examples of these studies are funded by the Dutch Diabetes Research Foundation, the Association Française des Diabétiques and the Juvenile Diabetes Research Fund) while its role in other health outcomes (such as cancer or cognitive function) is less studied. Diabetes UK has for instance funded a £82,700 PhD Studentship on renal and vision complications in diabetes.

Biomarkers that help predicting individual risk to develop Type II diabetes are also under study. Among the organizations promoting this research topic are, for instance, the Dutch Diabetes Research Foundation[6], the Juvenile Diabetes Research Fund[7], and The Diabetes Research & Wellness

[6] With projects such as "Biomarkers for the Prediction and Early Diagnosis of Diabetes and Diabetes-related Cardiovascular Complications (PREDICCt)"

[7] With projects such as "Developing and optimizing pHLA multimers as a biomarker for T1D

Foundation[8]. Also the European Commission has funded projects aimed at identifying novel diagnostic and predictive biomarkers (eg. EU FP7 project DEXLIFE on diabetes Type II). However, to this end there is still need to address the general lack of bio-banks of accessible human tissues and samples, which are of paramount importance for research (Bueno de Mesquita, 2015). This has also been observed by stakeholders during the interviews (see section 3).

Bio-banks also provide opportunities to include geographical and environmental information in diabetes research (Bellazzi, 2013). This would for instance enhance the development of lifestyle intervention strategies to prevent Type II diabetes and obesity based on specific genetic traits to enhance efficacy of this approaches. A better integration of activities and collaboration between European institutions is needed in this regard, with the academia and the industry, particularly the food & beverage sector, not only in terms of research funding but also in terms of policy/regulatory actions. As expressed by dr. Andrew JM Boulton, President of the European Association for the Study of Diabetes, this means for instance more attention to advertising of fast foods and sponsorship of sports events (Collins, 2014).

A considerable bulk of research has been focusing on the study of treatment for diabetes. One issue of consideration has been the development of a better understanding of molecular mechanisms underlying beta cell function, survival and regeneration, and how they are impacted by the fundamental disease process. Several EU funded projects in the period considered are focusing on topic as well as projects promoted by RFOs in different countries (eg. Diabetes UK, Dutch Diabetes Research Foundation, The Diabetes Research & Wellness Foundation and the Juvenile Diabetes Research Fund). A major challenge in this area is the comprehension of tissue-to-tissue communication in diabetes pathogenesis, particularly expanding knowledge beyond the classical tissues currently recognized as relevant in glucose-control (DIAMAP project, 2010).

Both the EU and national-level RFOs have funded several studies addressing the control of energy balance and weight regulation, with an essential focus on the translation into therapy to benefit the person with diabetes. For instance, the Horizon2020 program has funded a project on the delineation of a brain circuit regulating energy expenditure to impact body weight (RCN 195912).

When comparing current funded projects to strategies set in the past (EUDWG, 2010), some areas of research seem to have been more explored, while for what concerns other crucial issues there is still need for improvement both in research advancement and in coordination among stakeholders. For instance, it still emerges the need for better coordination of research and access to biological samples, registry data and research findings across Europe to avoid duplication and enhance effective use of funding. Communication also remains a critical issue with respect both to better dissemination strategies of advancements in research and effective engagement with diabetic patients and public opinion in activities aimed at raising awareness. Many of these themes emerging from the analysis of past and current research projects are common with the results of the informants interview data analysis presented in Section 3.

Juvenile Diabetes Research Fund", ": Validation of Novel and Candidate Biomarkers for Diabetic Kidney Disease in Large Cohorts of people with Type I Diabetes", "Biomarkers of heterogeneity: an integrated approach to clinical and metabolic phenotyping of individuals with established Type I diabetes"

[8] With projects such as "To use Mendelian randomisation to understanding the causal relationship between circulating biomarkers and Type II Diabetes in the UK Bio-bank".

2 Private Sector Investment in Diabetes

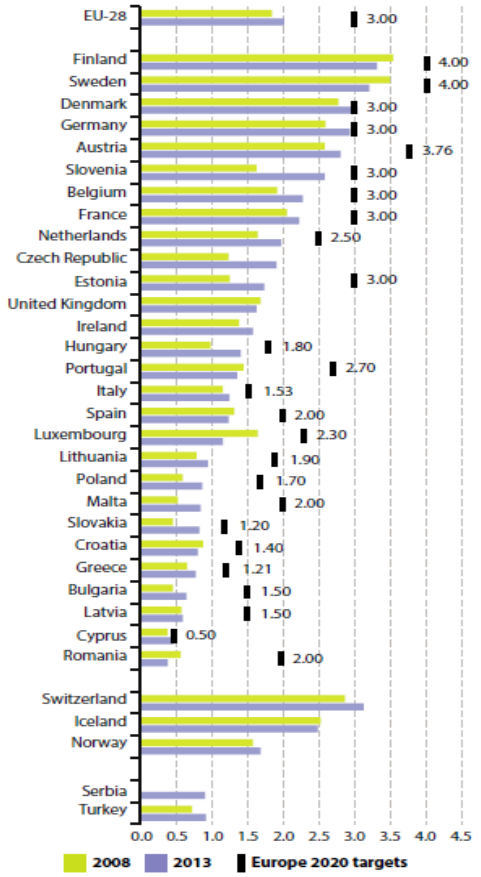
According to the Global Diabetes Plan 2011-2021, 4.6 million deaths annually are attributable to diabetes, which ranks in the top 10 causes of disability worldwide. After the UN High-Level Summit on Non-communicable Diseases (NCDs) in 2011, diabetes, together with the other NCDs, registered an increase in importance in the health agenda (IDF, 2011). Consequently, policy makers started to become more aware of the fact that investing in diabetes prevention and care can improve the quality of life of people affected, hinder diabetes-related complications and save lives.

Investments in NCDs research funding originate from a variety of sources: national governments, regional organizations, charities, non-governmental organizations and supranational organizations. In this section, we provide a comprehensive overview of private sector investment in NCDs research, considering both Pharmaceutical and Medical Device sectors, with a particular focus on diabetes R&D investment.

2.1.1 Background: Private Sector Investment in Research and Development

R&D investment is the milestone for the creation of new products and services that stimulate growth, improve welfare and create a knowledge-driven economy. According to the "Europe 2020 indicators - research and development", the financial crisis of 2008-2009 and its negative impact on GDP growth, accompanied by an increase in government spending on R&D, led to an increase in R&D intensity (i.e. R&D expenditure as a percentage of GDP) in most EU Member States. In order to hinder economic crisis, in fact, some EU countries, supported by the European Commission, increased public R&D expenditure to boost economic growth and encourage private R&D investment, which constitutes the largest source of R&D expenditure in Europe (63.8% of total R&D investments in 2013) (Eurostat, s.d.).
Figure 3 shows R&D intensity by EU country for the years 2008 and 2013. It is possible to observe that, despite the crisis, most European states experienced an increase in R&D commitment between 2008 and 2013.

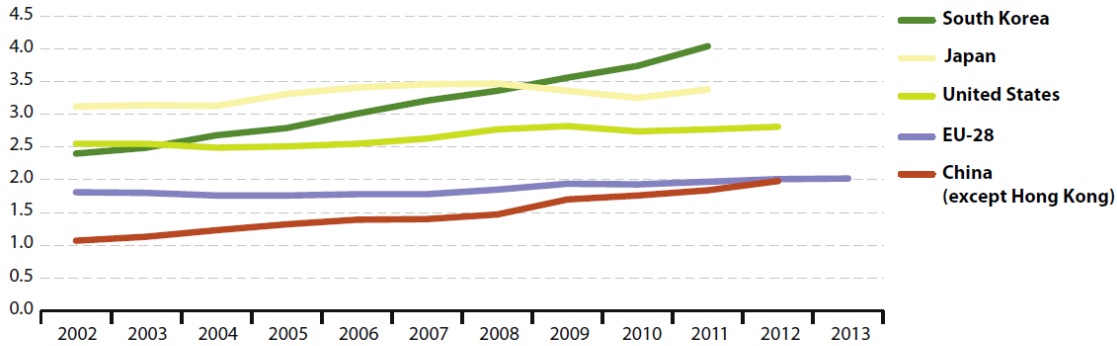
Figure 3 Proportion of GDP dedicated to R&D by EU country, 2008 and 2013



Source: Europe 2020 indicators - research and development

Despite the increased efforts of some EU Members States, the EU is still lagging behind other jurisdictions such as the United States, Japan and South Korea in terms of private sector R&D investments, as outlined in Figure 4. In fact, while only 62 % of EU R&D intensity originated from the business enterprise sector in 2010, the United States, China, South Korea and Japan registered between 68.5% and 76.6% of R&D intensity from this sector (Eurostat, s.d.).

Figure 4 International comparison of R&D intensity, 2002-2013

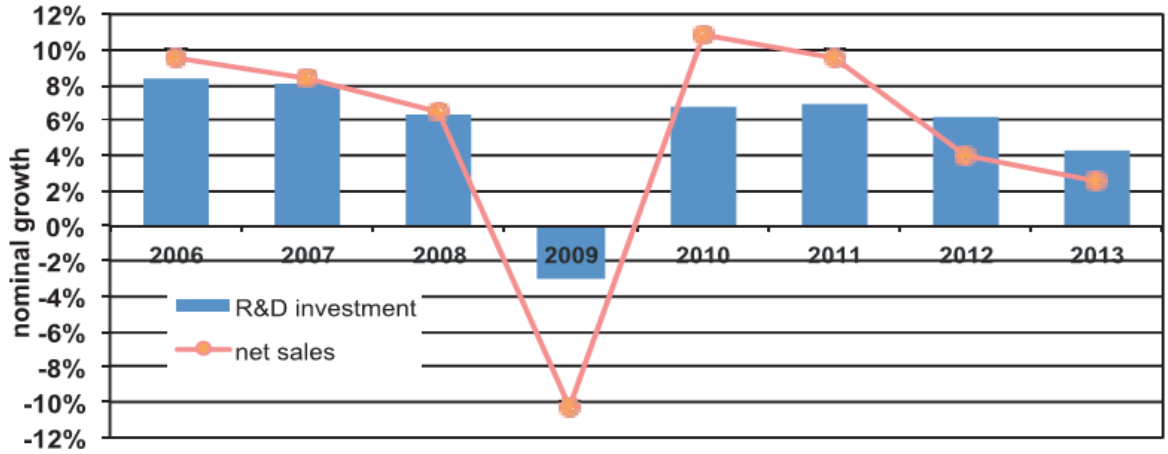


(*) EU-28 data for 2002–03 and 2013 are estimates; break in series for KR (2007), JP (2008) and CN (2009); US data for 2012 are provisional; definition differs for KR (2002–06) and US (whole time series).

Source: Europe 2020 indicators - research and development

The "2014 EU Industrial R&D Investment Scoreboard" (the Scoreboard), published by the European Commission, provides economic and financial data of the world's top 2500 private companies for R&D expenditures, which account for 90% of the world's industrial investment in research and development. The sample contains 633 EU based companies and 1867 companies located elsewhere. Across the various sectors of industry, these top 2500 R&D private investors recorded a quick rebound in sales and R&D investments after the financial crisis of 2009 (Figure 5). Sales and R&D expenditures have been continuously growing in the following years, although at a lower rate, and in 2013 private companies' increase in R&D commitment (+4.9% on average) was higher than the growth of net sales (+2.8%). However, the EU companies of the sample showed an annual R&D investment growth rate of 2.6%, substantially below the world average.

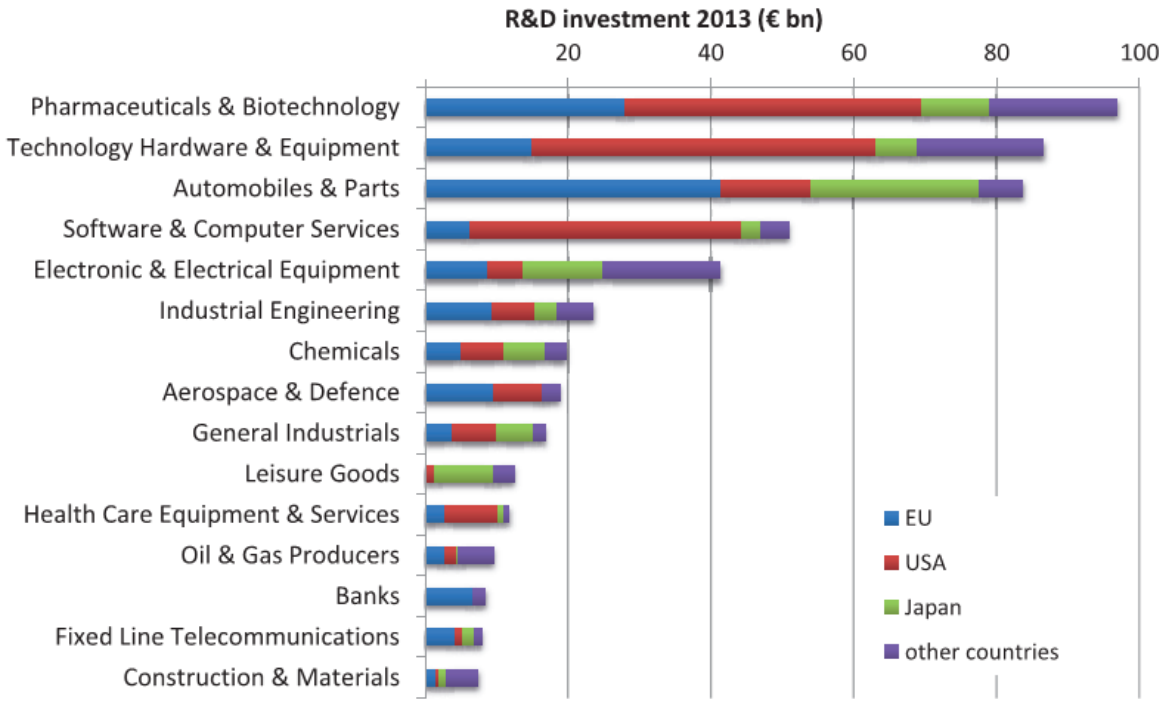
Figure 5 R&D investment and net sales growth, 2006-2013



Source: The 2014 EU Industrial R&D Investment Scoreboard, European Commission, JRC/DG RTD.

Figure 6 displays R&D trends among the 2014 top R&D investors aggregated by industrial sectors, showing the relative R&D share by main world region. The Pharmaceuticals & Biotechnology sector includes companies specialized on pharmaceuticals, medical devices, chemistry and biotechnologies. This sector occupies the first position in the R&D ranking, and its share of total R&D investment amounts to 18%. It is interesting to underline that the growing R&D expenditure is driven especially by biotechnology industry, which registered an increase of 22.3% in research investments, while traditional pharmaceutical companies decreased R&D expenditures by 1.8% with respect to 2012 (European Commission, 2014b). The Figure also shows that the leading world region in Pharmaceuticals & Biotechnology R&D investments are the USA, immediately followed by Europe. As regards the Pharmaceuticals sub-sector, the EU and the US have similar amounts of R&D investment and intensity, while in the Biotechnology sub-sector the US dominates the EU in number of companies (5 times more numerous), R&D investment (10 times larger) and larger average R&D intensity per company (European Commission, 2014b).

Figure 6 R&D ranking of industrial sector and share of main world regions in 2013



Source: The 2014 EU Industrial R&D Investment Scoreboard, European Commission, JRC/DG RTD.

Although R&D investment in the pharmaceutical industry has increased substantially in absolute terms, R&D productivity has dropped as witnessed by the lack of a corresponding increase in the number of new drugs being approved, mainly due to the increased costs associated with the development of new medicines (European Commission, 2014a). The average R&D cost per new chemical entity brought to the market is estimated to be $2,558 million[9], and this high cost is imputable to three reasons (Danzon et al; 2003):

- high input costs for both drug discovery and drug development;
- the time value of money: it takes 12-15 years to advance a drug from discovery through regulatory approval;
- high failure rates: it is estimated that only 1 out of 5000 compounds screened becomes an approved drug, and the cost of "dry holes" (i.e. compounds that fail) is included in the average cost per approved molecular entity.

In this context of declining R&D productivity but increasing total expenditures, it becomes important to investigate private sector R&D commitment in NCD research funding in order to provide an accurate analysis of how the business world is currently dealing with R&D challenge in the five therapeutic areas that are of interest for the MAPPING NCD project.

[9] http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014..pdf

2.1.2 Mapping the Private Sector Research Pipeline

As anticipated above, the main objective of this section is to map out private sector R&D investment in diabetes, considering both Pharmaceutical and Medical Device industries. Mapping R&D expenditures allows to quantify R&D composition and size across NCDs, providing a deeper understanding of where the research is mainly directed for each NCD and which are instead the underfunded areas. Both European and US based companies are considered in the sample of R&D investors; this comparison could show potential discrepancies in terms of R&D commitment between industries of the two world regions.

In order to map Pharmaceutical sector's R&D expenditures in diabetes, we considered the top European and US pharmaceutical companies in terms of R&D investment in 2014[10]. Financial data of each company were collected from freely available annual reports for the period 2011-2014. Figure 7 shows the top 20 pharmaceutical companies based in the US and Europe by investment in R&D. On top of industry's research investment in diabetes research, in the following paragraphs we also describe the research pipeline for the top pharmaceutical companies in terms of Molecules in Phase I, Phase II, Phase III, Submission and Approval. These data were collected from the 2011-2014 annual reports available at the companies' global websites.

Figure 7 Top 20 European and US pharmaceutical and biotechnology companies

Pharma Co. Rank	World Co. Rank	Company	Country	Total R&D Investment, 2013 (Mil EURO)
1	5	NOVARTIS	Switzerland	7173.5
2	6	ROCHE	Switzerland	7076.2
3	8	JOHNSON & JOHNSON	US	5933.6
4	12	MERCK US	US	5165.0
5	14	SANOFI-AVENTIS	France	4757.0
6	15	PFIZER	US	4750.2
7	21	GLAXOSMITHKLINE	UK	4154.3
8	23	ELI LILLY	US	4010.8
9	34	BAYER	Germany	3259.0
10	37	ASTRAZENECA	UK	3202.8
11	38	AMGEN	US	2960.6

[10] Sourced at 'The 2014 EU Industrial R&D Investment Scoreboard' available at: http://iri.jrc.ec.europa.eu/scoreboard14.html

12	39	BOEHRINGER INGELHEIM	Germany	2743.0
13	40	BRISTOL-MYERS SQUIBB	US	2705.4
14	52	ABBVIE	US	2059.3
15	65	CELGENE	US	1603.4
16	66	NOVO NORDISK	Denmark	1567.4
17	68	GILEAD SCIENCES	US	1537.1
18	70	MERCK DE	Germany	1504.3
19	95	ABBOTT LABORATORIES	US	1052.9
20	96	BIOGEN IDEC	US	1047.1

In order to map Medical Device industry R&D investments, we identified a list of top 15 medical device manufacturers worldwide ranked by total revenue[11] (updated to October 9, 2014) as detailed in Figure 8. Based on website interrogations and annual reports, general information and total R&D expenses for each MD company were collected for the period 2011 to 2014. Data on research pipelines of these companies were generally not available on annual reports therefore information were collected from a range of different sources (see Section 2.5).

Figure 8 Top 16 European and US medical device companies

MD Co. Rank	World Co. Rank[12]	Company	Country	Total revenues, 2014 (Bil USD)[13]	Total R&D Investment 2014 (Mil)[14]
1	34	JOHNSON & JOHNSON	US	28.7	8,494 (USD)
2	9	GENERAL ELECTRIC CO.	US	18.1	4,233 (USD)
3	249	MEDTRONIC INC	US	17.1	1,477 (USD)
4	54	SIEMENS AG	Germany	17.0	4,065 (EURO)
5	346	BAXTER INTERNATIONAL INC	US	16.4	1,421 (USD)
6	283	FRESENIUS MEDICAL CARE AG & CO. KGAA	Germany	15.2	369 (EURO)

[11] Sourced at http://www.mddionline.com/article/top-40-medical-device-companies
[12] http://www.forbes.com/global2000/list/#tab:overall
[13] http://www.mddionline.com/article/top-40-medical-device-companies
[14] Data were derived from an analysis of financial reports disclosed by the companies.

7	472	KONINKLIJKE PHILIPS NV	herlands	11.8	1,635 (EURO)
8	327	CARDINAL HEALTH INC.	US	11.0	NA
9	52	NOVARTIS AG (ALCON)	Switzerland	10.7	903 (USD)
10	349	COVIDIEN PLC[15] (MEDTRONIC)	Ireland	10.4	546 (USD)
11	719	STRYKER CORP.	US	9.3	614 (USD)
12	610	BECTON, DICKINSON AND CO.	US	8.3	550 (USD)
13	1047	BOSTON SCIENTIFIC CORP.	US	7.2	817 (USD)
14	732	ESSILOR INTERNATIONAL SA	France	7.2	188 (EURO)
15	753	ALLERGAN INC. (ACTAVIS)[16]	Ireland	6.7	1,085.9 (USD)
16	957	ST. JUDE MEDICAL INC.	US	5.6	692 (USD)

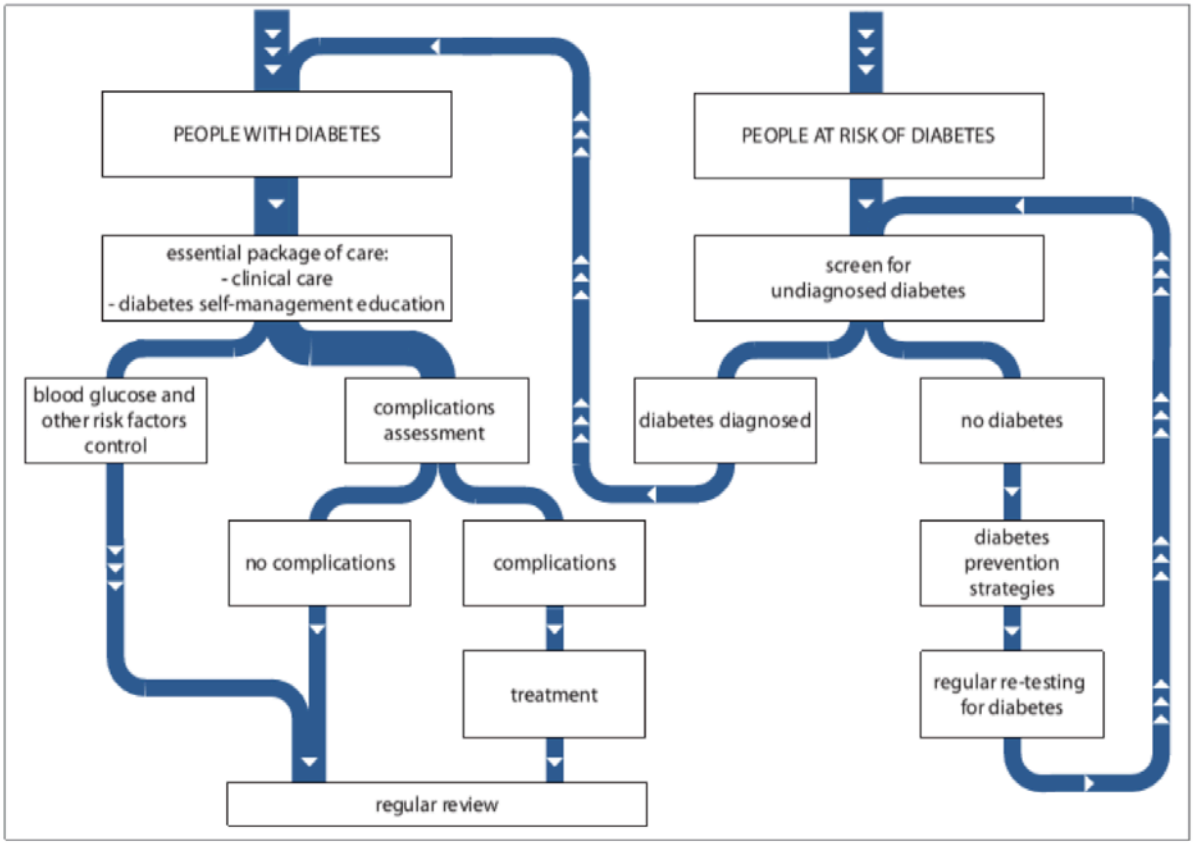
[15] Medtronic plc (NYSE: MDT) has completed the acquisition of Covidien plc (NYSE: COV) in 2015
[16] Actavis plc (NYSE: ACT) has completed the acquisition of Allergan, Inc. (NYSE: AGN) in 2015

2.2 Unmet Need for Diabetes

The growing global epidemic of diabetes registered in the past years, due to rapid increase in overweight and physical inactivity, made political and business leaders more aware of the magnitude and drawbacks of this non-communicable disease. It is estimated that 347 million people worldwide have diabetes and, according to the WHO, diabetes is predicted to become the 7th leading cause of death in the world by the year 2030[17].

Lack of awareness about diabetes, accompanied by inadequate access to health services and drugs, can lead to severe complications such as heart attack, stroke, visual impairment and blindness, kidney failure, lower limb amputation and erectile dysfunction (IDF, 2011). Appropriate interventions to control blood glucose levels are crucial in order to avoid those disabling and life-threatening complications that are largely preventable through relatively simple and cost effective treatments. Figure 9, extracted from the "Global Diabetes Plan 2011-2021" document, displays how effective diabetes management should work in order to prevent or delay its complications.

Figure 9 Diabetes management



Source: Global Diabetes Plan 2011-2021, IDF

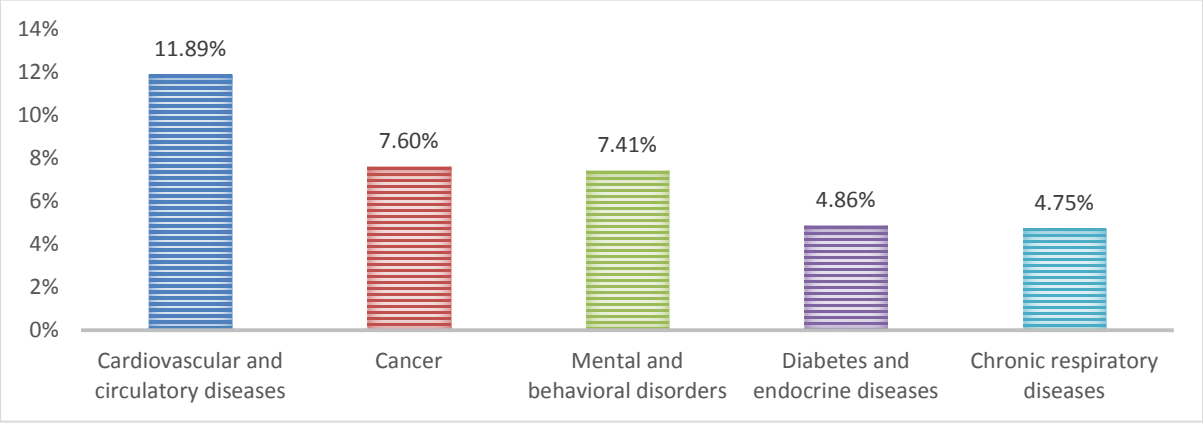
Despite the increasing awareness of the importance of diabetes care, there are still important disparities in the access to diabetes treatment and prevention. According to the National Diabetes

[17] http://www.who.int/features/factfiles/diabetes/facts/en/index1.html

Statistics Report 2014 published by the CDC (Centers for Disease Control and Prevention), in the United States about 27.8% of people with diabetes are undiagnosed and the percentage of undiagnosed people heavily varies with ethnicity, age and gender. It is worth underlining that in the US the indirect medical cost of diabetes, such as disability, productivity loss and premature death, amounted to $69 billion in 2012, a cost that could be significantly reduced through adequate access to diabetes interventions. As regards Europe, IDF (2014) highlighted significant inequalities in access to medicines and medical devices for diabetes care, which, in the long-term, can multiply the social and indirect costs of diabetes-related complications.

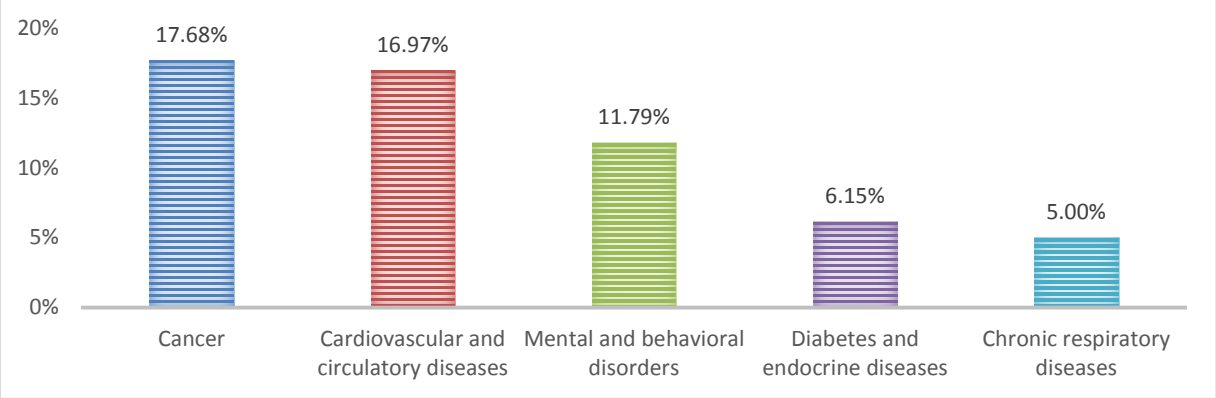
In order to provide an accurate picture of the levels of unmet need for NCDs and for diabetes in particular, we reported data on the percentage of DALYs (disability-adjusted life years) lost extracted from the Global Burden of Diseases, Injuries, and Risk Factors Study database. The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) is the largest and most comprehensive database on epidemiological levels and disease trends worldwide. The data, maintained by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington and collected and analyzed by a consortium of more than 1,000 researchers in over 100 countries, capture premature death and disability from more than 300 diseases and injuries in 188 countries. Information on death and disability are classified by age, sex and world area, from 1990 to the present, allowing comparisons over time, across age groups, and among populations.
As shown by Figure 10, Figure 11 and Figure 12 respectively, diabetes and endocrine diseases are the fourth leading cause of lost DALYs among NCDs at global, European and American level.

Figure 10 NCDs Global (2010): Percentage of Lost DALYs by Disease Category



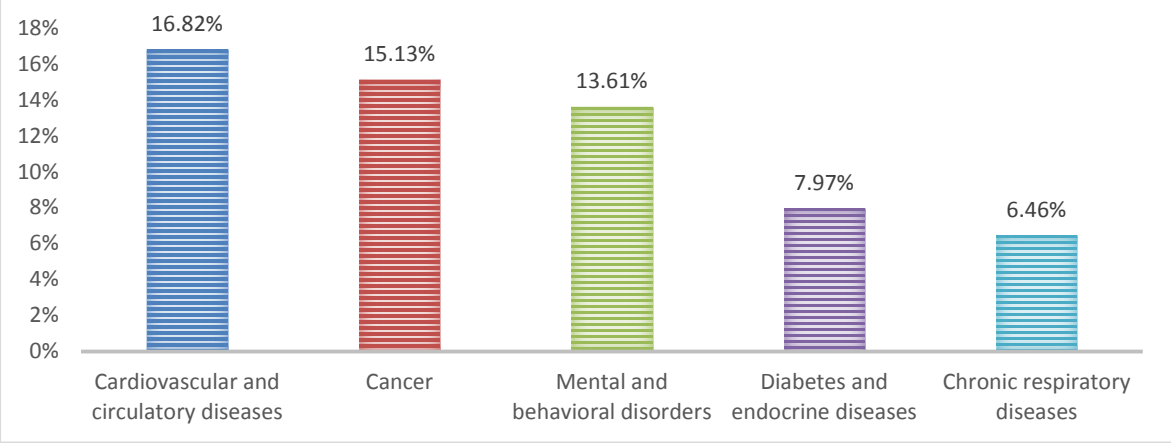
Source: http://vizhub.healthdata.org/gbd-compare/

Figure 11 NCDs in Europe (2010): Percentage of Lost DALYs by Disease Category



Source: http://vizhub.healthdata.org/gbd-compare/

Figure 12 NCDs in the United States (2010): Percentage of Lost DALYs by Disease Category

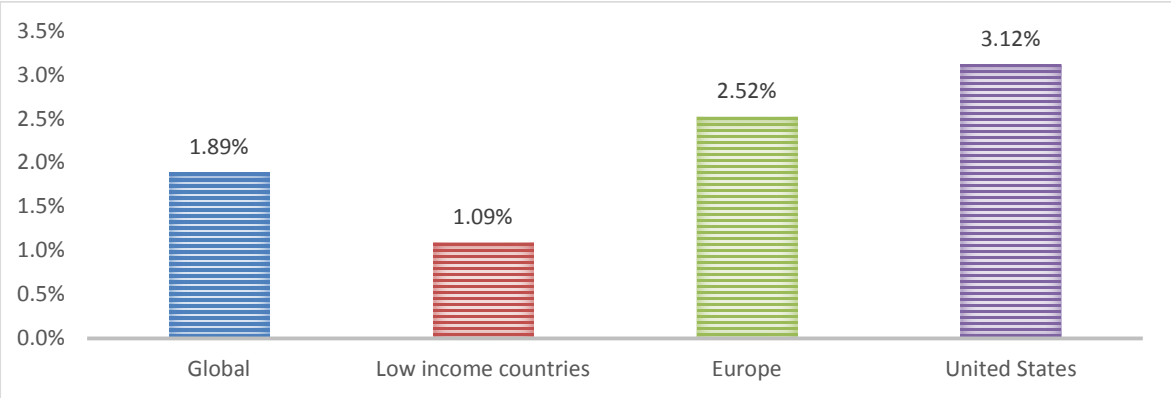


Source: http://vizhub.healthdata.org/gbd-compare/

Figure 13 shows the percentage of years lived with disability due to diabetes mellitus specifically. It is worth noting that diabetes' percentage of lost DALYs is higher for high income countries (Europe and the United States) than for low income countries (Figure 13). Prevalence of diabetes, ironically, is higher in those countries that experience positive economic developments, such as increased wealth, better healthcare and ageing populations, because people can afford richer diets and usually adopt a more sedentary lifestyle. Among high income countries, diabetes burden is more serious in the United States than in Europe.

After an introduction on the unmet needs related to NCD and diabetes in particular, we proceed to the investigation of how the private sector addresses diabetes related issues. In the next sections we present information on R&D investments and research pipeline of pharmaceutical and medical devices companies.

Figure 13 Percentage of Lost DALYs by World Area: Diabetes Mellitus



Source: http://vizhub.healthdata.org/gbd-compare/

2.3 Pharmaceutical Sector: Research Pipeline for Diabetes

Among the identified 20 top pharmaceutical companies, 9 firms have their headquarters in Europe and 11 in the United States.
According to the European Commission (2014a), the EU pharmaceutical sector was worth € 220 billion in 2012. In the same year, it was responsible for the employment of approximately 800,000 people, accounting for 1.8% of the total manufacturing workforce. EU pharmaceutical industry has one of the highest labour productivity, with a growth in labour productivity per person employed estimated in 3.6% over the period 2006-2011.
As regards the Unites States, they are the world's largest market for pharmaceuticals and, according to data from the National Science Foundation, the U.S. biopharmaceutical sector employs more than 810,000 workers and has the largest share of US business R&D.

Sixteen pharmaceutical companies among the 20 identified reported to have at least one diabetes relevant molecule under development. In the next subparagraphs we will examine in detail the R&D expenditures and research pipelines of firms investing in diabetes research.

2.3.1 NOVARTIS (EUR)

Novartis, a global healthcare company based in Switzerland, was created in 1996 through the merger of Ciba-Geigy and Sandoz, two companies founded in Basel between the 18th and 19th centuries. Novartis operates through five segments: Pharmaceuticals, Alcon, Sandoz, Vaccines and Diagnostics, and Consumer Health. The Pharmaceuticals segment develops patent-protected prescription medicines and is a leader in oncology, primary care and specialty medicines. The Alcon segment offers surgical, ophthalmic pharmaceuticals, and vision care products. The Sandoz segment provides generic pharmaceuticals and is a leader in biosimilars. The Vaccines and Diagnostics segment provides human vaccines and blood testing diagnostics. The Consumer Health segment provides over-the-counter medicines (OTC) and animal health treatments. Novartis employs more than 119,000 people worldwide and operates in approximately 180 countries.

Although R&D expenditures declined between 2011 and 2012, they recovered in the following years as shown by Figure 14**.** Moreover, the ratio of R&D investment to sales continued to increase over the entire period.

Figure 14 NOVARTIS (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	9,900	17.1	9,640	16.6	9,120	16.1	9,240	15.8
% Change	2.7		5.7		-1.3			

Currently, Novartis has only one relevant molecules in its pipeline, devoted to the treatment of type 2 diabetes mellitus (Figure 15).

Figure 15 NOVARTIS (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2012	LIK066	Type 2	II

2.3.2 ROCHE (EUR)

Roche was founded in 1898 by Fritz Hoffmann-La Roche and is headquartered in Basel, Switzerland. Roche is a leader in both pharmaceutical and diagnostic areas. Roche Pharmaceuticals is focused on oncology, immunology, infectious diseases, ophthalmology and neuroscience and it is the world's largest biotech company. Roche is also a leader in in-vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. The company has a workforce of over 8,500 people operating across more than 150 countries.

Since 2012, Roche's total investment in R&D has been increasing but the ratio of R&D investment on sales, after a slight decrease between 2011 and 2012, remained constant over the period 2012-2014 as can be seen in Figure 16.

Figure 16 ROCHE (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	**Amount (Mil USD)**	**% Sales**	**Amount (Mil USD)**	**% Sales**	**Amount (Mil USD)**	**% Sales**	**Amount (Mil USD)**	**% Sales**
	8,900	18.6	8,700	18.6	8,500	18.6	8,100	19.0
% Change	2.3		2.4		5.0			

Figure 17 shows the company's research pipelines for diabetes. For the period 2011-2014 two relevant molecules have been developed, one for the treatment of type 2 diabetes mellitus and the other for diabetic retinopathy, a complication of diabetes which can lead to severe vision loss or blindness.

Figure 17 ROCHE (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2013	GIP/GLP-1 dual	Type 2	I
2014	Lucentis (ranibizumab)	Diabetic retinopathy	Pendant

2.3.3 JOHNSON & JOHNSON (US)

Johnson & Johnson is a global company which manufactures pharmaceuticals, medical devices and consumer healthcare products. The company was founded by the three Johnson brothers in 1886 and is headquartered in New Brunswick, New Jersey. The Pharmaceutical segment of the company is dedicated to some key therapeutic areas such as oncology, immunology, neuroscience, infectious disease, cardiovascular and metabolic diseases. Johnson & Johnson has a workforce of approximately 126,500 people and operates through its affiliates in more than 60 countries.

Over the period 2011-2014, the company's R&D expenditures have been progressively increasing, reaching their peak in 2014 as displayed by Figure 18. The R&D ratio on sales remained quite stable over the same period, suggesting that the increase in R&D investment was probably driven by a general increase in sales.

Figure 18 JOHNSON & JOHNSON (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	8,494	11.4	8,183	11.5	7,665	11.4	7,548	11.6
% Change	3.8		6.8		1.6			

Johnson & Johnson developed two approved diabetes relevant molecules (Figure 19), one for the treatment of type 2 diabetes mellitus and the other for diabetic peripheral neuropathy, the most common complication of diabetes which, causing nerve damage, can lead to numbness, loss of sensation, and sometimes pain in feet, legs, or hands.

Figure 19 JOHNSON & JOHNSON (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2012	**NUCYNTA® ER** (tapentadol)	Diabetic peripheral neuropathy	Approved
2013	**INVOKANA®** (canagliflozin)	Type 2	Approved

2.3.4 MERCK US (US)

Merck US is an American pharmaceutical company headquartered in Kenilworth, New Jersey. The company was created in 1891 as the United States subsidiary of the German company Merck, founded in 1668 at Darmstadt, Germany. Merck US is involved in the research and production of vaccines for many diseases; moreover, it manufactures more than 50 prescription products in key

therapeutic areas, such as cardiovascular disease, respiratory disease, oncology, endocrinology, neuroscience, infectious disease, immunology and women's health.

Merck US R&D investments have been progressively falling over the period 2011-2014, and also the R&D ratio on sales suffered from a moderate decrease as shown by Figure 20.

Figure 20 MERCK US (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	7,180	16.9	7,500	17.0	8,200	17.4	8500	17.7
% Change	-4.3		-8.5		-3.5			

The company research pipeline for diabetes is focused on molecules that address type 1 and type 2 diabetes mellitus (Figure 21).

Figure 21 MERCK US (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	MK-0431D (sitagliptin + simvastatin)	Type 2	Under review
2014	MK-3102 (omarigliptin)	Type 2	III
2014	MK-8835 (ertugliflozin)	Type 2	III
2014	MK-1293 (insulin glargine)	Type 1/ Type 2	III

2.3.5 SANOFI-AVENTIS (EUR)

Sanofi was founded by René Sautier and Jean-François Dehecq in 1973. The company has grown significantly by acquiring and investing in some of the most important French, European and American pharmaceutical companies. Sanofi finally merged with Aventis in 2004, giving birth to Sanofi-Aventis. Sanofi-Aventis is headquartered in Paris, France, and has core strengths in diabetes solutions, human vaccines, consumer healthcare, rare diseases & multiple sclerosis, other innovative products, animal health and emerging markets. The company has a workforce of more than 110,000 people worldwide and is present in over 100 countries.

Sanofi-Aventis' total R&D expenditures registered a decrease between 2012 and 2013, although they recovered the following year (Figure 22). R&D ratio on sales has been moderately fluctuating over the entire period considered.

Figure 22 SANOFI-AVENTIS (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,824	14.3	4,770	14.5	4,922	14.1	4,811	14.4
% Change	1.1		-3.1		2.3			

Sanofi-Aventis's diabetes research concerns the development of drugs, the correction of metabolic disorders and their cardiovascular consequences, and the treatment of pathological conditions induced by diabetes such as nephropathy, neuropathy, retinopathy, etc. The company's pipeline for diabetes is currently focused on developing new insulin molecules, devoted to the treatment of type 1 and type 2 diabetes mellitus (**Figure 23**).

Figure 23 SANOFI-AVENTIS (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Lantus (glargine insulin)		III
2013	Lyxumia (glargine insulin)	Type 2	Approved
2014	Lispro insulin biosimilar	Type 1	III
2014	Toujeo (glargine insulin U300)		III
2014	Lixilan Ratio-Fixe (glargine insulin)		III
2014	SAR425899	Type 2	I

2.3.6 PFIZER (US)

Pfizer is a global biopharmaceutical company founded by cousins Charles Pfizer and Charles Erhart in 1849, and headquartered in New York City, with its research headquarters in Groton, Connecticut. The pharmaceutical segment of the company invests in some important therapeutic areas, including oncology, neuroscience, immunology, cardiovascular and metabolic diseases, vaccines, and rare diseases. Pfizer employs approximately 78,000 people and has affiliated companies all over the world.

Pfizer registered an important decrease in R&D expenditures in 2012 and 2013, and also the R&D ratio on sales fell over the period 2011-2013, reaching its lowest level in 2013 as shown by Figure 24. The company's investment, however, substantially recovered in 2014 but did not reach the 2011 levels.

Figure 24 PFIZER (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	8,393	16.9	6,678	12.9	7,870	13.7	8,681	14.2
% Change	25.7		-15.1		-9.3			

Pfizer has some diabetes relevant molecules under development, all aimed at treating type 2 diabetes mellitus (Figure 25).

Figure 25 PFIZER (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2014	Ertugliflozin (PF-04971729)	Type 2	III
2014	PF-04937319	Type 2	II
2014	PF-05175157/ PF-05231023/ PF-06291874/ PF-06342674	Type 2	I

2.3.7 GLAXOSMITHKLINE (EUR)

GlaxoSmithKline plc (GSK) is a British multinational pharmaceutical company headquartered in Brentford, London, created in 2000 through the merger of Glaxo Wellcome and SmithKline Beecham. The company researches and develops innovative products in three segments: Pharmaceuticals, Vaccines and Consumer Healthcare. The Pharmaceuticals business develops medicines against acute and chronic diseases, the Vaccines segment produces pediatric and adult vaccines to prevent a range of infectious diseases and the Consumer Healthcare business markets a range of consumer healthcare products based on scientific innovation. The company employs around 98,000 people worldwide and operates across 115 countries.

GSK registered a substantial decrease in R&D expenditures over the years 2011-2014, accompanied by fluctuating ratios of R&D investment to sales as outlined in Figure 26.

Figure 26 GLAXOSMITHKLINE (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil GBP)	% Sales	Amount (Mil GBP)	% Sales	Amount (Mil GBP)	% Sales	Amount (Mil GBP)	% Sales
	3,100	13.5	3,400	12.8	3,500	13.2	4,000	14.6
% Change	-8.8		-2.9		-12.5			

GSK has in its research pipeline some relevant molecules for the treatment of type 1 and type 2 diabetes mellitus, currently tested in phase II clinical trials (Figure 27).

Figure 27 GLAXOSMITHKLINE (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2014	Otelixizumab	Type 1	II
2014	2330672	Type 2	II
2014	Eperzan (albiglutide)	Type 2	II

2.3.8 ELI LILLY (US)

Eli Lilly, founded in 1876 by Colonel Eli Lilly, is a global pharmaceutical company headquartered in Indianapolis, Indiana. The company operates in five business areas: Bio-Medicines, Diabetes, Animal Health, Emerging Markets and Oncology. The Bio-Medicines segment deals with several therapeutic areas, including neuroscience, cardiovascular, urology, musculoskeletal and autoimmunity. Lilly Diabetes has been a global leader in diabetes care since 1923 when they introduced the world's first commercial insulin, and Lilly Oncology is one of the top 10 oncology companies in the world. Eli Lilly has a workforce of approximately 41,000 people and its products are marketed in 120 countries.

As shown by Figure 28, Eli Lilly's R&D expenditures have been progressively increasing between 2011 and 2013, accompanied by a boost in the R&D ratio on sales. However, in 2014 the company suffered from a substantial decrease in R&D expenditures but the R&D ratio on sales increased with respect to previous years. This suggests that the decrease in total R&D investment was probably driven by a decrease in sales.

Figure 28 ELI LILLY (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,734	24.1	5,531	23.9	5,278	23.4	5,021	20.7
% Change	-14.4		5.0		5.0			

Lilly is the world leader in R&D for diabetes. One of the most significant advance in diabetes care was marked by Lilly's 1982 introduction of Humulin, an insulin identical to that produced by the human body. The company has developed several diabetes relevant molecules over the period 2011-2014 for the treatment of type 2 and type 1 diabetes mellitus (Figure 29).

Figure 29 ELI LILLY (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Trajenta®	Type 2	Approved
2013	Empagliflozin	Type 2	Under review
2013	Dulaglutide	Type 2	Wait for approval
2013	Insulin glargine	Type 2	Submitted
2014	Insulin peglispro	Type 1	III

2.3.9 BAYER (EUR)

Bayer is a global firm founded in Barmen, Germany, in 1863, and with headquarters in Leverkusen, Germany. The company is specialized in the fields of health care, agriculture and high-tech polymer materials. The Healthcare subgroup has four operating divisions: Animal Health; Consumer Care (including OTC medicines, dietary supplements, dermatology products, foot care products, sunscreens and other non-prescription products; prescription dermatology products); Medical Care (blood glucose monitoring systems, contrast agents, injection systems for diagnostic procedures) and Pharmaceuticals (prescription medicines). Bayer has around 118,900 employees worldwide spread in 75 countries.

Bayer's R&D expenditures increased substantially over the period 2011-2014, registering a boom between 2012 and 2013, when investments grew of about 13% and R&D ratio on sales reached its peak as witnessed by Figure 30.

Figure 30 BAYER (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	3,574	8.5	3,406	8.5	3,013	7.6	2,932	8.0
% Change	4.9		13.0		2.8			

Bayer has one relevant molecule under development for the treatment of macular edema (Figure 31) a complication of diabetic retinopathy and the most common form of vision loss for people with diabetes.

Figure 31 BAYER (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Eylea (VEGFTrap-Eye)	Macular edema	III

2.3.10 ASTRAZENECA (EUR)

AstraZeneca was founded in 1999 after the merger of Astra AB (Sweden) and Zeneca Group PLC (UK) and is headquartered in London, United Kingdom. The global biopharmaceutical company focuses on three key therapy areas: Cardiovascular and Metabolic disease; Oncology; Respiratory, Inflammation and Autoimmunity. AstraZeneca is involved in the entire life-cycle of a medicine, that is in R&D, manufacturing, supply and commercialization. The company employs approximately 57,500 people worldwide working across more than 100 countries.

AstraZeneca, despite the decrease of total R&D expenditures between 2011 and 2013, registered an overall increase in R&D investment over the period 2011-2014 thanks to the recovery of expenditures in the last year considered (Figure 32). R&D ratio on sales has been progressively increasing over the period 2011-2014, witnessing the company's decision to invest more in research and development.

Figure 32 ASTRAZENECA (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	5,579	21.4	4,821	18.8	5,243	18.7	5,523	16.4
% Change	15.7		-8.0		-5.1			

As outlined in Figure 33, AstraZeneca's research pipeline for diabetes is focused on molecules for the treatment of diabetes mellitus (type 1 and type 2). The company is not currently developing any drug for the treatment of pathological conditions induced by diabetes.

Figure 33 ASTRAZENECA (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Kombiglyze (saxagliptin)	Diabetes	III
2011	Onglyza (saxagliptin)	Diabetes	III
2012	Forxiga/Farxiga (dapagliflozin)	Diabetes	III
2012	Bydureon (exenatide)	Type 2	III

2.3.11 AMGEN (US)

Amgen (Applied Molecular Geics Inc.), one of the world's leading biotechnology companies, was founded in 1980 by William K. Bowes and is headquartered in Thousand Oaks, California. The company manufactures medicines for key therapeutic areas including cancer, kidney disease, rheumatoid arthritis, bone disease and other serious illnesses. Amgen employs approximately 18,000 people worldwide and is present in more than 75 countries.

The company's commitment to R&D investment has been increasing over the period, with a boost between 2012 and 2013. This is reflected both by total R&D investment and R&D ratio on sales as displayed by Figure 34.

Figure 34 AMGEN (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,297	21.4	4,100	22.5	3,400	20.4	3,200	20.9
% Change	4.8		20.6		6.3			

The company has several diabetes molecules in its research pipeline as shown by Figure 35. The majority of them are aimed at treating type 2 and type 1 diabetes mellitus and one for the treatment of diabetic retinopathy, the most common eye complication of diabetes which can lead to vision loss.

Figure 35 AMGEN (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Trajenta® (linagliptin)	Type 2	Approved
2011	Arxxant (Ruboxistaurin)	Diabetic retinopathy	Registration
	Empagliflozin	Type 2	Registration
	Dulaglutide	Type 2	Registration
	Insulin Glargine	Type 1/ Type 2	Registration
	Peglispro (basal insulin)	Type 1	III

2.3.12 BOEHRINGER INGELHEIM (EUR)

Boehringer Ingelheim was founded in 1885 by Albert Boehringer in Ingelheim am Rhein and is still headquartered in Ingelheim, Germany. The company develops medicines for the treatment of diseases, some of which chronic, with an unmet therapeutic need: cardiovascular disease, respiratory diseases, diseases of the central nervous system, metabolic diseases, virological diseases and oncology. Boehringer Ingelheim employs a workforce of over 47,700 employees and operates globally with 146 affiliates.

Boehringer Ingelheim registered a substantial increase in R&D expenditures between 2011 and 2012, and experienced a small decrease in the following years as outlined in Figure 36**.** Despite this absolute decrease, the ratio of R&D investment to sales increased in 2014 with respect to the previous year, suggesting that the decrease in R&D expenses was probably driven by a general decrease in sales.

Figure 36 BOEHRINGER INGELHEIM (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	2,654	19.9	2,743	19.5	2,795	19.0	2,516	19.1
% Change	-3.2		-1.9		11.0			

As shown by Figure 37, the company has several diabetes relevant molecules in its research pipeline, the majority of them devoted to the treatment of type 2 diabetes mellitus and one for the treatment of both types of diabetes.

Figure 37 BOEHRINGER INGELHEIM (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	Trajenta (linagliptin)	Type 2	Approved
2012	Jentadueto (Linagliptin+metformin)	Type 2	Approved
	Empaglifozin	Type 2	Submitted
	Empagliflozin+linagliptin	Type 2	III
	Empagliflozin+metformin	Type 2	III
	Newinsulinglargine	Type 1/ Type 2	Submitted

2.3.13 BRISTOL MYERS SQUIBB (US)

Bristol Myers Squibb is a global biopharmaceutical company founded by Edward R. Squibb in 1858 in Brooklyn and headquartered in New York City, New York. The company develops pharmaceutical products in a number of serious disease areas with significant unmet medical need: oncology, immunology, cardiovascular, metabolic, neuroscience, fibrotic diseases and genetically-defined diseases. Bristol Myers Squibb has a workforce of about 24,000 employees worldwide and markets its products in 57 countries.

The company's total R&D expenditures have been fluctuating over the period 2011-2014, with a substantial increase in 2014 as shown by Figure 38. Despite the decrease of absolute investment in 2013, the R&D ratio on sales steadily increased between 2011 and 2013, gaining more than 8 percentage points.

Figure 38 BRISTOL MYERS SQUIBB (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,534	28.5	3,731	30.3	3,904	28.6	3,839	21.8
% Change	21.5		-4.4		1.7			

The company received the approval of three diabetes relevant molecules during the period considered, all devoted to the treatment of type 2 diabetes mellitus (Figure 39).

Figure 39 BRISTOL MYERS SQUIBB (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2012	Forxiga® (dapagliflozin)	Type 2	Approved
	Bydureon® (exenalide)	Type 2	Approved
	Kombiglyze XR® (saxagliptin+metformin)	Type 2	Approved

2.3.14 ABBVIE (US)

AbbVie is a global biopharmaceutical company formally created in 2013 after its divestment from Abbot Laboratories started in 2011. The company manufactures and develops a broad range of medicines in some key therapeutic areas, including immunology, kidney disease, liver disease, neuroscience, oncology and women's health. AbbVie employs approximately 28,000 people worldwide and markets its products in more 170 countries.

As shown by Figure 40, , the company's commitment to R&D investments (total investment and R&D intensity) has been gradually increasing since 2011, reaching the peak in 2014.

Figure 40 ABBVIE (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	3,297	16.5	2,855	15.2	2,778	15.1	2,618	15.0
% Change	15.5		2.8		6.1			

Focused on other therapeutic areas, AbbVie does not have any diabetes relevant molecules under development.

2.3.15 CELGENE (US)

Celgene is a global biopharmaceutical company founded in 1986 and headquartered in Summit, New Jersey. The company develops and commercializes innovative medicines and therapies for the treatment of hematological and solid tumor cancers and immune-inflammatory related diseases. Celgene has a workforce of approximately 4,000 employees and markets its products in more than 50 countries.

The company experienced an important increase in R&D expenditures over the period considered (Figure 41), and from 2011 to 2014 total R&D expenses grew by approximately 52%. Celgene's R&D investments account for a very high percentage of sales, the highest among the top pharmaceutical companies identified.

Figure 41 CELGENE (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	2,431	32.1	2,226	35.0	1,724	32.0	1,600	34.0
% Change	9.2		29.1		7.8			

Focused on other key therapeutic areas, Celgene does not have any diabetes relevant molecules under development.

2.3.16 NOVO NORDISK (EUR)

Novo Nordisk is a global healthcare company leader in diabetes care and headquartered in Bagsvaerd, Denmark. Novo Nordisk A/S, the world's leading producer of insulin, was formally created in 1989 after a series of mergers but its history dates back to the 1920s when two small Danish companies, Nordisk Insulinlaboratorium and Novo Terapeutisk Laboratorium, were founded. Today, the company has five product areas: Diabetes care; Haemophilia; Growth hormone therapy; Obesity; Hormone replacement therapy. Novo Nordisk has a workforce of approximately 39,000 people in 75 countries and markets its products in more than 180 countries.

The company's R&D expenditures have been substantially increasing over the period 2011-2014, registering a boom between 2013 and 2014, when both absolute value of investment and R&D ratio on sales reached their peak (Figure 42).

Figure 42 NOVO-NORDISK (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil DKK)	% Sales	Amount (Mil DKK)	% Sales	Amount (Mil DKK)	% Sales	Amount (Mil DKK)	% Sales
	13,800	15.5	11,700	14.0	10,900	14.0	9,300	14.5
% Change	17.9		7.3		17.2			

Being a leader in diabetes care, Novo Nordisk has a great number of diabetes relevant molecules in its research pipeline as displayed by Figure 43. In fact, 17 molecules have been developed and tested over the period considered, all devoted to the treatment of type 1 and type 2 diabetes mellitus, while none to the treatment of diabetes related consequences.

Figure 43 NOVO-NORDISK (EUR) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
2011	NN1953	Type 1/ Type 2	I
2011	Liraglutidedepot	Type 2	I
2011	NN9924	Type 2	I
2012	Tresiba (insulindegludec)	Type 1/ Type 2	Approved
2012	Ryzodeg (insulindegludec+insulinaspart)	Type 1/ Type 2	Approved
2012	OI362GT	Type 1/ Type 2	I
2012	OI338GT	Type 1/ Type 2	I
2012	OG987GT	Type 2	I
2012	OG987SC	Type 2	I
2012	LAI287	Type 1/ Type 2	I
2013	Semaglutide	Type 2	III
2013	FIAsp (faster-actinginsulinaspart)	Type 1/ Type 2	III
2013	LATIN T1D	Type 1	III
2013	OG217SC	Type 2	II
2013	OI287GT	Type 1/ Type 2	I
2014	Xultophy (insulindegludec+liraglutide)	Type 2	Approved
2014	LA338	Type 1/ Type 2	I

2.3.17 GILEAD SCIENCES (US)

Gilead Sciences is a research-based biopharmaceutical company founded in 1987 and headquartered in Foster City, California. Gilead Sciences develops medicines in areas of unmet medical need, such as HIV/AIDS, liver diseases, cancer, inflammatory and respiratory diseases, and cardiovascular conditions. The company has a workforce of over 7,000 employees across six continents.

Gilead Sciences' total R&D expenditures have been progressively increasing over the period 2011-2014, so that the amount of R&D investment in 2014 more than doubled that of 2011 as displayed by Figure 44. R&D ratio on sales registered a constant increase until 2013 but decreased in 2014, when revenues increased more than R&D expenditures.

Figure 44 GILEAD SCIENCES (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	2,854	11.4	2,120	19.6	1,760	18.7	1,230	15.2
% Change	34.6		20.5		43.1			

The company is developing two diabetes relevant molecules, one for the treatment of type 2 diabetes mellitus and the other for diabetic nephropathy, a diabetes complication which can lead to kidney failure (Figure 45).

Figure 45 GILEAD SCIENCES (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
	Ranexa® (ranolazine)	Type II	II
	GS-4997	Diabetic nephropathy	I

2.3.18 MERCK DE (EUR)

Merck DE is a German multinational chemical, pharmaceutical and life sciences company headquartered in Darmstadt, Germany. The company was founded in 1668 by Friedrich Jacob Merck, an apothecary, and is the world's oldest operating chemical and pharmaceutical company. Merck DE is organized in three business sectors: Healthcare, Life Science and Performance Materials. The healthcare segment develops prescription medicines used in neurodegenerative diseases, oncology, fertility, endocrinology, cardiometabolic diseases and general medicine. Moreover it

produces over-the-counter pharmaceuticals, products for diagnostic testing and treatment of allergies and biosimilars.

After a not significant decrease in R&D expenditures between 2011 and 2013, the company's R&D commitment to R&D investments increased substantially in 2014 as displayed by Figure 46.

Figure 46 MERCK DE (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	1,704	15.0	1,504	14.0	1,511	14.0	1,517	15.3
% Change	13.3		-0.5		-0.4			

Although Merck DE invests also on medicines for the treatment of metabolic diseases including diabetes, the company has not developed any diabetes relevant molecules over the period considered.

2.3.19 ABBOTT LABORATORIES (US)

Abbott Laboratories was founded by physician and drug store proprietor Wallace Calvin Abbott in 1888 and is headquartered in Abbott Park, Illinois. In 2013 the company announced its separation into two companies, one specialized in medical products and the other in research-based pharmaceuticals. The medical products company retained the Abbott name, while the research-based pharmaceutical company took the name AbbVie. Abbott Laboratories operates in four business areas: Pharmaceuticals, Medical Devices, Diagnostics, and Nutrition. The Pharmaceutical segment provides generic medicines that treat persistent health conditions. The company employs approximately 73,000 people in over 150 countries.

As shown by Figure 47, the company experienced a general decrease in R&D investment over the period, perhaps related to its divestment of AbbVie. Abbott Laboratories records the lowest R&D intensity among the sample of pharmaceutical companies.

Figure 47 ABBOTT LABORATORIES (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,345	6.6	1,452	6.7	1,544	7.2	1,512	7.1
% Change	-7.4		-6.0		2.1			

Abbott Laboratories has currently only one diabetes relevant molecule under development, aimed at treating type 2 diabetes mellitus (Figure 48).

Figure 48 ABBOTT LABORATORIES (US) Research Pipeline: Diabetes

Year	Product Name	Indication	Phase
	Paricalcitol	Type 2	II

2.3.20 BIOGEN IDEC (US)

Biogen is a global biotechnology company founded in 1978 in Geneva and currently headquartered in Cambridge, Massachusetts. The company is specialized in developing therapies for neurodegenerative, hematologic and autoimmune disorders and has the world's most extensive portfolio of multiple sclerosis therapies and innovative treatments for hemophilia patients. Biogen employs approximately 7,500 people worldwide.

The company's R&D investment has been progressively increasing over the period 2011-2014 as shown by Figure 49. Although R&D expenditures grew in absolute terms, R&D ratio on net sales constantly declined in the same years.

Figure 49 BIOGEN IDEC (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,893	19.5	1,444	20.8	1,335	24.2	1,220	24.2
% Change	31.0		8.2		9.4			

Focused on other key therapeutic areas, Biogen does not have any diabetes relevant molecules under development.

2.4 Discussion: The Pharmaceutical Research Pipeline for Diabetes

Figure 50 reports synthesis results elaborated from the tables above. Column 3 displays for each company the percentage change in total R&D investment between 2011 and 2014. Column 4 shows the mean R&D intensity (i.e. R&D ratio on net sales) calculated over the time frame.

Over the period 2011-2014, the European pharmaceutical sector has generally increased its R&D expenditures (column 3) and, among the top nine European companies identified, only GSK suffered from a substantial decrease in investments (-22.5%). Novo Nordisk, on the contrary, registered the highest increase in R&D expenditures which, between 2011 and 2014, grew by approximately 48%. US pharmaceutical companies' commitment to R&D investments has been more heterogeneous. Seven firms out of 11 registered an increase in R&D expenditures, and the most substantial increase was registered by smaller pharmaceutical companies (Gilead Sciences, Celgene and Biogen). By contrast, companies at the top of the scale, like Merck and Pfizer, have substantially reduced their levels of investment. Gilead Sciences registered the highest increase in R&D expenditures of the whole sample: between 2011 and 2014, investments grew by approximately 132%.

If we look at column 4, however, we notice that, despite European companies registered higher increase in absolute levels of investment than US companies, the situation is reversed for R&D intensity. In fact, US companies reported on average higher values of R&D ratio on sales over the period 2011-2014 (US average=19; EUR average=15.6). R&D intensity is a measure that allows to capture the relative importance of R&D among firms in the same industry, and the current findings suggest that US pharmaceutical companies generally allocate more resources in research and development activities than European firms.

Figure 50 Synthesis Results: Pharmaceutical Industry R&D Investment

Company	Country	% change R&D expenditures (2011-2014)	Mean R&D intensity (2011-2014)
Novartis	EUR	7.1	16.4
Roche	EUR	9.9	18.7
Johnson & Johnson	US	12.5	11.5
Merck US	US	-15.5	17.3
Sanofi-Aventis	EUR	0.3	14.3
Pfizer	US	-3.3	14.4
GlaxoSmithKline	EUR	-22.5	13.5
Eli Lilly	US	-5.7	23.0
Bayer	EUR	21.9	8.2
AstraZeneca	EUR	1.0	20.5

Amgen	US	34.3	21.3
Boehringer Ingelheim	EUR	5.5	19.4
Bristol Myers Squibb	US	18.1	27.3
AbbVie	US	25.9	15.5
Celgene	US	51.9	33.3
Novo Nordisk	EUR	48.4	14.5
Gilead Sciences	US	132.0	16.2
Merck DE	EUR	12.3	14.6
Abbott Laboratories	US	-11.0	6.9
Biogen Idec	US	55.2	22.2

When focusing specifically on research pipelines for diabetes, despite being the world leader for R&D investment in the pharmaceutical and biotechnology sector, US companies lose their leader role. They have overall less diabetes relevant molecules in their pipelines than European companies (26 molecules under development for US companies compared to 40 for EUR firms). The majority of molecules developed by US and European top pharmaceutical firms are aimed at treating type 1 and type 2 diabetes mellitus, while only few companies have developed molecules for the treatment of diabetes complications such as diabetic retinopathy, neuropathy and macular oedema.

Among the eleven top US firms, three do not have any diabetes relevant molecules under development because they are focused on other therapeutic areas; however, major companies such as Johnson & Johnson, Merck, Pfizer, Eli Lilly and Amgen show a commitment to diabetes in terms of pipeline development. It is worth underlining that research pipelines of US pharmaceutical companies cover a broad range of therapeutic areas, in particular serious non-communicable diseases. Only Eli Lilly, the world leader in R&D for diabetes, is specialized in developing diabetes relevant molecules among US based companies.

Among European companies, only one (Merck DE) is not currently active in developing new molecules for diabetes, although diabetes is a key therapeutic area for the firm and receives an important part of investments. Interestingly, in Europe the majority of diabetes relevant molecules is developed by companies in the bottom end of the list, while only one in the top (Sanofi-Aventis) is specialized in these disease. Novo-Nordisk expressed the greatest commitment to diabetes in terms of research pipeline among the top 20 pharmaceutical firms identified, with 17 diabetes molecules in development over the period 2011-2014.

When linking these data to the the epidemiology of NCD as emerged by GBD study previously discussed, it seems that US top pharma companies' R&D commitment to diabetes is limited by the secondary level of burden of disease in the country while European firms are more involved in developing innovative molecules for the treatment of diabetes and its complications, regardless the perceived importance of the unmet need in the field.

The observed discrepancy between increasing R&D investment and stalling number of new molecules discovered can be traced back to several factors, including rising attrition rates of drug

development projects, especially in late-phase clinical trials (Scannell et al., 2012), which make it difficult for new molecular entities to enter the market. According to Pammolli et al. (2011), part of the declining R&D productivity, measured as the ratio of R&D outputs to inputs, can be explained by an increasing focus of research activities in the development of drugs in complex research areas that are characterized by a low probability of success. Consequently, the cost of R&D (input) of new drugs has risen but the probability of producing a new molecule (output) has fallen. As the authors underlined, however, we should be careful in interpreting the decreasing R&D productivity because *"[…] the number of NMEs is an imperfect measure of R&D outcomes, as it does not reflect changes in the quality of the output. In addition, the productivity crisis might be a temporary phenomenon, as radical technological changes, such as the genomic revolution, could initially increase the time lag between investment and outcome, thereby reducing R&D productivity in the short term".*

2.5 Medical Device Sector: Research Pipeline for Diabetes

According to the Council Directive 93/42/EEC on Medical Devices, a Medical Device (MD) is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Among the 16 world's top medical device companies identified in Figure 8, seven companies are based in Europe while nine companies have headquarters in the US.
According to European Commission[18], the medical devices industry (i.e. firms which manufacture, repackage, relabel, and/or import medical devices) is a major employer in Europe, employing 575,000 people in the EU, with a market size of around €100 billion. The regulation of medical devices in Europe was harmonized in the 1990s with three Directives issued in 1990, 1993 and 1998. Before been introduced into clinical practice, devices have to be approved and certified, obtaining a CE (Conformité Européene) mark (Boulton and Del Prato, 2012).
The United States is the largest medical device market in the world (the U.S. market value represented about 38 percent of the global medical device market in 2012) and its total sales amount to $110 billion[19]. There are more than 6,500 medical device companies in the U.S., which, overall, employ 400,000 Americans directly and almost 2 million indirectly. In the US, regulation of medical device industry is in the hands of FDA's Center for Devices and Radiological Health (CDRH)[20].
According to Millennium Research Group (MRG), the global authority on medical technology market intelligence and the leading provider of strategic information to the healthcare sector, the increase in the prevalence of diabetes, combined with an expansion of insurance coverage as a consequence of healthcare reform, will cause the US diabetes care device market to grow to nearly $16 billion by 2017[21].

Among the identified MD companies, only three of them (i.e. Alcon, Medtronic Inc. and Becton, Dickinson & Co.) have in their research pipeline a device for diabetes, while the other firms are specialized in different NCDs. In the next paragraphs we will examine the top MD companies' research pipelines and other minor companies not listed above which manufacture diabetes medical devices.

[18] http://ec.europa.eu/growth/sectors/medical-devices/index_en.htm
[19] http://selectusa.commerce.gov/industry-snapshots/medical-device-industry-united-states
[20] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/
[21] http://mrg.net/News-and-Events/Press-Releases/Diabetes-Care-Devices-011513.aspx

2.5.0 Search strategy

In order to identify new medical device under development we relied on different sources as no information on research pipelines was available from MD companies' annual reports.

With the aim of identifying new products at the clinical assessment stage, a database of clinical studies (i.e. clinicaltrials.gov) was searched for recently (≥2011) closed and ongoing clinical studies funded by each MD company identified (see Appendix 4 for detailed search strategy).

Also databases of new approved MDs (i.e. FDA premarket approval, de novo database, EuroScan) have been searched according to the same time frame (2011-2015). At the European Level, a database of CE marked products exists since 2009, called EUDAMED. This database is only accessible to government agencies in charge for the market surveillance in each country (e.g. Ministero della Salute in Italy). In the US, instead, the relevant authority, the Food and Drug Administration, has a whole section on the website with approval dossiers for all medical devices. Although there is not a direct link between technologies approved in the US and technologies licensed in the EU, knowledge of the most recent innovations approved overseas will provide an idea of the most up-to-date technologies that are available to improve clinical practice for the management of NCDs.
Therefore, the FDA premarket approval (PMA) and de novo databases have been searched for new approved products between 2011 and 2015 (see Appendix 5 and 6 for detailed search strategy). The 510(k) clearance will not be considered as this refers to products "substantially equivalent" to others already on the market. In this case, unlike the previous steps, the search have been performed according to indication in cancer, respiratory disease, cardiovascular disease, diabetes, mental health.

Besides the FDA databases, the EuroScan Database has been searched. In Europe there is not an equivalent of the FDA online databases of new approved devices. We therefore relied on the EuroScan database. EuroScan is the International Information work on New and Emerging Health Technologies, a collaborative work of member health technology assessment (HTA) agencies for the exchange of information on important emerging new drugs, devices, procedures, programmes, and settings in health care. Many European HTA agencies are members of the work (e.g. Agenas from Italy, NIHR Horizon Scanning Centre from UK, Osteba from Spain, SBU from Sweden etc.). As for the FDA databases, the search has been performed according to indication in the five NCD areas (see Appendix 7 for detailed search strategy).

2.5.1 JOHNSON & JOHNSON (US)

Johnson & Johnson is a global company which manufactures pharmaceuticals, medical devices and consumer healthcare products. It is the world's largest and most diverse medical devices company. Johnson & Johnson was founded by the three Johnson brothers in 1886 and it is headquartered in New Brunswick, New Jersey. The Medical Device segment produces a broad range of innovative products in some therapeutic areas, including orthopaedics, neurovascular, surgery, vision care, diabetes care, infection prevention, cardiovascular disease, sports medicine, and aesthetics. Johnson & Johnson has a workforce of approximately 126,500 people and operates through its affiliates in more than 60 countries.

As displayed by Figure 51, the company's total R&D expenditures increased over the period considered, although R&D ratios on sales remained quite stable, suggesting that R&D investments grew after a general increase in sales.

Figure 51 JOHNSON & JOHNSON (US) Total R&D Investment*

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	8,494	11.4	8,183	11.5	7,665	11.4	7,548	11.6
% Change	3.8		6.8		1.6			

**R&D expenses refer to all business segments of Johnson & Johnson (i.e. Consumer; Pharmaceutical; Medical Devices and Diagnostics)*

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.2 GENERAL ELECTRIC CO. (US)

General Electric Co. is a global technology and financial services company headquartered in Fairfield, Connecticut. Its history traces back to 1892, when the General Electric Company was formed by merging the Edison General Electric Company and the Thomson-Houston Company. The company operates through eight segments: Power & Water, Oil & Gas, Energy Management, Aviation, Healthcare, Transportation, Home & Business Solutions and GE Capital. The Healthcare segment provides healthcare technologies such as medical imaging and information technologies, medical diagnostics, patient monitoring systems, disease research, drug discovery and biopharmaceutical manufacturing technologies.

The company's R&D expenditures have been fluctuating over the period 2011-2014 (Figure 52). In 2014 investments registered their lowest level, both in terms of total expenditures and in terms of R&D ratio on sales.

Figure 52 GENERAL ELECTRIC CO. (US) Total R&D Investment*

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	4,233	2.8	4,750	3.3	4,520	3.1	4,601	3.1
% Change	-10.9		5.1		-1.8			

**R&D expenses refer to all business segments of General Electric Co, not only to the healthcare business area*

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.3 MEDTRONIC INC. (US)

Medtronic was founded in 1949 as a medical equipment repair shop by Earl Bakken and his brother-in-law, Palmer Hermundslie, and today is headquartered in Minneapolis, Minnesota. The company develops and manufactures a broad range of medical technologies, including implantable mechanical devices, drug and biologic delivery devices and surgical instruments. Medtronic operates in three major business areas: Cardiac and Vascular, Restorative Therapies, and Diabetes. It has a workforce of more than 80,000 employees worldwide across over 160 countries.

As shown by Figure 53, the company's R&D investments have been fluctuating over the period 2011-2014. Both total R&D expenditures and R&D ratio on sales decreased in 2014 with respect to previous years.

Figure 53 MEDTRONIC INC. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,477	8.7	1,557	9.4	1,490	9.2	1,508	9.5
% Change	-5.1		4.5		-1.2			

Medtronic has developed or is still developing several medical devices for the treatment of type 1 and type 2 diabetes mellitus. We found relevant results through the searches in Clinical Trials database (Figure 54), FDA premarket approval (Figure 55) and EuroScan database (Figure 56).
The majority of diabetes devices produced by the company are insulin pumps, which are small computerized devices that continuously deliver insulin through a catheter, and glucose monitoring systems, test systems for use at home to measure (and thus control) the amount of sugar in blood. MEDTRONIC also developed infusion sets and an artificial pancreas, which automatically control blood glucose level of diabetic people by providing the substitute endocrine functionality of a healthy pancreas.

Figure 54 MEDTRONIC INC. (US) Company Clinical Trials: Diabetes*

Year	Device	Study name	Application	Study status
2010-ongoing	Medtronic Minimed Paradigm® VEO	*OpT2mise Glucose Control in Type 2 DM With Insulin Pump Therapy*	Type 2	Ongoing
2011-2012	Enlite Sensor	*A Performance Evaluation of the Enlite Glucose Sensor to Support a Full 144 Hours(6Days) of Use*	Type 1/ Type 2	Completed
2011-2013	Paradigm® VEO™ Pump	*ASPIRE (Automation to Simulate Pancreatic Insulin Response): Pivotal In Home Study to Determine Safety and Efficacy of the LGS Feature in Sensor-augmented Pumps*	Type 1	Completed
2012	Medtronic Hospital Glucose Management System (HGMS)	*A Multi-Phased, Multi-Center Study to Evaluate Safety and Device Performance of the Medtronic Hospital Glucose Management System (HGMS) in Critically Ill Adult Patients*	Diabetes mellitus	Completed
2012	Integrated sensor and infusion set	*Feasibility Study to Assess Performance of an Integrated Sensor and Infusion Set. TRIAL II*	Type 1	Completed
2012-2013	Integrated sensor and infusion set	*FEASIBILITY STUDY TO ASSESS PERFORMANCE OF THE INTEGRATED SENSOR AND INFUSION SET. WITH HIGH INSULIN NEED USERS (TRIAL III)*	Type 1/ Type 2	Completed
2012-2014	iPro2 Continuous Glucose Monitoring System	*Use of iPro™2 in Real Life Diabetes Management of Type 2 Patients in India*	Type 2	Completed

2013	CareLink Connect	*A Multi-center, Non-randomized Study in Subjects With Diabetes Mellitus Treated With Sensor-Augmented Pump Therapy to Evaluate the Performance and Safety of CareLink Connect Transferring Pump Data to Web Connected Devices Via CareLink*	Type 1/ Type 2	Completed
2013-2014	Closed Loop Insulin Delivery System	*Feasibility and Safety of a Closed Loop Insulin Delivery System (Aka AAGC) With an Artificially Induced Calibration Error During the Overnight Period*	Type 1	Completed
2013-ongoing	Overnight Closed Loop (OCL) System	*In-Clinic Feasibility Study to Observe the Overnight Closed Loop System*	Type 1	Ongoing
2013-ongoing	Sensor-augmented pump (SAP)	*Sensor Augmented Pump Therapy Versus Multiple Daily Injection Therapy for Hospitalized Patients in China With Type 2 Diabetes; Time to Target*	Type 2	Ongoing
2013-ongoing	MiniMed® 620G and 640G Insulin Pumps/ Guardian® Link Transmitter	*A User Evaluation of the MiniMed® 620G and 640G Insulin Pumps and Guardian® Link Transmitter*	Type 1/ Type 2	Ongoing
2015-ongoing	Enlite Glucose Sensor	*Accuracy and Performance Evaluation of the Medtronic New Generation Enlite Glucose Sensor in Conjunction With the Medtronic 640G System Components - in Clinic and at Home*	Type 1/ Type 2	Ongoing
2014-ongoing	Predictive Low Glucose Management Feature in Insulin pump	*In-Clinic Evaluation of the Predictive Low Glucose Management (PLGM) System in Adult and Pediatric Insulin Requiring Patients With Diabetes Using the Enlite 3 Sensor*	Type 1	Ongoing
2014-ongoing	Enlite® 3 Sensor	*A Performance Evaluation of the Enlite® 3 Sensor to Support a Full 168 Hours (7 Days) of Use*	Type 1/ Type 2	Ongoing

2015-ongoing	MMT-670G insulin pump	*Safety Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Diabetes*	Type 1	Ongoing
2015-ongoing	Harmony 1 Sensor	*A Performance Evaluation of the Harmony 1 Sensor to Support a Full 168 Hours (7 Days) of Use*	Type 1/ Type 2	Ongoing
2015-ongoing	Enlite Sensor™/ Enlite 3 Sensor	*A Performance Evaluation of the Enlite™ and Enlite 3 Glucose Sensor to Support Use in Children*	Type 1	Ongoing

**Source:* https://clinicaltrials.gov/

Figure 55 MEDTRONIC INC. (US) PMA Medical Devices: Diabetes*

Year of approval	Device	Application
2013	MINIMED 530G SYSTEM	Diabetes mellitus

**Source:* http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/

Figure 56 MEDTRONIC INC. (US) EuroScan International work: Diabetes*

Year of approval	Device	Study name	Application	Agency
2015	Medtronic artificial pancreas	*Medtronic artificial pancreas system for the closed-loop control of type 1 diabetes*	Type 1	NIHR-HSC

**Source:* http://euroscan.org.uk/technologies/public/search?advance-search=on

2.5.4 SIEMENS AG (EUR)

Siemens AG is a multinational conglomerate company headquartered in Berlin and Munich, Germany. Siemens AG operates in several business areas, including healthcare. Siemens Healthcare is one of the world's largest suppliers of technology to the healthcare industry and is headquartered in Erlangen, Germany. The company history traces back to 1847, when Ernst Werner von Siemens founded a small family business. The name Siemens Medical Solutions was adopted in 2001, and the change to Siemens Healthcare was made in 2008. The company is a leader in medical imaging, laboratory diagnostics and healthcare IT and it has a workforce of approximately 43,000 employees worldwide.

As displayed by Figure 57, Siemens AG registered an increase in R&D expenses between 2011 and 2013 but investments dropped in 2014. This can be due to a general decrease in sales since the R&D ratio on sales remained stable between 2013 and 2014.

Figure 57 SIEMENS AG (EUR) Total R&D Investment*

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	4,065	5.7	4,291	5.7	4,238	5.4	3,925	5.3
% Change	-5.3		1.3		8.0			

** R&D expenses refer to Siemens group, not only to the Healthcare business area*

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.5 BAXTER INTERNATIONAL INC. (US)

Baxter International Inc. is an American healthcare company headquartered in Deerfield, Illinois, whose history dates back to 1931, when two Iowa physicians, Drs. Ralph Falk and Don Baxter, founded the Don Baxter Intravenous Products Corporation as the first manufacturer of commercially prepared intravenous solutions. Today, the company has two global business units: Hospital Products and Renal. The Hospital Products segment manufactures products used in the delivery of fluids and drugs to patients, while the Renal business addresses the needs of patients with kidney failure or kidney disease. Baxter employs approximately 50,000 people worldwide and serve patients and clinicians in more than 100 countries.

Baxter's commitment to R&D investments has been substantially increasing over the period 2011-2014, and also R&D ratio on sales registered a continuous increase as witnessed by Figure 58.

Figure 58 BAXTER INTERNATIONAL INC. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,421	8.5	1,246	8.2	1,156	8.1	946	6.8
% Change	14.0		7.8		22.2			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.6 FRESENIUS MEDICAL CARE AG & CO. KGAA (EUR)

Fresenius SE is a global health care group headquartered in Bad Homburg v.d.H., Germany, with products and services for dialysis, hospital and medical care of patients at home. The Fresenius Group consists of four business areas: Fresenius Medical Care, Fresenius Kabi, Fresenius Helios and Fresenius Vamed. Fresenius Medical Care is the world's leading provider of products and services for people with chronic kidney failure. The dialysis products includes dialysis machines, dialyzers and related disposables and these products are marketed in approximately 120 countries. The company employs around 100,000 people in more than 50 countries.

Fresenius' levels of investment in R&D have steadily increased since 2011, although the R&D ratio on sales remained constant over the period 2011-2014 as shown by Figure 59.

Figure 59 FRESENIUS (EUR) Total R&D Investment*

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	369	1.6	348	1.7	305	1.6	267	1.6
% Change	6.0		14.1		14.2			

** R&D expenses refer to Fresenius group which includes Fresenius Medical Care business area*

Again, searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.7 KONINKLIJKE PHILIPS NV (EUR)

Philips is a technology company founded by Gerard Philips and his father Frederik Philips in 1891 in Eindhoven, the Netherlands, and is currently headquartered in Amsterdam, the Netherlands. The company operates in three business areas: Healthcare, Consumer Lifestyle and Lighting. Philips is a global leader in cardiac care, acute care and home healthcare. The Healthcare business is organized around four strategic business groups: Imaging Systems, Patient Care & Clinical Informatics, Home Healthcare Solutions, and Healthcare Transformation Services. They focus on delivering the most technologically advanced products and solutions, helping the diagnosis and treatment of some of the most prevalent diseases. The Philips group employs approximately 108,000 people worldwide, and the Healthcare business has a workforce of around 37,000 employees.

Philips' commitment to R&D investment has been gradually decreasing since 2012, although the R&D ratio on sales increased over the period (Figure 60). This suggests that the fall in absolute R&D expenditures was probably driven by a decrease in sales.

Figure 60 KONINKLIJKE PHILIPS NV (EUR) Total R&D Investment*

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales	Amount (Mil EURO)	% Sales
	1,635	7.6	1,733	7.4	1,810	7.3	1,610	7.1
% Change	-5.7		-4.3		12.4			

** R&D expenses refer to Philips group and not only to Philips Healthcare business area*

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.8 CARDINAL HEALTH INC. (US)

Cardinal Health Inc. is a health care services company headquartered in Dublin, Ohio. The company provides medical, pharmaceutical products and services to pharmacies, hospitals and ambulatory surgery centers, clinical laboratories and physician offices. Cardinal Health provides medical products to over 75% of hospitals in the United States and employs around 34,000 people worldwide.

The company's annual reports did not provide any information on R&D expenditures, moreover searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for Cardinal Health in terms of relevant medical devices for diabetes over the period 2011-2014.

Figure 61 CARDINAL HEALTH INC. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	NA		NA		NA		NA	
% Change								

2.5.9 ALCON (EUR)

Alcon, founded in 1945 as a small ophthalmic shop in Fort Worth (Texas), was definitely acquired in 2011 by Novartis AG, a global healthcare company based in Switzerland, becoming its second-largest division. Alcon is the world's leading manufacturer of eye care innovative medicines and devices to treat eye diseases and conditions, including cataracts, glaucoma, age-related macular degeneration, retinal diseases, dry eye, eye infection and eye inflammation, ocular allergies, refractive errors, and other ocular health issues. Alcon has more than 25,000 associates in 75 countries and employs approximately 14,000 people worldwide.

Over the period 2011-2014, the company registered first an increase in R&D expenditures and R&D ratio on sales, but from 2013 onwards both total R&D expenditures and R&D ratio on sales suffered a modest decrease as shown by Figure 62.

Figure 62 ALCON (EUR) Total R&D Investment *

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	903	8.3	939	8.9	950	9.3	869	8.7
% Change	-3.8		-1.2		9.3			

** R&D expenses refer to ALCON business area (not to NOVARTIS group)*

Through the searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database), we found that Alcon has in his research pipeline a medical device for the treatment of glaucoma (Figure 63), one of the complications of diabetes that affects eyes and which can lead to progressive, irreversible vision loss.

Figure 63 ALCON (EUR) Company Clinical Trials: Diabetes*

Year	Device	Study name	Application	Study status
2014-ongoing	Ex-PRESS™ Glaucoma Filtration Device, Model P50PL	*Alcon Ex-PRESS™ Glaucoma Filtration Device in Japanese Patients*	Glaucoma	Ongoing

**Source: https://clinicaltrials.gov/*

2.5.10 COVIDIEN PLC (EUR)

Covidien is an Irish-headquartered global health care products company and manufacturer of medical devices and supplies, established in 2007 after the separation of Tyco Healthcare from Tyco

International. In 2015, the firm was acquired by Medtronic Inc., creating a global medical technology and services company. Covidien is involved in the development, manufacture and sale of the following healthcare products: Early Technologies, Advanced Surgical Technologies and General Surgical Products, Medical Supplies, Respiratory & Monitoring Solutions, and Venous Solutions.

The company's R&D expenditures and R&D ratio on sales have been fluctuating over the period 2011-2014; after a substantial decrease registered in 2013, in 2014 R&D investments recovered but did not reach the 2012 level (Figure 64).

Figure 64 COVIDIEN PLC (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	546	5.1	508	5.0	623	5.3	554	4.8
% Change	7.5		-18.5		12.5			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.11 STRYKER CORP. (US)

Stryker Corp. is a medical technology company founded in 1941 by Dr. Homer Stryker, an orthopaedic surgeon, and headquartered in Kalamazoo, Michigan. The company provides a broad range of innovative products and services in orthopaedics, medical and surgical, and neurotechnology and spine. Stryker has a workforce of approximately 25,000 people worldwide and is active in more than 100 countries.

The company's commitment to R&D investments has been increasing over the period 2011-2014, witnessed by an increase in both total R&D expenditures and R&D ratio on sales (Figure 65).

Figure 65 STRYKER CORP. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	614	6.3	536	5.9	471	5.4	462	5.6
% Change	14.6		13.8		1.9			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.12 BECTON, DICKINSON AND CO. (US)

Becton, Dickinson And Co. (BD) is a medical technology company founded in 1897 and headquartered in Franklin Lakes, New Jersey. The company produces a broad range of medical supplies, devices, laboratory equipment and diagnostic product. It operates through three segments: Medical, Diagnostics and Biosciences. In particular, the BD Medical segment is specialized in the production of needles and syringes to reduce the spread of infection, enhance diabetes treatment and advance drug delivery. The company has a workforce of approximately 30,000 people worldwide and is present in more than 50 countries.

BD's R&D expenditures registered an overall increase from 2011 to 2014. In particular, R&D ratio on sales increased in 2014 with respect to previous years (Figure 66).

Figure 66 BECTON, DICKINSON AND CO. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	550	6.5	494	6.1	471.8	6.1	476.5	6.1
% Change	11.3		4.7		-1.0			

Through the search in Clinical Trials database, we found that BD developed several diabetes devices over the period 2011-2014 (Figure 67), in particular pen needles, used for the injection of insulin in type 1 and type 2 diabetes mellitus, and infusion sets, which contain the thin plastic tubing that delivers insulin from the pump to body.

Figure 67 BECTON, DICKINSON AND CO. (EUR) Company Clinical Trials: Diabetes*

Year	Device	Study name	Application	Study status
2012	BD CGM with Outer Layer/ BD CGM without Outer Layer/ Medtronic iPro2 Professional CGM	*Three-day, In-clinic Evaluation of the BD 2nd Generation Continuous Glucose Sensor Device in Type 1 Diabetics*	Type 1	Completed

2010-2012	4 mm x 32G Pen Needle/ 8mm x 31G Pen Needle/ 12.7mm x 29G Pen Needle	*Comparison of Glycemic Control in Obese Diabetics Using Three Different Pen Needles*	Type 1/ Type 2	Completed
2012	BD NEXT 31G x 5 mm pen needle/ BD NEXT 31G x 8mm pen needle/ BD NEXT 32G x 4mm pen needle	*Clinical Evaluation of BD NEXT Pen Needle*	Type 1/ Type 2	Completed
2012	Subcutaneous delivery via Medtronic Quick-Set/ Intradermal delivery via the BD Research Catheter Set	*Multi-day (3) In-patient Evaluation of Intradermal Versus Subcutaneous Basal and Bolus Insulin Infusion*	Type 1	Completed
2014	BD Scarlett Infusion set/ Medtronic QuickSet Infusion Set	*Monitoring the Infusion Pressure in Insulin Infusion Sets in Healthy Adults*	Type 2	Completed

**Source:* *https://clinicaltrials.gov/*

2.5.13 BOSTON SCIENTIFIC CORP. (US)

Boston Scientific Corp. is a worldwide developer, manufacturer and marketer of medical devices with headquarters in Marlborough, Massachusetts. It was founded in 1979 by Pete Nicholas and John Abele as a holding company to purchase Medi-Tech, a firm that was pioneering the field of interventional medicine. Boston Scientific Corp. produces a broad range of medical technologies which are used to diagnose or treat several medical conditions, including heart, digestive, pulmonary, vascular, urological, women's health, and chronic pain conditions. The company counts approximately 23,000 employees worldwide and markets its products in more than 40 countries.

As shown by Figure 68, the company's total R&D expenditures have been continuously decreasing over the period 2011-2014.

Figure 68 BOSTON SCIENTIFIC CORP. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	817	11.1	861	12.1	886	12.2	895	11.7
% Change	-5.1		-2.8		-1.0			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.14 ESSILOR INTERNATIONAL SA (EUR)

Essilor International SA was created in 1972 after the merger of Essel and Silor, two companies which dominated the French optical eyewear market in the mid-20th century, and is headquartered in Charenton-le-Pont, France. Essilor is the world leader for corrective lenses; it manufactures high performance lenses, reading and sunwear glasses, and a range of instruments used by eye care professionals, plus specialist diagnostic equipment used by preventive healthcare institutions. The company has a workforce of approximately 55,000 employees in 62 countries.

As shown by Figure 69, Essilor's total R&D expenditures increased over the period 2011-2014, although R&D ratio on sales decreased slightly with respect to 2011.

Figure 69 ESSILOR INTERNATIONAL SA (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	188	3.3	164	3.2	161.9	3.2	151.5	3.6
% Change	14.6		1.3		6.9			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.15 ALLERGAN INC. (EUR)

Allergan is a global healthcare company founded in the spring of 1983 and headquartered in Dublin, Ireland. In 2015, the company was definitely acquired by Actavis. Allergan manufactures branded products in some key therapeutic areas, including dermatology and aesthetics, CNS, eye care, women's health and urology, GI and cystic fibrosis, cardiovascular and infectious disease. Moreover, it produces generics, over-the-counter medicines and biologic products. Allergan employs approximately 30,000 people worldwide.

The company's R&D investments increased massively over the period 2011-2014 (Figure 70). This increase could be explained by a greater availability of money due to the ongoing acquisition by Actavis.

Figure 70 ALLERGAN INC. (EUR) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	1,085.9	8.4	616.9	7.2	401.8	6.9	227.7	6.9
% Change	76.0		53.5		76.5			

Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

2.5.16 ST JUDE MEDICAL INC. (US)

St. Jude Medical Inc. was founded in 1976 in St. Paul, Minnesota, as a pioneering manufacturer of bi-leaflet implantable mechanical heart valves. The company is specialized in the production of medical technologies for the treatment of a broad range of serious clinical conditions, including heart failure, heart rhythm disorders, vascular disease, structural heart disease, chronic pain and movement disorders. St. Jude Medical employs approximately 23,000 people worldwide.

After a decrease in R&D expenditures registered in 2012, the company's investments recovered in the following years although they did not reach the 2011 level (Figure 71). R&D ratio on sales remained quite stable over the period.
Searches in the selected databases (Clinical Trials, FDA premarket approval (PMA), de novo database and EuroScan Database) did not reveal any results for the company in terms of relevant medical devices for diabetes over the period 2011-2014.

Figure 71 ST JUDE MEDICAL INC. (US) Total R&D Investment

R&D Investment	2014		2013		2012		2011	
Total R&D Expense	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales	Amount (Mil USD)	% Sales
	692	12.6	691	12.6	676	12.3	705.1	12.6
% Change	0.1		2.2		-4.1			

2.5.17 OTHER MINOR MD COMPANIES

Through the search in the PMA database (Figure 72) and EuroScan website (Figure 73) we identified a list of new and emerging health technologies for diabetes care manufactured by EU and US medical device companies not comprised in the top companies identified previously.

Figure 72 MINOR MD COMPANIES PMA Medical Devices: Diabetes*

Year	Device	Application	Company
2012	DEXCOM G4 PLATINUM CONTIUOUS GLUCOSE MONITORING SYSTEM	Diabetes mellitus	DEXCOM, INC.
2014	ANIMAS VIBE SYSTEM	Diabetes mellitus	ANIMAS CORP.

*Source: http://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/

Figure 73 MINOR MD COMPANIES EuroScan International work: Diabetes*

Year	Device	Study name	Application	Company	Agency
2011	Endobarrier ®	*Endobarrier ® for type 2 diabetes mellitus with obesity*	Type 2	GI Dynamics Inc	NIHR-HSC
2012	SCOUT DS® / Diab-spot	*SCOUT DS® and Diab-spot for type 2 diabetes screening*	Type 2	VeraLight Inc/ DiagnOptics BV	NIHR-HSC
2013	Afrezza	*Afrezza Inhaled Insulin for Diabetes Mellitus*	Diabetes mellitus	Sanofi Diabetes	CADTH
2015	Inreda's artificial pancreas	*Inreda's artificial pancreas for the closed-loop control of type 1 diabetes*	Type 1	Inreda Diabetic BV	NIHR-HSC
2015	GlucoSitter	*GlucoSitter for the closed-loop control of type 1 diabetes*	Type 1	DreaMed Diabetes	NIHR-HSC

2015	Florence	*Florence for the closed-loop control of type 1 diabetes*	Type 1	University of Cambridge	NIHR-HSC
2015	Diabetes Assistant (DiAs)	*Diabetes Assistant (DiAs) for the closed-loop control of type 1 diabetes*	Type 1		NIHR-HSC
2015	Closed Loop Glucose-Sensing Insulin-Delivery System	*Closed Loop Glucose-Sensing Insulin-Delivery System for the closed-loop control of type 1 diabetes*	Type 1		NIHR-HSC
2015	Bio-inspired Artificial Pancreas (BiAP)	*Bio-inspired Artificial Pancreas (BiAP) for the closed-loop control of type 1 diabetes*	Type 1	Imperial College London	NIHR-HSC

**Source: http://euroscan.org.uk/technologies/public/search?advance-search=on*

2.6 Medical Devices Industry Output Data: Bibliometric Evidence

In order to offer a picture of Medical Devices industry as much comprehensive as possible, we gathered information on research outputs funded by the MD companies in the diabetes area for the period 2009-2013 (Figure 74). The search was performed on Web of Science (see Section 4 for methodological details) and carried out under the bibliometric DIABE filter.

It must be noted that the aliases/spelling errors in naming the RFOs by WoS means that not all them may have been captured or that other organizations may have accidentally been captured due to the simplistic terms used. In cases in which a company had only generic codes, the name of the company itself was searched instead of the code. In RESPI and DIABE the funding data searched also include papers in which the company was listed among the addresses; for the other NCDs only the funding data were searched. It should also be noted that some of the companies also develop pharmaceutical products, thus the counts of papers may include them.

Johnson & Johnson and Alcon seem to dominate diabetes research outputs, with 271 and 267 scientific papers respectively published between 2009 and 2013. It is worth underlining, however, that these two companies also develop medicines for the treatment of diabetes, so the numbers above may have captured also scientific studies regarding pharmaceutical products. Medtronic, the major producer of diabetes medical devices in our sample, published 127 studies, but, contrary to Johnson & Johnson and Alcon, it produces only medical technologies so the count of papers does not include any pharmaceutical product. Overall, with the exceptions of Stryker Corp and the two companies not searched, all top MD firms have published several studies on diabetes over the period considered. These results are quite in contrast with the findings of the analysis of research pipelines, since we found that only 3 companies are currently investing in new MD. There are three possible explanations for this discrepancy: 1) as already underlined, some companies are involved also in the pharmaceutical segment so the counts of papers may have also included drugs; 2) some companies may not be lead sponsor in clinical trials so our search in clinicaltrials.gov database may have not found them; 3) study protocols might have been registered elsewhere or not registered at all; 4) some studies published may regard existing products, which are not captured in the search of pipelines because only innovative MDs were considered.

Figure 74 Top Medical Devices Companies Bibliometric Output Data

Company	Country	Code	Name of Alternative Code	Output Papers DIABE
Johnson & Johnson	US	JJJ-IP-US	Johnson & Johnson	**79**
		AZC-IN-US	Alza Corporation (SUBSID)	**0**
		CDM-IN-US	Codman (SUBSID)	**0**
		DPY-IN-UK	DePuy International Healthcare (SUBSID)	**0**
		ETC-SP-US	Ethicon Inc (SUBSID)	**58**
		ETH-IN-AU	Ethnor (SUBSID)	**0**

		JJJ-IP-US	Cougar Biotechnology (SUBSID)	**0**
		LFD-IN-US	LifeScan (SUBSID)	**53**
		MNP-IN-US	McNeil Pharmaceutical (SUBSID)	**7**
		SJV-BT-US	Scios (SUBSID)	**1**
		VIO-BT-BE	Virco (Tibotec) (SUBSID)	**0**
		X15-IN-US	Neutrogena Corporation (SUBSID)	**0**
		JNA-SP-AU	Janssen Pharmaceutical / Cilag (SUBSID)	**0**
		JNS-SP-BE	Janssen Pharmaceutica N V, Beerse (SUBSID)	**73**
		JNU-SP-UK	Janssen Pharmaceutical Ltd, Wantage, Oxon (SUBSID)	**0**
		CCR-IN-NL	Centocor (SUBSID)	**0**
		CLG-IN-BE	Cilag Biotech (SUBSID)	**0**
		ORJ-BT-US	Ortho Biotech / Division (SUBSID)	**0**
General Electric Co.	US	XXG-IN-US	General Electric Co.	**30**
Medtronic Inc	US	MDI-BT-US	Medtronic Inc	**127**
Covidien plc	IE	Y1B-BT-IE	Covidien plc	**4**
		Y15-IN-IE	Covidien plc	
		HUF-IN-IE	Covidien	**4**
Siemens AG	DE	SMN-IN-DE	Siemens AG	**17**
Baxter International Inc	US	BXT-IN-US	Baxter International Inc	**7**
		BXW-SP-BE	Baxter Medical A B, Bromma, Sweden (SUBSID)	**0**
		CLH-SN-UK	Clinitec, Nutrition Ltd (Baxter) (SUBSID)	**0**
		BAX-SP-UK	Baxter Healthcare Ltd, Newbury, Berks (SUBSID)	**0**
		BXR-SP-BE	Baxter R & D Europe, Nivelles (SUBSID)	**0**
Fresenius Medical Care AG & Co. KGAA	DE	XFN-IP-DE	Fresenius Medical Care AG & Co. KGAA	**6**
		FRS-SP-UK	Fresenius Ltd (FHC Holdings Ltd), Runcorn, Cheshire (SUBSID)	**0**
Koninklijke Philips NV	NL	PHG-IN-NL	Koninklijke Philips NV	**2**
		NO CODE	Saeco	**0**
		RSR-IN-US	Respironics Inc.	**0**
Cardinal Health Inc.	US	X15-IN-US	Cardinal Health Inc.	**1**
		CJD-IN-US	Cordis (UK) Ltd, Brentford, Middx / Cardinal Health	**7**
Novartis AG (Alcon)	CH	NVP-IP-CH	Novartis AG	**235**

		ALC-IN-CH	Alcon Inc./Laboratories (SUBSID)	**4**
		CBP-FO-UK	Novartis Foundation (formerly Ciba Foundation), London	**27**
		CBG-IP-CH	CIBA-Geigy (SUBSID)	**1**
		CBJ-SP-US	Ciba (now 'Novartis') Corporation, Summit NJ	**0**
		CGP-SP-UK	CIBA-Geigy A G (Since 1996 'Novartis') , Basel, Switzerland	**0**
		NGY-SP-NL	Ciba - Geigy B V, Arnhem, herlands	**0**
		CIB-IP-JP	Japan: CIBA - Geigy Foundation, Takarazuka	**0**
		CRN-BT-US	Chiron Corporation (SUBSID)	**0**
		SDZ-IP-CH	Sandoz Pharmaceuticals (SUBSID)	**0**
Stryker Corp.	US	X1B-BT-US	Stryker Corp.	**0**
Becton, Dickinson and Co.	US	X1B-BT-US	Becton, Dickinson and Co.	**28**
		BDC-IN-US	Beckton, Dickinson (BD), Franklin Lakes, NJ	
Boston Scientific Corp.	US	JBS-IN-US	Boston Scientific Corp.	**34**
Essilor International SA	FR	NO CODE	optical lenses	**Did not search**
Allergan Inc. (Actavis)	IE	ALL-IP-US	Allergan Inc. (Actavis)	**8**
		AVF-IP-US	Actavis Inc. / Aptalis	**6**
		AZG-SP-UK	Allergan Therapeutics Ltd (UK), High Wycombe, Bucks (SUBSID)	**0**
St. Jude Medical Inc.	US	NO CODE	CARDI	**Did not search**
TOTAL PAPERS DIABE				**819**

2.7 Discussion: The Medical Device Research Pipeline for Diabetes

Figure 75 Figure 75 Synthesis Results: Medical Device Industry R&D Investmentreports synthesis results elaborated from the tables above. Column 3 displays for each MD company the percentage change in total R&D investment between 2011 and 2014. Column 4 shows the mean R&D intensity (i.e. R&D ratio on net sales) calculated over the time frame.

Over the period 2011-2014, the medical device sector commitment to R&D investments has been substantially heterogeneous. Among companies based in Europe, one firm (i.e. Allergan) registered an impressive increase in absolute R&D investments (+378% between 2011 and 2014), another (i.e. Covidien) experienced a slight decrease in expenditures, and the remaining companies registered a moderate growth of expenditures. The landscape for US firms is more heterogeneous, in fact half companies experienced a modest decrease in R&D investments and the other half a more substantial increase.

As regards R&D intensity, US firms generally record higher levels of R&D ratio on sales than European companies: US mean R&D intensity is approximately equal to 8.5, while for Europe is 5.6. These findings suggest that, overall, US medical devices companies allocate more resources in research and development activities than EUR firms.

Figure 75 Synthesis Results: Medical Device Industry R&D Investment

Company	Country	% change R&D expenditures (2011-2014)	Mean R&D intensity (2011-2014)
Johnson & Johnson	US	12.5	11.5
General Electric	US	-8.0	3.1
Medtronic	US	-2.1	9.2
Siemens	EUR	3.6	5.5
Baxter International	US	50.2	7.9
Fresenius Medical Care	EUR	38.2	1.6
Philips	EUR	1.6	7.4
Alcon	EUR	3.9	8.8
Covidien	EUR	-1.4	5.1
Stryker	US	32.9	5.8
Becton, Disckinson & Co	US	15.4	6.2
Boston Scientific	US	-8.7	11.8
Essilor International	EUR	24.1	3.3
Allergan	EUR	376.9	7.4
St. Jude Medical	US	-1.9	12.5

Despite the general, although modest, growth of R&D commitment, most companies in the sector have not developed any diabetes relevant medical devices over the period. Only three companies out of 16 (i.e. Medtronic; Alcon; Becton, Dickinson & Co.) are currently involved in the production of innovative diabetes medical devices. Medtronic has been the major developer over the period considered, followed by Becton, Dickinson & Co. and then by Alcon, with only one MD in its pipeline. Many top companies identified are specialized in other NCD categories, but some (for example Johnson & Johnson and Boston Scientific), despite providing solutions for diabetes, are not currently developing any innovative medical device in this area.

Diabetes medical devices consist of a wide range of products that, according to the European Association for the Study of Diabetes (EASD), include insulin pumps, insulin pens, aids for insulin users, glucose monitoring devices (self-monitoring blood glucose and continuous glucose monitor), glucose products, blood glucose meters and infusion sets. Medtronic is mainly involved in the development of insulin pumps, glucose monitoring devices and infusion sets. Becton, Dickinson & Co. is specialized in the production of pen needles, but it also develops infusion sets and CGM (continuous glucose monitor) systems. These two companies produce devices for the treatment of type 1 and type 2 diabetes mellitus, while Alcon is focused on devices for the treatment of eye problems induced by diabetes.

Probably the most striking observation from the analysis of companies' research pipelines is that, among top medical device firms, only few of them invest in research and development of diabetes devices. This seems to suggest that diabetes is still receiving low attention by the MD world, despite being one of the top 10 causes of disability worldwide. Another reason could be that it is difficult to tackle through medical device technologies a disease which is essentially metabolic and to address with pharmacologically active substance in first instance. In any case, there are known existing limitations that hinder the innovation process for the MD sector, especially in Europe. For example, European medical device industry recognizes that *"[…] the regulatory system needs an overhaul due to increased expectations and technological advances, and acknowledges that positive change is necessary to improve Europe's medical device regulatory framework"* (Eucomed, 2014). Moreover, as underlined by IDF's report "Access to quality medicines and medical devices for diabetes care in Europe", European countries do not have the same availability of treatment options due to the unequal number and types of products marketed in each country. Moreover, accessibility to optimum diabetes treatment is undermined by inequalities in access to appropriate continuous education for people with diabetes and their relatives. According to the European Association for the Study of Diabetes (EASD)[22], it is necessary to develop collaborations between academic medical societies, regulatory bodies and industry in order to improve diabetes care in the area of medical devices. These aspects are also picked up in the next section as emerging themes from the stakeholders' interviews (see section 3).

[22] http://www.imdrf.org/docs/imdrf/final/meetings/imdrf-meet-131112-belgium-presentation-easd-mds-in-diabetes-care.pdf

3 Stakeholder Interviews: Diabetes

An established trend observed across the EU over the last decades is a decline in diffusion of infectious and communicable diseases that, however, makes people more exposed to develop and suffer from debilitating NCDs, among which diabetes has a primary role (Lozano et al., 2012). According to the World Health Organization (WHO), diabetes is a chronic disease characterized by an increased and maintained concentration of glucose in the blood. Prolonged raised blood sugar levels lead to serious microvascular and macrovascular complications that may result in organ and system failure. Four main aetiological categories of diabetes mellitus (DM) have been identified: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other specific types of DM and gestational DM (WHO, 1999). The former is characterized by a lack of insulin production and it is often called childhood-onset diabetes or insulin-dependent diabetes. On the other hand, type 2 diabetes is caused by cells' ineffective use of insulin, often due to overweight and lack of exercise. Gestational diabetes is a state of hyperglycaemia that develops during pregnancy without previously known diabetes, whilst other specific types of diabetes include rare forms collectively identified as monogenic diabetes (Colom and Corcoy, 2010) or diabetes secondary to other pathological conditions (WHO, 1999).

Long-term prevalence and incidence in diabetes show increasing trends (Chen et al., 2012). In 2014, the WHO estimated the global prevalence of diabetes to be 9% among adults (≥ 18 years), with 1.5 million of directly associated deaths. Although, more than 80% of diabetes deaths occur in low- and middle-income countries, in the European Region this condition accounts for 634.000 deaths every year and 11% of all deaths in the age 20-79 years (Roglic and Unwin, 2010). Almost half are people aged under 70 years (Roglic and Unwin, 2010). Diabetes deaths worldwide almost doubled between 1990 and 2010, in contrast to what happened for most diseases, including major vascular diseases, chronic obstructive pulmonary disease, most forms of cancer, liver cirrhosis, and maternal disorders (Lozano et al., 2012).

Epidemiological studies suggest that diabetes is related to non-modifiable risk factors, as ageing of the population, genetic factors and gender, but the increasing prevalence is mostly due to modifiable risk factors as overweight and obesity, tobacco use, unhealthy diet and physical inactivity, and socioeconomic disadvantage. Of course, these risk factors are closely connected to the risks for other NCDs, such as CVDs, CRDs and cancer. Hence, diabetes represents a critical issue in all discussions and publications around NCDs prevention and control, and health strategies for diabetes must be integrated into population approaches to prevent NCDs as a group (Jakab, 2010).

Because of the many modifiable risk factors, diabetes is largely preventable. Across Europe, policy-makers engaged in funding research not only for developing interventions but also to promote prevention strategies to mitigate the impact of this disease. Through the survey stage of MAPPING_NCDs project, we identified 120 Research Funding Organizations (RFOs) investing in diabetes research. In Eastern Europe, all RFOs are government organizations, and third sector RFOs do not exist. In Western Europe, there is a greater number of charitable and voluntary sector RFOs. In all cases, however, few of these RFOs (13, 11%) are devoted exclusively to diabetes research, and

the majority makes research investments in other NCD disease areas.
While accurate mapping of RFOs and their funding activities via surveys and bibliometrics can assist government in identifying the most fruitful approaches to NCD investments research; policy makers must also take account of the often strong visions and firm priorities of leaders in the field of diabetes research. To this end, MAPPING_NCDs necessarily involves the conduct of semi-structured interviews as a means for eliciting the preferences and opinions of key diabetes stakeholders. In this way, the project opens a dialogue with diabetes researchers and investors on the basis that qualitative interviews hold the potential to develop wider theory and hypothesis for both mapping diabetes research funding, and also improving the relevance, efficiency and impact of research investment (Wright et al., 2014). To some extent, new strategies and funding initiatives for diabetes research must align with the scientific, clinical and economic priorities and interests of leaders in the field. For this reason, the mapping of diabetes research activities needs to consider stakeholder motivation and views for improving research investment strategies and outcomes for diabetes.

Stakeholders are located at various points of the diabetes research process. For the purpose of this project, stakeholders can either be directly associated with NCD research or involved in making research investments in NCD research. At both of these points, MAPPING_NCDs makes contact with stakeholders, seeking their views on both the current and future state of funding for diabetes research. In terms of funding in diabetes, this typically originates from a variety of sources: national governments (EU MSs), international organizations or non-governmental organizations with regional or global reach (e.g. OECD, WHO Regional Office for Europe), the private sector (pharmaceutical, biotechnology and medical device industry), charities or not-for-profit organizations (e.g. European Diabetes Foundation, Diabetes UK, Italian Banking Foundations), and, importantly, supranational organizations (e.g. European Commission) as well as public-private partnerships (e.g. the Innovative Medicines Initiative).

As a research methodology, semi-structured interviews provide opportunity to develop hypotheses about the future shape of research funding in diabetes. Enabling close collaboration between the interviewers and stakeholders, interviews allow stakeholders to describe their views of the current state of research and to improve interviewer's understandings of the key factors influencing the current and future shape of research on diabetes. They hold a capacity to answer the 'how' and 'why' of diabetes research funding, allowing interviewers to understand how funding activities are influenced by individuals and the contexts in which they are embedded (Baxter and Jack 2008, 556). Consequently, interviews have the potential to improve the quality of the wider mapping exercise by providing researchers with more complete understandings of causes and effects, enabling them to develop better ideas for future funding strategies that target more relevant factors. Ultimately, the purpose of the stakeholder interviews is to open a sophisticated and collaborative dialogue between decision makers and key personnel involved in the diabetes research system with a view to producing a more nuanced map of research funding activities, and thereby heighten the potential for future research investment in the area.

3.1 Methods

Stakeholders were purposively selected to reflect a range of factors including: expertise in diabetes research, geographic location and expertise in awarding research funding or conducting research as a principal investigator (PI). The interview questions explored (1) current threads of research; (2) future research areas; (3) types of collaborations; (4) working with collaborators; (5) working with the private sector; (6) types of funding organizations; (7) working with funding organizations; (8) future strategies for funding NCD research, with slight differences for PIs or RFOs' representatives. A copy of the interview guide is available in the Appendix 8. All interviews were recorded and transcribed. Consent was gained for all interview subjects and their anonymity. Transcripts were typed verbatim, proof read and corrected, while notes and comments were collected and made into memos. They were analysed qualitatively using inductive thematic analysis (Silverman, 2004). Constant comparative approach was used to iteratively identify emerging themes that will contribute to generate a vision about future research funding strategies across the EU to tackle gaps and challenges currently perceived by experts in the field (Bradley EH, Curry LA, and Devers KJ 2007). Quotes from the interviews are included to explain or illustrate key points. While retaining anonymity, the speakers have been identified by a numerical code in order to allow readers to distinguish different voices.

3.2 Results

In total, 11 interviews were conducted. Personnel were selected to reflect a range of geographical regions across the EU. We had interviewees from Italy (3 out of 11), UK (3 out of 11), Ireland (1 out of 11), France (1 out of 11), Portugal (1 out of 11), Estonia (1 out of 11) and the Netherlands (1 out of 11). The aim was to solicit views and experiences of people involved in both the conduct (4 out of 11) and funding (7 out of 11) of research across the EU area. Principal investigators had different scientific interests within diabetes research: from drugs mechanisms evaluation to clinical development of therapeutic alternatives in childhood and adolescence to understanding the pathophysiology of vascular complications of diabetes and identification of suitable interventions. They were all affiliated with University Hospitals around the EU. In terms of RFOs represented, most of them were private not-for-profit organizations or charities dedicated to advance the understanding of causes, prevention and cure of diabetes through research. In two cases, the RFOs were funding research across a spectrum of diseases, including many other NCDs that are the focus in the MAPPING_NCD project. Below major emerging themes are presented and illustrated through direct quotes from the interviews.

3.2.1. Challenges in diabetes research

The informant touched upon several themes when asked to reflect on the challenges perceived in the current research environment in diabetes.

A first major theme relates to financial challenges. Informants generally claim that more money are needed or that they have observed a decrease in available funding over time, also due to the harsh economic crisis that hit Europe since 2008. This observation is common to informants from different geographic origins:

> *"Funding has decreased over time."* (2)
>
> *"Economic recession has resulted in less money going to foundations"* (6)
>
> *"A main challenge is to be able to continue to fund high quality research, which is obviously difficult given the financial situation in [country]."* (4)

On the same theme, the informants emphasize the competition among sponsors and research teams to get access to adequate level of funding, to cover for infrastructure, consumables, technical support and staff.

> *"We really see that researchers are applying a lot, this means there isn't enough money available for them in [country]. […] This is very critical for them, they are fighting to get the money they need for the best projects they have."* (8)
>
> *"The answer is more money but I don't think that's going to happen somehow! […] you are scoping so much out to get the money in, that you spend half of your life to get grants in and there is such a small proportions of people achieving but I don't know how that's going to change in the near future."* (11)

The competition and the unstable level of funding put team leaders under pressure to secure continuous funding for the team. The management of human resources can be critical within the

current research environment for both financial or organizational constraints, such as the requirement for trainees to rotate across labs or units (2) or to limit the possibility to apply for grants only to researchers who have already a permanent post (11):

> *"What's important then is having more stable funding for the team […] it can be very tough for your people […] If you don't have other money you have to stop their contracts."* (8)

> *"[…] young researchers, being able to help them find a career path that allows them to stay after they reach a certain level."* (4)

Given this context, one of the PIs pointed out the importance of good management skills training for researchers, something that is often overlooked in their curricula (11).

According to the informants, the private sector is the main source of funding in diabetes research sometimes because it is perceived to be more accessible compared to public funding, particularly for Southern and Eastern EU researchers.

> *"In terms of research activity, considerable funding comes from private sources, pharmaceutical companies. Public funding is limited and difficult to access. […] Funding from EU level is also limited. […] Private funding sources will continue to be the most relevant"* (2)

In any case, this is considered to be a problem as private companies do not necessarily have the interest to invest in all areas where there is need or where risks are higher.

> *"[…] the treatment trials, 99% are funded by the industry, so this is clearly a problem."* (10)

> *"[…] industry, which of course invests in research but invests in research in these areas where there are huge returns, some of the chronic diseases may not, and therefore the research in really really new therapies, not the one slightly improving existing drugs, may be neglected."* (7)

The heterogeneity of funding opportunities is therefore something to preserve and develop into different forms of collaboration within and between countries, and across different types of RFOs. An example that was cited from overseas is the joint effort between the National Institute of Health (NIH) in the United States and the Juvenile Diabetes Research Foundation (JDRF) that wind together supporting research (5). Another example was about Diabetes UK and British Heart Foundation joining up to look at areas of interest at the intersection between the mission of the two organizations (11).

> *"Heterogeneity across Europe can be a good thing, national governments are supplementary in funding research."* (10)

> *"How do you make sure that all these pieces [ndr, individual PhDs or large scale programs] come together, that actually we can make a significant step forward instead? […] You need to find a way of collaborating, it's almost like seeding money to make sure that people develop small scale ideas, and if it turns out to be fruitful then maybe it becomes a large scale consortia."* (6)

This cooperation between funding bodies seems a useful strategy to tackle the complex and multidimensional issues posed by diabetes as a health condition.

> *"The more we get to know about diabetes, the more we get to see it's a complicated condition. […] we need to combine all this research and various methods and various areas of research to really come up with a significant progress of understanding diabetes and finding betters ways of preventing and treating it."* (6)

The collaborative approach is also needed from the researchers side. The creation of strong and stable collaborative networks within and between countries will speed up the pace at which we will move forward on achieving the important targets set for global diabetes research.

> *"High quality research requires collaboration between researchers […] It takes a long time to recruit patients, to get enough patients, unless we have collaborative or network research not just within countries but between countries"* (5)

In terms of challenges, a final aspect was mentioned by one of the informants and seemed very relevant to the whole MAPPING_NCDs project. This expert marked as "huge political error" (7) the recent trend of combining chronic diseases under the same umbrella term of 'non-communicable diseases' and the same provision of services for conditions that are inherently different. The critique to the combined NCD-wide approach should be discussed and motivated further by health policy makers:

> *"The emphasis on NCDs, it means that the specific disease within the NCDs definition loses out, they may have a communality of being non communicable but the other commonalities are few […] each of diseases is specific in its own rights and burden of complication, needing a very different approach. […] they are now all under one common umbrella and nothing has been done properly. A real adverse effect in terms of health policy."* (7)

3.2.2. Duplication in diabetes research

The debate on waste in scientific research is a contemporary one (Macleod et al., 2014). We asked our informants whether they perceived a significant level of duplication in diabetes research and if so, whether this has negative implications. The general feeling was that there is a degree of duplication of studies in diabetes, however this is not necessarily a bad thing. The risk is with the publication bias that reduces the likelihood of publishing negative results. That means there is unfortunately a higher probability of repeating unsuccessful research projects. However, particularly for intervention studies where the external validity dimensions play a significant role in determining the outcomes of the treatments, it is somehow beneficial to be able to replicate results in different settings:

> *"If it is at biomedical level than obviously there is no point in repeating the research but if it is a patient-services level it may be beneficial to repeat the research on different target populations"* (4)

> *"I think there is (ndr, duplication) particularly when you get negative findings or negative studies because there is a bias in publication or people don't like to publish negative results. But I also do think is good to have things confirmed in research because I think sometimes what you read in the paper isn't necessary the whole story, so some degree of duplication can be good because it can verify some aspects or in slight different patients groups."* (11)

One informant refers to EU projects, in particular making the point that they may appear redundant at first glance, whilst in reality they are complementary and cover all different sides of the problem:

> *"I think sometimes we even see duplication in the EU projects themselves. But I think that's only at first look. If you look closely the different projects come with different approaches […] in a way some of them have a focus in research, others have a focus in policy, others have a focus in producing new services and products. In reality they can help each other*." (9)

From the perspective of the researchers, although there is a great pressure to *"match the funder's expectations"* (11), duplication of calls is considered as a good opportunity to pursue research on the subject of interest. However, what does not seem acceptable is to have different grants paying into the same research projects. When a research proposal is successful with more than one sponsor, it would make sense to keep one of the grants to fully fund the project, and move the other funding to a different still promising research idea.

> *"I don't think that there is unnecessary duplication either by funding bodies or indeed researchers. I think in many ways is good to have many of these funding bodies offering opportunities to do research in an area where we are interested in through specific calls. So I wouldn't look at the duplication, because it's not a hindrance but it's actually perhaps a way for us offering more opportunities to secure funding."* (5)

> *"We know that our teams who get funding from us also get other grants. But we can't go against this because we have a scientific committee that select all the best projects, and it's true is likely that these projects will be also selected by other committees. We try to be careful […] we ask them to choose which money to keep, from one or the other […] to stop our funds because ERC are paying millions Euros."* (8)

3.2.3. Research gaps

Clinically, informants pointed out significant scope remains for improving outcomes for diabetes patients, particular in terms of aetiology, prevention and development of new treatments research. According to the informants, the *"pathogenesis of hypoglycemic/hyperglycemic events"* or *"pathogenesis of chronic complications"* needs further understanding (1, 11). In terms of new treatments, on the short-term the focus could be on the study of *"the molecular basis of actions of insulin or optimization of insulin pumps"* (2), whilst in the long-term the identification of *"new molecular targets, the development of the artificial pancreas, beta-cells transplant, conversion of cell lines not producing insulin and control of auto-immunity"* seem all promising but still underinvestigated areas (2). Childhood or adolescence diabetes, or more generally type 1 diabetes is the specific condition where a cure is much needed (6) and there is more limited funding available (5). In T1DM, another area that deserves more interest is:

> *"[…] the use of what we call adjunct therapies, so these are additional drug agents [ndr enhancement of insulin action, (e.g. the biguanides and thiazolidinediones), alteration of gastrointestinal nutrient delivery (e.g. acarbose and amylin), and other targets of action (e.g. pirenzepine and insulin-like growth factor-1 [IGF-1], which reduce growth hormone secretion, and glucagon-like peptide-1, which acts to stimulate insulin secretion] in addition to insulin for managing type 1 diabetes."* (5)

Prevention becomes more relevant in terms of type 2 diabetes and concerns not only typical public health interventions aiming at eradicating sedentary lifestyles but also genetic, environmental and other risk factors that predispose to the development of the disease:

> *"[…] developing diabetes prevention cause we still have a very big prevalence that is being fed by high number of people with pre-diabetes and of course all the societal challenges that drive the incidence of diabetes."* (9)

> *"As a foundation we still believe that's something that we should be funding [ndr, prevention of type II diabetes] cause we want to prevent people from having diabetes in the future […] there is more in terms of preventing diabetes than just focusing on diet and physical activity. […] There may be something in genetics, something in our environment or other factors that are still unknown and we need to research in order to do something about them."* (6)

At a more generalized level, and as emerging from other NCD stakeholders' interviews, some informants insisted that the future for research lay in relation to personalized medicine. Sometimes called 'stratified medicine', personalized medicine involves the practice of subdividing patients into groups based on their responses to therapies or their risk profile for developing certain disease conditions. Ultimately, stratified medicine is using knowledge of patients and disease pathways to ensure that the right patients, receive the right types of medicine at the right times. Towards this end, it is also about early diagnosis and predicting the onset of disease using biological markers that divide patients in to groups for the purpose treating the disease much earlier.

> *"The key element that should be invested in is personalized medicine, genomics. So I think it does need to be a great investment in this area so that it can be speeded up. There is some evidence on personalized medicine for cancer drugs but in diseases such as diabetes this remains a neglected area."* (7)

However, genomics is not the panacea to defeat diabetes *("We all have the wish that genetics will give us the answer to diabetes but it is complex!"* (6)). The informants have raised the attention on the psychosocial aspects of living with diabetes and the need to improved the health related quality of life of this group of patients. One of the informants told us this was a topic emerging from a survey conducted among diabetes patients who said:

> *"We want more focus on the psycho-social aspects of diabetes. Diabetes is a lot more than measuring or administering medications, diabetes is something that you have 24h a day, 7 days a week and especially for type I the impact is very high. So they asked what about this psychological aspects, what about depression, what about quality of life"* (6)

This view was confirmed by a PI as well:

> *"[…] more funding on psychosocial management of diabetes or psychosocial aspects of diabetes, because my feeling is […] I think we are almost at the limit of both technologies and currently available therapies and the limitations with these therapies is very much down to patients and carers […] I think we need to address how we make patients and families more engaged with the treatment and how we get them to use the treatment much more effectively."* (5)

In terms of tools or infrastructure that might be useful to speed the research up bio-banks or patient registries should be set up and maintained to allow high quality studies on significant sample sizes and across countries.

> *"The availability of bio-banks and funding to set them up. This is an issue that should be addressed in order to move on to the next level. So for instance if I wanted to research on people newly diagnosed with diabetes, there isn't a registry available to researchers and neither are samples kept. Other countries would be able to access the bio-banks of tissues and bloods that may be reserved as part of their practice."* (4)

> *"And also the other aspect is that, with the exception of Sweden which is the only country that has a reliable up-to date diabetes register of disease, no other country has this. The other important aspect in relation to the research in diabetes is also the accurate recording of clinical outcome, not done!"* (7)

In terms of most important stages of research to invest in translational research is a common one (9,3). Translational research "translates" findings of basic research into medical and nursing practice in order to obtain meaningful health outcomes. In other words, it implements the "bench-to-bedside" paradigm, from laboratory experiments through clinical trials to practical applications, clinically or commercially available.

> *"the type of research that produces (more easily) new knowledge. To address unsolved medical issues you need to start from preclinical research, that is our aim, to find new solutions to health and scientific problems"* (3)

However, *"funding research that allows immediate impact on the lives of people with diabetes"* (4) or very innovative and highly risky research, as *"some projects between different disciplines, really at the hedge of innovation research"* (8) were also identified as priorities. Finally, the research in the *"economic impact of the disease"* may be missing in some countries, even if the assessment of the costs for both the patients and the healthcare system could better inform some of the policies. (9)

3.2.4. Defining impact of research and setting priorities

The informants reflected on what achieving impact means from the perspective of a funder or a researcher. Both group mentioned the scientific publication as a propaedeutic step (1,2,3,8,9,11).

> *"Of course publication and dissemination are vital"* (4)

Some RFOs actively track acknowledgements to the sponsor in the published outputs in order to increase their prestige and encourage future donations (1,3,8). A published academic publication can also be a formal requirement for receiving the last tranche of money or future grants by particular funders (11). In terms of dissemination, other showcases reaching the general public seem also important.

> "*Is there any patent? Publication? Presentation at meetings? Have your research been in the newspapers? Have you been interviewed by scientific TV programmes? And also one thing that is important for us as a way to measure impact of the research we are trying to see whether these people are getting ERC funding."* (8)

This informant also gives a metric to understand whether the research being funded at her organization is valuable. However, the definition of impact goes beyond academic publishing.

> *"I think there is a broader dimension, the impact on common goods, a rapid shift onto the diagnostic or therapeutic practice as expressed by the change in the clinical guidelines. However, this is difficult to measure as behind this change there could be one, two or three interrelated papers and a long sequence of propaedeutic research that lead until the final update."* (1)

How to account for partial contributions to the advance in the biomedical and clinical research, then? Another broader view was on the impact as *"development of Health Services in [country]"* (4) or impact on "patients and the big society" (5):

> "*The impact is on patient health outcomes. I think every time we are submitting funding applications we have to address the impact aspect, it's no longer just acceptable to be focussed on the science so to speak but also on how this might be transferable into improvement of healthcare or healthcare delivery."* (5).

> *"Findings can be very interesting from a scientific point of view but if there is no relevance of these findings for people with diabetes than for us that means that the impact is reduced. It takes a long time before the results reach a person […] hence, we include patients in the selection process as well."* (6)

Priorities may change as a result of this broader view on what to expect from biomedical and clinical research. Although many calls are still *"open, to reward quality rather than steer research"* (1), meaning that there is no prespecified topic to do research on, showing impact on the patients and society beyond scientific excellence may lead to different approaches to priority-setting. On the one hand, research into the communication and implementation of previous results become more important (*"I think many research come up with very interesting findings but it has proven to be very difficult to then make the next step and make sure that these results are communicated or implemented or find a way into a product or a service that people with diabetes can use."* (6)*)*. On the other hand, donors' awareness has improved over time so that transparency and a greater accountability of all research funders is needed to keep the engagement high in the research environment.

> *"Before we used to have very generic research programs, and basically asking people if they wanted to support our research programs and that was enough, but nowadays we have to be much more specific and say this is what we are trying to do in curing type I diabetes."* (6)

3.2.5. Working with different stakeholders

During the interviews the opportunity and different modality of cooperation between funders and researchers emerged under several themes. First of all, there could be different reasons to engage in a collaboration with other stakeholders during the overall research process, from the basic need to co-finance big projects (1, 5, 9, 11) to allocation of different roles. It has been highlighted that foundations or not-for-profit organizations' activities could have the status and expertise to act as promoters of education or dissemination to the general public of the findings from the major research initiatives.

> *"We as a foundation can also play an important role in disseminating the findings of projects to a wider audience. We do it for a number of EU funded projects, and I think it helps to the goals not only of the EU commission but also of the MS that the researchers"* (6)

As regards T1DM research, *"a more direct engagement with the major scientific societies"* (5) was invoked to steer the agenda setting for major European projects. In Northern EU countries, the good practice of involving member of the public or patients associations in every stage of the research process, from the identification of priorities for multiyear research programs to design of specific projects was reported. Public and patient involvement (PPI) in research is more and more expected if not required by funders (Greenhalgh, 2009). According to the NHS advisory group INVOLVE, PPI is "research being carried out 'with' or 'by' members of the public rather than 'to', 'about' or 'for' them" and ideally encompasses involvement, participation and engagement of the general population (INVOLVE, 2015). This approach is missing according to the experience of PIs in Southern EU countries (2).

> *"Some programs also have a patient advisory boards especially for funding programs that are aimed at either incrementing research or communication or valorization of research funding where we say these projects should be not only be of scientific excellence but it should also be very clear what is the societal relevance for people with diabetes. That part of the project we ask a group of patients to give their judgment on. So it is a combination of scientific judgment as well as the people judgment that advise us on what projects to fund."* (6)

> *"Some funders require you to have a PPI member on the steering committee or even as an applicant to the funding, or some others require that you have consulted some sort of PPI group and you have involved them in the process."* (11)

The almost unanimous consensus on the need of collaboration in research seems to contradict the emerging theme of the national approach to the funding of diabetes research by the charities or not-for-profit RFOs. This finding confirms a previous result from the survey of RFOs across the EU showing that 45% of the survey RFOs operates at national level and 29% at sub-national level.

> *"Our aim is to keep or attract good scientists to do research in [country]."* (3)

> *"To improve the availability of research funding to researchers in [country] so that they can have a better career path"* (4)

> *"We try to fund research that teams in [country] can apply to."* (8)

One informant mentioned research funding initiatives beyond the national territories as a way for the local teams to progress and improve as a result of the exposure to international collaborations (9).

3.2.6. The EU role

The role played by the EU in the field of research funding across the region encompasses different levels of action. First of all, the EU is perceived as one of the biggest funders, although some informants point out the inadequate level of investment of EU in diabetes (2, 5, 10):

> *"One of the problems that I see particularly with EU funding for pediatric diabetes is often there isn't much available"* (5)

Although, they also recognize that resources are scarce and competition to access the funding is justified by the need to cover several different fields of research. Some informants express satisfaction for current and prospective research plans.

> *"Well, you can always ask for more money. Of course Horizon 2020 is very competitive and the fact that when you submit projects it's more likely that won't win than win but I think the opportunities are there […] "* (9)

> *"I am one of the happiest persons with EU collaboration […] The projects actually running try to cover empowerment of patients, professional training, healthcare policies, new tools like ICT, so more or less the areas that I can think about are covered. […] I think I am happy with the current policy and strategies."* (9)

> *"So I think it's very important and it does give opportunities through these targeted big programs. I think they are just doing one in diabetic retinopathy and age-related macular degeneration and that's really good for us. They have a very critical role in current and future research in diabetes."* (11)

On a different note, some informants expressed disappointment in the priority-setting for EU calls in childhood diabetes, associating the misidentification to failing in consulting the appropriate type of experts (i.e. paediatric endocrinologists):

> *"Particularly with EU funding for pediatric diabetes there isn't much available and it is often not focussed on the main issues. I suspect the problem with funding through the EU is the advice or expert advice that they are getting is not perhaps in tune with what really needs to happen and by whom. […] I think they need to have better advice from the available experts in the EU. I think the committees – my understanding is – often do not have pediatricians nor people who have got any particular expertise in childhood and young people diabetes. I think a wider net has to be cast to get those experts to get that advice."* (5)

According to the experts, *"the EU is the best position for an umbrella view coordination"* (6), or *"one body where research can be done, Europe-wide"* (4). As nicely expressed by one of the informant PI, the opportunity to take part in big cross-country initiatives, with many academic and non-academic partners involved is highly valued and also attached to a legacy that will likely turn out into new ideas for international collaborations:

> *"I think that's been a really good initiative [ndr, a EU FP7 Project in diabetes] […] All the network, all pharma together, all different academic partners and it has given a chance to build up a whole big program with time, and I think the legacy effect of these collaborations occurring, and some feeding into many other big projects in the future."* (11)

EU is also in a leadership role to recommend, guide and commission highly specialized research on unfashionable topics:

> *"Recommendations at the EU level obviously have an important impact locally, so any suggestion they can make is obviously a great benefit."* (4)

> *"If other agencies (universities or industries) are not doing it - the (European) Commission itself takes on the responsibility to ask to particular actors to work on specific topics. […] In my view they could take the lead to commission maybe particular universities, who have a good record, in a collaborative way."* (7)

What the EU seem to fail in the process is a fruitful discussions with all the stakeholders. It would be much more beneficial to involve all different funding bodies, including charities and not-for-profit organizations, in strategic discussions around research funding priorities that it only seems a missed opportunity failing to achieve such participatory approach, also because in many countries non-public organizations often spend more than public organizations in diabetes research.

> *"EU discusses these things with national member states, national funding agencies, and that perfectly makes sense but I think we should consider there are more funding agencies not only government subjects […]. So involving not only member state agencies but also other funders, we are the major funder in [country], but it's our national government that has a discussion with the EU on how we should address diabetes, that doesn't make sense. The same can be said of the UK, Diabetes UK is a major funder of diabetes research in the UK but it's the Medical Research Council that is part of the discussion within the EU and the Commission. That's a challenge for Europe, not only talk with the representatives of MS but also include the private foundations and other funding agencies in various member states."* (6)

The engagement of different stakeholders should be agreed upon with all parties. On this same theme, the opposite position was recorded by a RFO's representative claiming autonomy and independence in setting her foundations' research priorities based on donors' preferences:

> *"The problem is we are a private organization, we have private money […] We are very independent and we want to be independent because it's people's money and private donors. We have our own policy to define what we want to fund, trying not to be redundant with things that are done by the Government or other Foundations. It's not public money."* (8)

Finally, there were heterogeneous suggestions in terms of specific requests to raise to the EU to facilitate or speed up the research process and efficiency within the region. From harmonized fiscal policies around deductions on donations for research initiatives (8) to enforcing the set up of national bio-banks, updated at national level and accessible through an adequate process of ethical approval for well-designed projects (4). A more critical task would be *"try to help diminish a little those gaps in terms of diabetes healthcare"* (9). This statement was associated to the observation that insulin pumps are not equally provided around Europe, mainly due to financial constraints but also to different healthcare and reimbursement systems that bring different choices and opportunities for citizens in each EU country.

3.3 Discussion and Conclusion

The themes emerged from the stakeholders interviews were organized in six major areas: i) challenges in diabetes research, ii) duplication in diabetes research, iii) research gaps, iv) impact of research and priority-setting, v) partnerships and vi) the role of the EU. According to the informants, the challenges faced by researchers and RFOs in diabetes research are financial (i.e. a perceived decrease in targeted funding over the last years, mainly associated with the economic crisis that hit Europe in 2008) and organizational. In particular, human resources management can be difficult in a very competitive environment, with scarce resources available and long prospects of temporary or insecure employment for most of the workforce. The majority of diabetes research funding was coming from private pharmaceutical companies according to our informants. They suggest that industry has implemented conservative management practices for the purpose of increasingly the predictability of drug discovery and the sustainability of returns on capital investment in R&D. Sources in the literature argue that investments in R&D produce NMEs that are, at best, only marginally better than existing therapies, thereby stifling innovation and amplifying a sense of crisis across the industry (Munos and Chin 2011). Looking at the future, sources in the literature fear that unless industry ceases to pursue "safe" risk-averse management strategies, unless it adopts more collaborative approaches to knowledge creation and costs sharing, few breakthroughs will reach patients and sufferers of disease (Munos and Chin 2011). Developing the right balance through cooperation between heterogeneous lists of funders is therefore critical to foster the advance in scientific and clinical research. Duplication can only apparently be considered a challenge. Turning redundant funding in opportunities to tackle the most underinvestigated areas or replicating results in settings where generalizability can be an issue, were common discussion points. A general broader view on the impact of research was supported. Stakeholders recognized the importance of looking beyond academic publications, beyond "scientific excellence" to promote impact on delivery of services and patient health outcomes. This approach involves a relatively higher consideration of translational or implementation research and highlights the importance of general public involvement in all stages of research. Establishing partnerships for the funding and conduct of research seems a successful strategy to be able to co-fund bigger project, to explore research questions on large scale or to achieve dissemination targets otherwise unlikely. In terms of research gaps or unmet need, informants pointed out the broad area of aetiology (i.e. pathogenesis of hypo/hyperglycaemic events, pathogenesis of chronic complications), prevention (i.e. genetic factors linked to the adult development of T2DM) or treatment (i.e. adjunct therapies, artificial pancreas, beta-cell transplantation, cell line conversion). Personalized medicine was also promoted in this field as it has already spread in other areas such as oncology. However, the unspecific NCD-wide approach to research and management of very different conditions only grouped for the fact of not being infectious was criticized. As regards infrastructures, bio-banks development was the most recommended suggestion to speed up genetic-based studies. Another probably unexpected topic suggested for future research was on the social and health related quality of life aspects of people living with the disease, how it is possible to make patients and families more engaged with the treatment and how to get them to use the treatment more effectively. In this regard, a wide set of skills and multidisciplinary research projects are necessary to tackle a disease that is more complex than the genetics behind it. Finally, the role attributed to the EU is one of coordination and leadership. Recommendations from the field to one of the major public government funding body

goes from engagement in fruitful discussions with all stakeholders (e.g. inviting charities and private not-for-profit funders to major discussion tables on research initiatives) and better scoping of experts in drafting programs calls.

We find the points emerged from the interview particularly interesting however we wish to highlight some limitations with this part of the analysis. First and foremost, there was not any representative of public national or supranational RFOs in our informants' sample. This means the views we have captured are mainly from PIs and funders from the charities and private not-for-profit organizations and may not be transferable to other sponsors. Second, we sought to interview more experts from the list of initially identified RFOs or stakeholders active in diabetes research. We managed to get 40% of the initially expected interviews. Although a level of saturation was seen on many of the topics emerged from our final pool of interviews, it could be that additional themes were underrepresented in the available set of data.

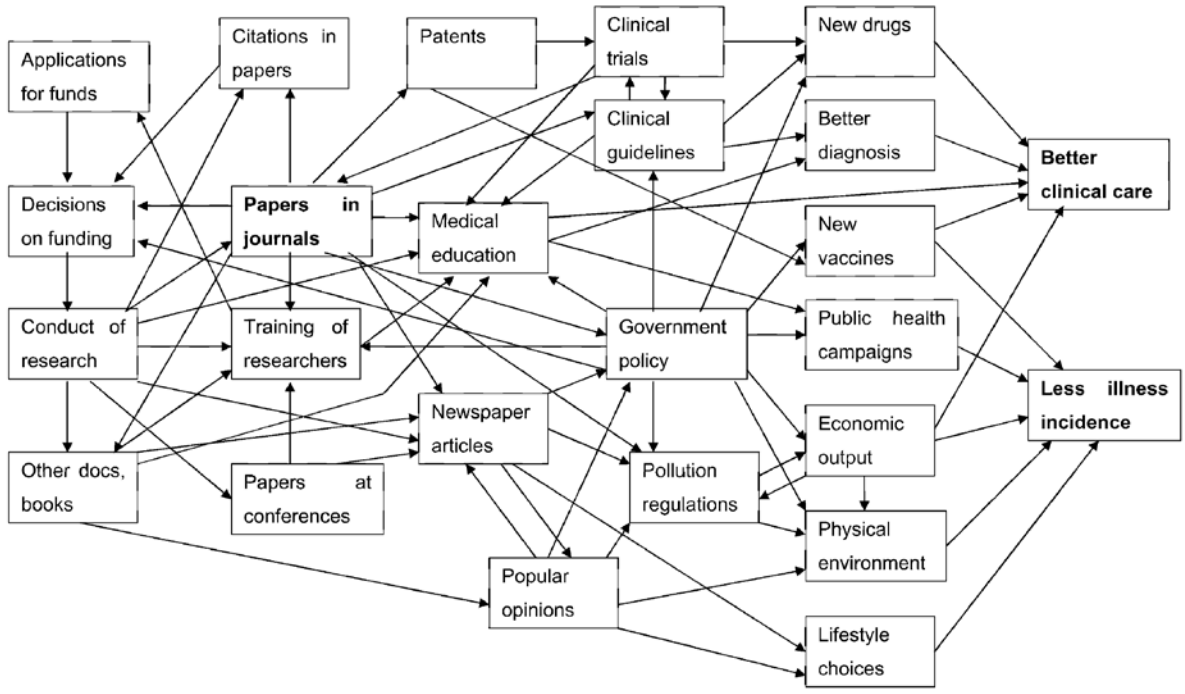
4 Bibliometrics: Impact of Diabetes Research Funding

A key aim of MAPPING_NCDs is to establish the impact of funding investments across five key NCD areas: cardiovascular disease, chronic respiratory diseases, diabetes, cancer and mental health. In this aim, MAPPING_NCD moves beyond the state of the art in the research area by pursuing a bibliometric exercise of research outputs in the EU and MSs relevant to these disease areas. The bibliometric tool assesses the impact of funding investments by mapping and analyzing of the volume, citations, funding sources, influence on clinical guidelines and newspaper stories of research papers and reviews in the Web of Science (WoS) published in EU MSs during the period 2002-2013. In this analysis, the production of scientific publications funded in the disease are and their five-year citation counts in other papers are considered. The bibliometric analysis has also considered the extent to which scientific papers have been used as the evidence base for clinical guidelines, as well as their impact on government policy documents and appearance in media-stories.

4.1 What is Research Impact?

Measuring the impact of research is a complex task. Often, health improvements depend on a host of different research discoveries, which are made at different times and in different places. The pathway from the conduct and publication of research to better health is usually indirect. In addition, the results of research contribute to better health in different ways, from the improved diagnosis and treatment of patients to the prevention of illness or the reduction incidence. Figure 76 details the manifold linkages between research funding and health impacts.

Figure 76 Some of the links between research and healthcare improvement



Among these many nodes and linkages, 'government policy' occupies a central position and has a several linkages to other nodes. Moreover, the 'reduction of illness incidence' also depends on a large number of inputs, including: environmental pollution, individual health behaviours, wealth, education and the effectiveness of public health campaigns. Thus, it can be observed that research impacts upon all these nodes, many of which are not specific to individual disease areas. Similarly, different types of research can also deliver advances in individual disease areas. And for these reasons, the norms for measuring both the effectiveness of research and its quality can also differ.

Nevertheless, all of these nodes are inter-connected. And at connection points, hard evidence of research impact necessarily accumulates. The evidence of research impact manifests itself in the paper trails that flow between one node and another. For example, research funding produces research, which produces papers in scientific journals, which in turn lead to citations in other journals, decision making influence, policy, media stories and even the allocation of additional research grants. Tracking and analyzing these paper trails, using them as a proxy for research impact, is the fundamental business of bibliometic research.

In this section of the paper, the bibliometric methodology is used to analyze data relevant for diabetes research at five of these: scientific research papers, funding sources (decisions on funding), citations, the evidence base of clinical guidelines, the stories in newspapers and the research papers that they cite.

4.2 Scientific Research Papers: Diabetes

The first means by which bibliometric analysis establishes funding impacts is the analysis of the number of published scientific papers. This section of the report details the number of papers on diabetes downloaded from the Web of Science (WoS), considering 31 European countries (the 28 EU MSs and Iceland, Norway and Switzerland), during the timeframe 2002-13. To this end, the bibliometric tool utilizes two overlapping databases, the Science Citation Index Expanded (SCI) and the Social Sciences Citation Index (SSCI), for the provision of knowledge on socio-economic impact and behavioral interventions associated with diabetes.

A filter to conduct the marking of relevant papers in diabetes research was designed. The filter used to retrieve publications on diabetes consisted in a set of specialist diabetes journals and a set of title words, but with a "no" statement to exclude papers with *cancer* or *carcinoma* in their title unless they also contained *diabet**. The original filter was developed in consultation with Dr Moira Murphy and Dr Jayne East of the British Diabetic Association (now Diabetes UK). It was updated to take into account of journals now included in the WoS and to reflect the definition of the subject provided in agreement between KCL and UB, which was as follows:

> *Research into causation, prevention, diagnosis and treatment of diabetes mellitus and its long-term consequences. Diabetes mellitus (in particular Type I and Type II) is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The effects of diabetes mellitus include long–term damage, dysfunction and failure of various organs*

The filter had precision, p = 0.900 and recall, r = 0.976. Details for the filter were written to an Excel spreadsheet for analysis. The main results were organized by country outputs, research levels (from clinical to basic) and type of research or type of disease. Each filter was applied to the Web of Science for the Science Citation Index (extended) (SCI) and for the Social Sciences Citation Index (SSCI) during the considered timeframe. Only published articles and reviews were identified. The papers included also had to refer to at least one address belonging to the EU31 geographic area. Table 5 lists the countries with their digraph ISO codes.

Table 5 List of 31 countries used to limit the downloaded papers

ISO	*Country*	**ISO**	*Country*	**ISO**	*Country*	**ISO**	*Country*
AT	*Austria*	**EE**	*Estonia*	**IS**	*Iceland*	**PL**	*Poland*
BE	*Belgium*	**ES**	*Spain*	**IT**	*Italy*	**PT**	*Portugal*
BG	*Bulgaria*	**FI**	*Finland*	**LT**	*Lithuania*	**RO**	*Romania*
CH	*Switzerland*	**FR**	*France*	**LU**	*Luxembourg*	**SE**	*Sweden*
CY	*Cyprus*	**GR**	*Greece*	**LV**	*Latvia*	**SI**	*Slovenia*
CZ	*Czech Rep.*	**HR**	*Croatia*	**MT**	*Malta*	**SK**	*Slovakia*

DE	*Germany*	**HU**	*Hungary*	**NL**	*Netherlands*	**UK**	*United Kingdom*
DK	*Denmark*	**IE**	*Ireland*	**NO**	*Norway*		

The "full record", which includes all addresses, e-mails and funding details (where given) were then downloaded to a series of 12 "year" files, 500 papers at a time. These were then processed by a special macro to produce one combined Excel spreadsheet.

Each paper in the combined sheet was given an individual index number, and the following parameters were recorded:

- Names of all authors, in the format SMITH-AB
- Paper title
- Source (journal name, year, volume, issue, pages)
- Journal name
- Document type (article or review)
- Addresses (all in upper case, separated by a forward slash). Note: in the WoS UK papers are attributed separately to ENGLAND, WALES, SCOTLAND or NORTH-IRELAND.
- Country of publication
- Year of publication
- Month of publication (for most papers where the date of the journal was given)
- Language (almost all were in English)
- E-mail address (es) of corresponding author, sometimes others
- Funders, FU (for late 2008 papers and subsequently)
- Funding acknowledgement text, FX
- Composite list of authors and their individual addresses (from 2008)
- Authors' full names (where given), in the format Wilhelm, Hans; Wanke, Isabel; Hirche, Herbert (this allows the sex of most of the authors to be determined)
- Whether in the SCI or SSCI only

Although most papers in the WoS have their keywords of reference and formal abstracts, these were not recorded in the main spreadsheet as they would have made it far too cumbersome.

Based on the publication title, a macro was applied to determine whether the paper could be classified as "clinical ", "basic" or "both", depending on the presence of one or more words of the two lists (Lewison and Paraje, 2004). The research focus of the journal where the paper was published was also determined from a master list: clinical journals were classed as RL = 1, basic ones as RL = 4, and the ones in between were given an RL value between 1.0 and 4.0. These RL values were determined for groups of five years, 2000-04, 2005-09 and 2010-14.

The world and European outputs, year by year, of diabetes research papers are given below.

Table 6 Outputs of diabetes research papers (DIABE) in the Web of Science from 2002 to 2013 from EUR31 group of countries, integer and fractional counts

Year	*DIABE*					*DIABE/BIOMED, %*	
	World	*EUR31 int*	*EUR31 frac*	*EUR %*	*Int'l, %*	*World*	*EUR31*
2002	5393	2368	2173	43.9	8.2	1.45	1.50
2003	5810	2535	2306	43.6	9.0	1.50	1.55
2004	6449	2736	2472	42.4	9.6	1.59	1.62
2005	6815	2908	2613	42.7	10.1	1.60	1.65
2006	7321	3033	2697	41.4	11.1	1.63	1.64
2007	8200	3288	2921	40.1	11.2	1.69	1.66
2008	9179	3664	3250	39.9	11.3	1.76	1.75
2009	9477	3677	3218	38.8	12.5	1.74	1.70
2010	10165	3805	3314	37.4	12.9	1.78	1.69
2011	10806	3963	3435	36.7	13.3	1.78	1.68
2012	11824	4169	3614	35.3	13.3	1.84	1.68
2013	12353	4404	3796	35.7	13.8	1.86	1.71

The presence of research on diabetes with respect to biomedical research shows an increase from 1.45% to 1.86% on a global scale, and from 1.5% to 1.71% in Europe. In general terms however, the number of publications in Europe over the world total scientific production has declined from 44% to 36%, mostly because of higher output growth in other geographical areas.

The results for the individual European countries are shown in Table 7. Figure 77 shows that certain countries, such as Denmark, Sweden and Finland are publishing more than expected. On the other hand, Romania and Norway are publishing only half as much as their wealth would suggest.

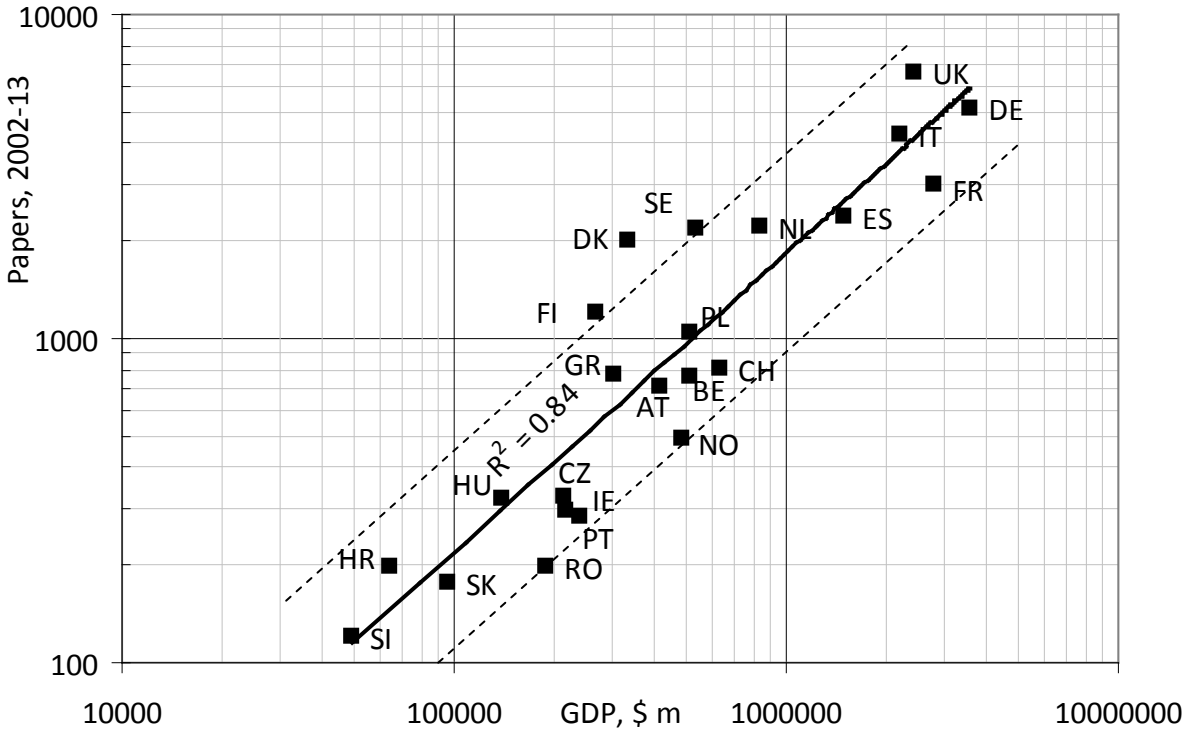
Table 7 Outputs of 31 European countries in diabetes research (DIABE), 2002-13 (12 years) in both the SCI and SSCI

ISO	*Int ct*	*Frac ct*	*% int'l*	*AAPG*		*ISO*	*Int ct*	*Frac ct*	*% int'l*	*AAPG*
UK	9557	6657	30.3	2.9		HU	513	322	37.3	5.7
DE	6847	5119	25.2	4.9		IE	492	295	40.0	12.9
IT	5589	4262	23.7	4.9		PT	381	282	26.1	20.2
FR	4219	2999	28.9	1.2		HR	249	197	20.7	11.5
ES	3054	2379	22.1	8.2		RO	268	196	26.7	29.8
NL	3251	2229	31.4	6.8		SK	257	178	30.9	1.8
SE	3400	2196	35.4	1.6		SI	186	120	35.4	10.9
DK	3127	2017	35.5	3.9		BG	97	66	32.1	4.7
FI	1782	1198	32.8	1.4		EE	71	39	44.5	15.9
PL	1288	1049	18.5	15.7		LT	65	36	44.5	15.2
CH	1504	803	46.6	5.4		IS	66	36	46.2	6.1
GR	992	779	21.4	12.7		LV	56	25	55.3	11.9
BE	1251	760	39.2	4.4		MT	30	25	17.2	7.9

AT	1156	708	38.8	4.4		LU	57	12	78.7	28.2
NO	833	490	41.2	11.0		CY	22	10	56.1	11.8
CZ	485	326	32.9	3.7						

Integer and fractional counts, the percent foreign contribution and the annual growth rate. The countries are ranked by their fractional count outputs. Codes are in Table 2.

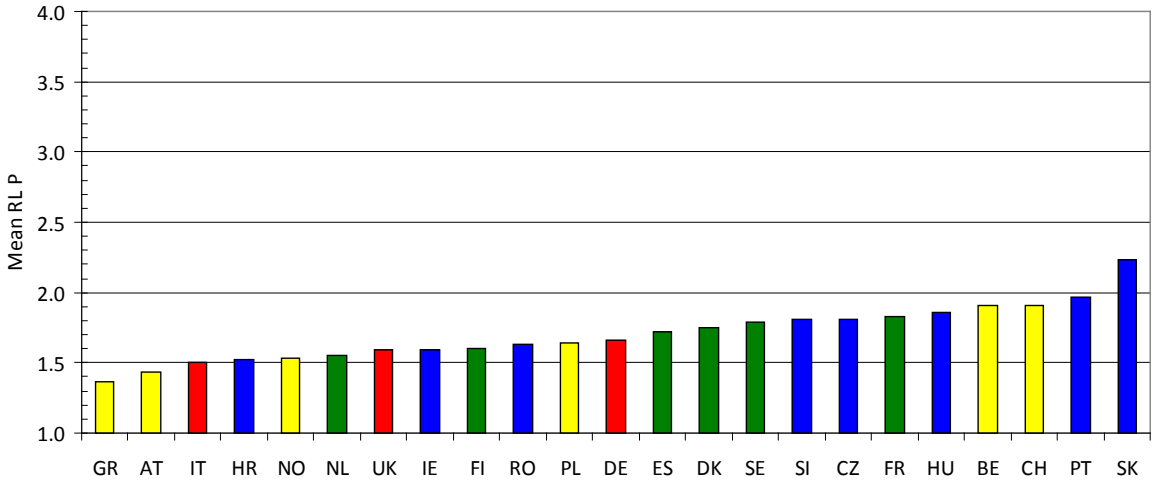
Figure 77 Plot of DIABE paper output, 2002-13, against GDP for 23 European countries



Note: BG, CY, EE, IS, LT, LU, LV and MT omitted. Dashed lines show values x2 or x0.5 relative to power trend-line. For codes, see Table 2.

The mean RL of the papers is 1.70, more towards clinical research rather than basic research. In line with what emerge in other disease-areas publications from Slovakia tend to be more basic research oriented. Over the study period, the research level has declined from 1.87 to 1.55, shifting more towards clinical work.

Figure 78 Chart showing the mean research level of DIABE papers from 23 European countries, 2002-13, with 100 or more classed papers



Red bars: > 3000 classed papers (frac. cts); green bars: > 1000 papers; yellow bars: > 300 papers; blue bars: > 100 papers

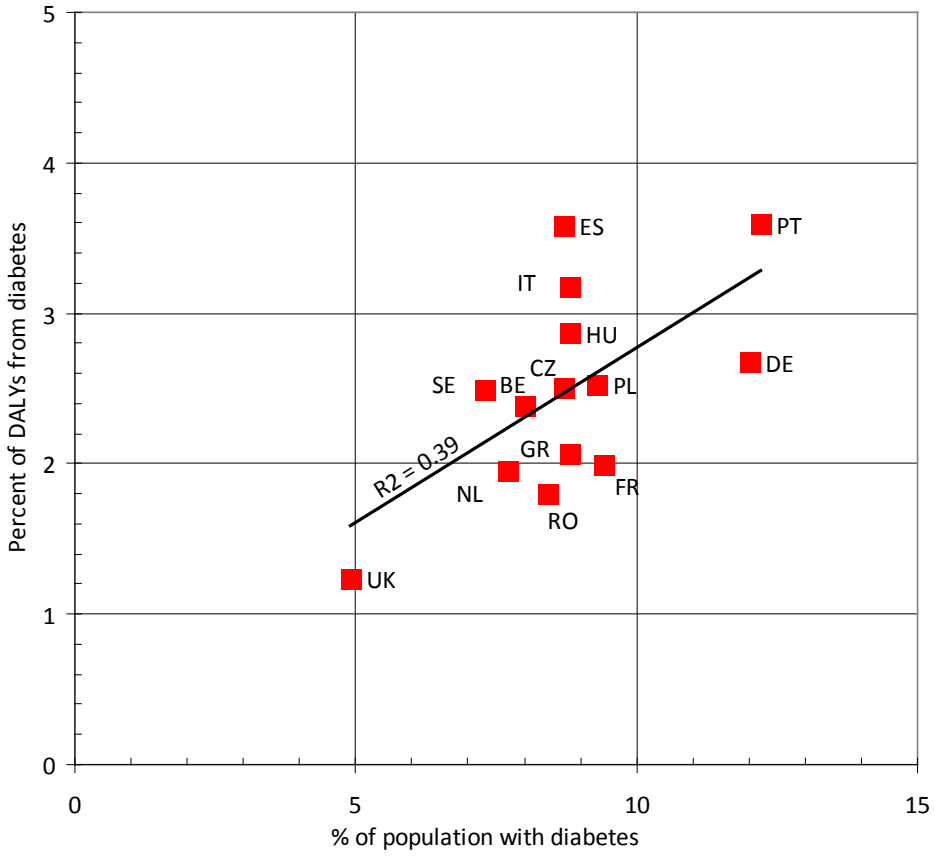
It is interesting to relate the information retrieved so far to the percentages of all DALYs accounted for by diabetes in each of the 31 European countries (Table 8). The data range from 4.6% for Cyprus to 1.2% for the UK. Despite having the lowest percentage disease burden for this pathology, the UK publishes substantially more papers than would be expected, more than many EU countries. The Mediterranean and Southern European countries appear to suffer from this disease relatively the most, with the notable exception of Greece.

Table 8 Percentages of total DALYs accounted for by diabetes in the EUR31 countries, 2010

ISO	*% DALYs*		*ISO*	*% DALYs*		*ISO*	*% DALYs*		*ISO*	*% DALYs*		*ISO*	*% DALYs*
CY	4.63		DK	2.93		PL	2.52		GR	2.07		LT	1.77
PT	3.59		CH	2.90		CZ	2.51		IE	2.06		FI	1.66
ES	3.58		HU	2.87		SE	2.50		FR	1.99		UK	1.24
NO	3.24		HR	2.82		BE	2.39		NL	1.95			
AT	3.17		BG	2.79		EE	2.38		LU	1.82			
IT	3.17		DE	2.67		SK	2.31		RO	1.80			
MT	3.07		SI	2.64		LV	2.17		IS	1.77			

These data were compared with figures on the prevalence of diabetes in countries with large populations provided by Shaw et al., 2009. The figure below shows Shaw's data (percentages of the population with the disease) as abscissa and the DALY burden (percent) as ordinate.

Figure 79 Scatter plot showing disease burden (DALYs) in 2010 for 14 European countries as a function of the estimated incidence of the disease in the same year (% of population affected)



While the correlation between the two sets of data is positive but not very strong, it is clear that on both measures the UK is suffering less from diabetes than any of the other European countries considered in the study. However, its DALY percentage is lower than the trend-line would suggest, and this could possibly be the result of a large investment in research. This however is just a partial explanation that could apply to Romania for instance, which also has a lower DALY percentage but it also conducts less research than expected.

To explore specific subject areas within diabetes, assistance from Diabetes UK, the leading specialist medical research charity in this subject area, was sought (particularly Dr Richard Elliott, their Director of Communications, and his colleague Dr Anna Morris). Fourteen subject areas were defined, Type I and Type II; four other types; and eight "complications" caused by diabetes. Each sub-filter consisted of title words (sometimes abbreviated to strings of characters) and of journal name strings, and they are listed in Table 9, with their outputs and percentages of the DIABE total.

Table 9 List of diabetes research subject areas, with codes used for the tables (in the first report) and figures that follow. N = number of DIABE papers in 2002-13

Code	*Subject area*	*N*	*%*		*Code*	*Complications*	*N*	*%*
ONE	Type I	5543	13.7		FEE	Feet	918	2.3
TWO	Type II	13310	32.8		CAR	Cardiovascular	5720	14.1
GES	Gestational diabetes	828	2.0		NEP	Nephropathy	2740	6.8
NEO	Neonatal diabetes	206	0.5		NEU	Neuropathy	1573	3.9
MOD	Maturity Onset Diabetes of the Young	346	0.9		LIV	Liver	1017	2.5
ADA	Latent Autoimmune Diabetes of Adults	76	0.2		HYP	Hypoglycaemia	638	1.6
RET	Complications: Retinopathy	1646	4.1		PSY	Psychosocial	730	1.8

The ratios between observed and expected numbers of paper for each European country in each diabetes subject area are calculated in Table 10. There is a tendency for the northern European countries, especially Estonia and Finland, to devote relatively more attention to Type I diabetes, while the contrary holds true for Southern Europe. The Scandinavian countries (Denmark being an exception) under-research the issue of complications. Diabetes effects on the liver are relatively under-researched by several other countries, notably the UK and Ireland, the Czech Republic and several other east European countries except for Latvia and Romania.

Table 10 Ratio of observed to expected outputs of papers from 31 European countries in 10 leading subfields of DIABE research, 2002-13

	TWO	*CAR*	*ONE*	*KID*	*RET*	*NEU*	*LIV*	*FEE*	*GES*	*PSY*
UK	0.79	0.74	0.84	0.65	1.19	0.87	0.49	1.26	0.62	1.33
DE	0.76	0.82	0.74	0.84	0.77	0.97	0.70	1.21	0.59	0.97
IT	0.99	1.27	0.90	1.03	0.69	0.92	1.68	0.74	0.86	0.54
FR	0.82	0.77	0.73	0.70	0.75	0.61	1.18	0.94	0.96	0.62
ES	1.01	1.00	0.67	1.20	1.22	0.66	1.39	0.70	1.21	0.53
NL	1.12	1.10	0.78	0.76	0.48	1.07	0.76	1.13	0.47	2.01
SE	0.88	0.79	1.17	0.72	0.42	0.80	0.42	0.66	0.95	0.73
DK	1.02	0.69	1.07	1.23	1.07	0.46	0.49	0.35	0.73	0.33
FI	0.99	1.04	1.90	0.92	0.68	0.47	1.08	0.21	1.43	0.70
PL	0.74	0.88	1.14	1.29	1.03	1.06	0.67	0.72	2.42	0.70
CH	0.81	0.70	0.62	0.60	0.58	0.69	1.21	0.66	0.36	0.53
GR	1.09	1.18	0.67	0.88	0.76	1.50	0.95	1.28	1.65	0.80
BE	0.70	0.66	1.28	0.62	0.46	0.88	0.89	1.03	0.59	0.99
AT	0.87	0.95	0.83	1.08	1.37	0.71	1.08	0.91	3.19	0.95
NO	0.81	1.05	1.26	0.85	0.61	0.72	0.69	0.66	1.01	1.33
CZ	0.94	0.84	1.50	1.15	0.82	1.94	0.35	0.68	0.37	0.45
HU	0.74	1.01	1.06	0.83	0.90	2.09	0.64	0.12	2.07	0.37
IE	0.84	0.70	0.80	1.11	0.85	0.47	0.47	0.71	2.94	1.09
PT	0.75	0.89	0.44	0.67	1.82	2.50	1.62	0.88	1.16	1.24

HR	0.82	0.62	1.61	0.81	2.70	1.84	0.83	0.94	0.60	2.71
RO	0.95	0.45	0.99	1.26	0.37	0.97	1.44	0.60	0.11	0.86
SK	0.52	1.44	0.76	0.90	0.84	2.15	0.75	0.88	0.10	0.14
SI	1.30	0.92	0.83	0.93	4.30	1.17	0.10	0.50	0.54	0.82
BG	0.86	0.44	0.65	0.29	0.50	2.43	0.00	0.15	1.31	0.75
EE	0.59	0.93	3.10	0.07	0.04	0.58	0.00	0.00	0.73	1.56
LT	0.84	1.03	1.42	0.00	1.49	0.63	0.00	0.00	2.40	0.00
IS	1.11	0.74	1.02	0.43	5.33	0.16	0.00	1.10	0.00	0.05
LV	1.18	0.91	1.08	0.00	0.35	0.85	1.41	0.00	0.00	0.00
MT	0.68	0.82	1.09	1.71	2.63	1.15	0.00	0.78	7.92	0.00
LU	0.39	0.48	0.95	0.18	0.00	0.23	0.00	0.00	0.00	0.00
CY	1.11	0.39	1.07	0.00	0.00	0.47	0.00	0.00	0.00	0.00

Values > 2.0 tinted bright green; values > 1.41 tinted pale green, values < 0.71 tinted pale yellow; values < 0.5 tinted pink.

4.3 Funding Sources

Funding is now recognized as an important source of information for the evaluation of research (Lewison & Dawson, 1998; Lewison & Devey, 1999; Lewison & van Rooyen, 1999; Lewison, Grant & Jansen, 2001; Roe et al., 2010; Rigby, 2013). At its simplest, the acknowledgement of a funding source on a paper indicates that an agency, usually an external one, has reviewed the research project and judged it worthy of support. Multiple funding sources would indicate that the project has met the interest of several stakeholders.

In the past, recording of funding sources for each paper was a labour-intensive task as each paper needed to be inspected individually. It was, however, worthwhile if the work could provide many different funding bodies with a tally of papers that they had supported. This was the principle behind the creation of the Wellcome Trust's Research Outputs Database (Jeschin et al, 1995; Dawson et al., 1998; Webster, 2005). The database covered all UK biomedical papers over a the period 1988-2001, and was based on the papers in the Science Citation Index on CD-ROM, which was purchased from the Institute for Scientific Information in Philadelphia (now Thomson Reuters) and operated under license from them. The data were made available to members of the "ROD club", who paid a graduated annual fee and in return received a list of their papers, together with access to consultancy advice.

Since the introduction of the Science Citation Index, the facilities available for searching and for retrieving data have been steadily enhanced. During 2008, Thomson Reuters started to provide details of funding for individual papers – quite likely stimulated by the earlier existence of the ROD. There are two individually searchable fields, FO = funding organization and FT = funding text. The FO field lists the names of the acknowledged funders and FT provides the full text of the acknowledgement, including recognition of individuals who have helped with the research. For some funding bodies, the FO field also lists the grant numbers, although they are often missing (for this reason they have not been considered in this analysis).

Authors of papers record their funding acknowledgements in a wide variety of ways. Many papers have multiple funding acknowledgements[23]. In order to determine the funding sources for diabetes and the four other disease areas, it was decided to use a coding system made of four parts:

- a trigraph (three character) code designating the individual funding body;
- a single letter code showing the form of support (no longer used);
- a digraph (two character) code designating the sector and sub-sector of the funder;
- and another digraph showing the country of the funder based on the ISO codes.

It also became apparent that some papers did not carry an acknowledgement because they had been supported internally – in a government lab (such as one supported by a research council or Government department), by a collecting charity or a commercial company. The decision was made to include these "implicit" acknowledgements along with the "explicit" ones in the

[23] There are also acknowledgements to individuals who have provided help or advice. These are not considered further in this report.

acknowledgement paragraph to form a composite acknowledgement[24]. Several papers (especially ones describing clinical work) do not report any formal acknowledgement. Probably, their authors are academics or medical personnel working in a hospital or clinic, supported by general university funds or by their own salaries from the health service. In this case however, research projects would have not been reviewed by external funders, which could perhaps lead to lower quality standards. For these reasons, it did not seem appropriate to record this type support, and the ROD was set up to record such papers as "unfunded". Only where a specific acknowledgement made to a university/department/hospital appeared it has been presumed the presence of some system of grants. In this cases, the contribution of the employing organisation was recorded with a code. This gave rise to three sub-sectors of the private-non-profit sector, namely HT = hospital trustees, MI = academic[25] and NP = other non-profit. The other two were CH = collecting charity and FO = endowed foundation.

The basic principle of the methodology used to extract funding information for papers whose details were downloaded from the Web of Science (WoS) was to assign a three-part code to each funding body, with a three-letter code to identify it uniquely, a two-character code to identify the sector and sub-sector, and another two-character code to identify the ISO designation. Codes were assigned to each funding body listed in the FO = funding organisation section of the WoS, subject to redaction if they were mentioned in a conflict of interest statement only as having paid for unrelated work. Codes were also assigned where there was an acknowledgement implicit from one (or more) of the addresses - a government department or agency, the laboratory of a collecting charity, or of an industrial company.

Once codes were assigned to each funding body, they were collected and written to two thesauruses for future use. The spreadsheet of papers was then completed with the explicit and implicit codes by means of a special macro, which also combined the codes into a single column. Another macro determined the division of funders by main sector for each European country (own government including local and regional authorities; own private-non-profit (PNP), industry, international, and other). These were doubly fractionated: to allow for the fractional presence of the target country on each paper, and to allow for the total number of funders on a paper.

The commercial sector was divided up into five sub-sectors, with companies divided into three groups: pharmaceutical, biotech and industrial. The first and third of these were further divided into independent and subsidiary. The purpose was to distinguish between the research activities of national subsidiaries of large multi-national companies which might be relatively independent of the parent, e.g., the Merck Neuroscience Park in Harlow, which did its own research and also gave funding to universities. However there were many takeovers of small biotech (and not so small pharma) companies and it seemed appropriate to regard the takeover as a way in which the new parent company would thereby gain the intellectual property of the new acquisition. This meant that many of the commercial codes became out-of-date. This had two consequences for the analysis of funding sources. First, the country of a company was effectively undefined, and second, the sub-

[24] Several of the ROD members maintained their own labs and also gave external research grants and this system allowed them to compare their respective outputs.

[25] This term was used because many universities and colleges are both endowed with capital and are still collecting money (*e.g.*, from their alumni).

sector could change when a biotech company had brought a new drug to market and had so become a pharma company.

The public sector was divided into three sub-sectors: government department (controlled by ministers), government agency (nominally independent of ministerial directives) and local authorities (including regions, counties and cities). They were given sectoral codes: GD, GA and LA, respectively. Although the latter form of support hardly exists in the UK, it is becoming increasingly common in several continental European countries (Länder in Germany, régions in France, provinces in Spain) and also in North America (provinces in Canada and states in the USA) and in Australia (states and territories). Most of these regions have been given their own trigraphs, although some smaller regions have generic codes, see below.

Because of international collaboration on biomedical research papers, many papers also had foreign partners and acknowledgements to foreign funding sources. The thesaurus soon began to run out of trigraph codes, and we started to use "generic" codes for the smaller organisations (in terms of their biomedical research spend). These consisted of a single letter (X, Y or Z) followed by one digit (to designate the country) and another to designate the sector and sub-sector. Individual countries that supported a lot of biomedical research were given their own digraph (e.g, X1 = USA); others were given one that showed their continent. There is, of course, some redundancy as the country and sector/sub-sector are also given by the second and third digraphs, but these are needed for the main analyses. For example, X1B-BT-US indicates a US biotechnology company in two ways. Generic codes for the UK were not used initially, but have been introduced to cater for the large number of new British funding bodies, and codes UK1, UK2 etc. are employed.

Figure 80 Digraphs for countries with generic codes and designated sector or sub-sector

Digits 1 & 2	ISO	Country		Digit 3	Code	Category
X0	NL	Netherlands		1	CH	Charity
X1	US	USA		2	FO	Foundation
X2	DE	Germany		3	GD/GA	Government
X3	JP	Japan		4	HT	Hosp. Trustees
X4	SE	Sweden		5	IN	Industry (non-pharma)
X5	NZ	New Zealand		6	IP	Pharma industry
X6	CA	Canada		7	LA	Local/regional authority
X7	FR	France		8	MI	Mixed (i.e., academic)
X8	ZA	South Africa		9	NP	Non-profit (e.g., professional body)
X9	IT	Italy		B	BT	Biotech company
Y0	BR	Brazil		Z0	EU	Europe

Y1	IE	Ireland		Z1	CN	China
Y2	CH	Switzerland		Z2	HU	Hungary
Y3	DK	Denmark		Z3	AT	Austria
Y4	NO	Norway		Z4	HK	Hong Kong
Y5	ES	Spain		Z5	AU	Australia
Y6	FI	Finland		Z6	XX	not known
Y7	BE	Belgium		Z7	AF	Africa
Y8	IL	Israel		Z8	AS	Asia
Y9	IN	India		Z9	LA	Latin America

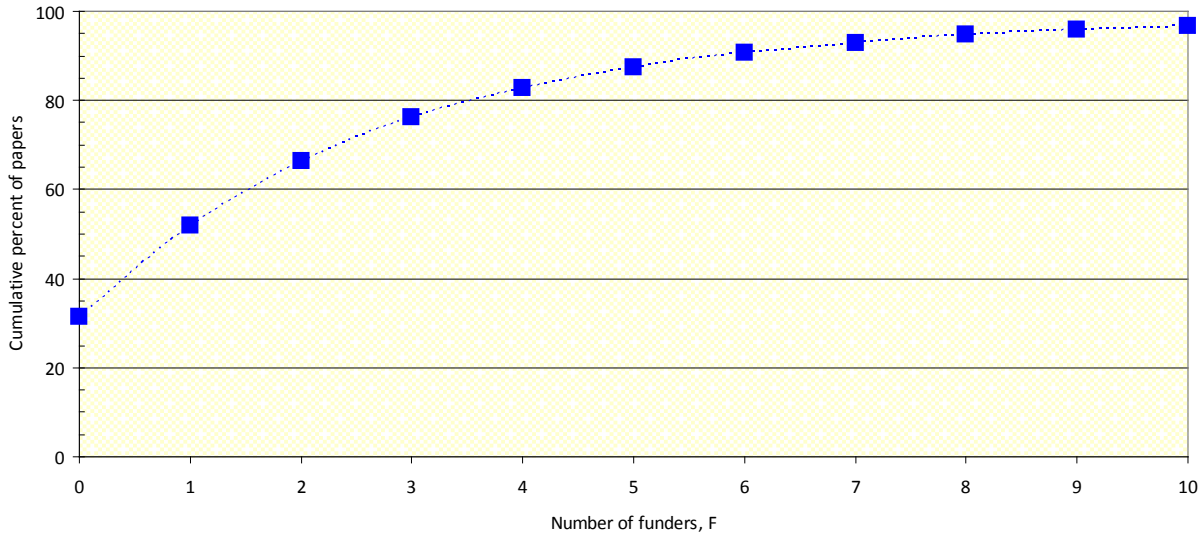
The code "Z4" for Hong Kong is still used, although the country digraph of CN for China shows that this is now part of the People's Republic.

These trigraphs, and the associated sectoral and country codes, were assembled into a large thesaurus of funding bodies. The thesaurus is structured so that the different names and formats given to a funding body (and in some cases its dependent agencies, bodies or companies) are all listed to facilitate the allocation of codes. At the time of writing, there were 17,485 entries and 10,045 (out of a possible 17,576) individual letter trigraphs. This suggests that there is still plenty of opportunity for new codes, but it is often difficult to find appropriate letter combinations for new organizations with many funded papers. These are appearing in continental European countries as work on the project develops, because the thesaurus was originally developed mainly for UK funding bodies.

4.4 Diabetes: Funding Sources

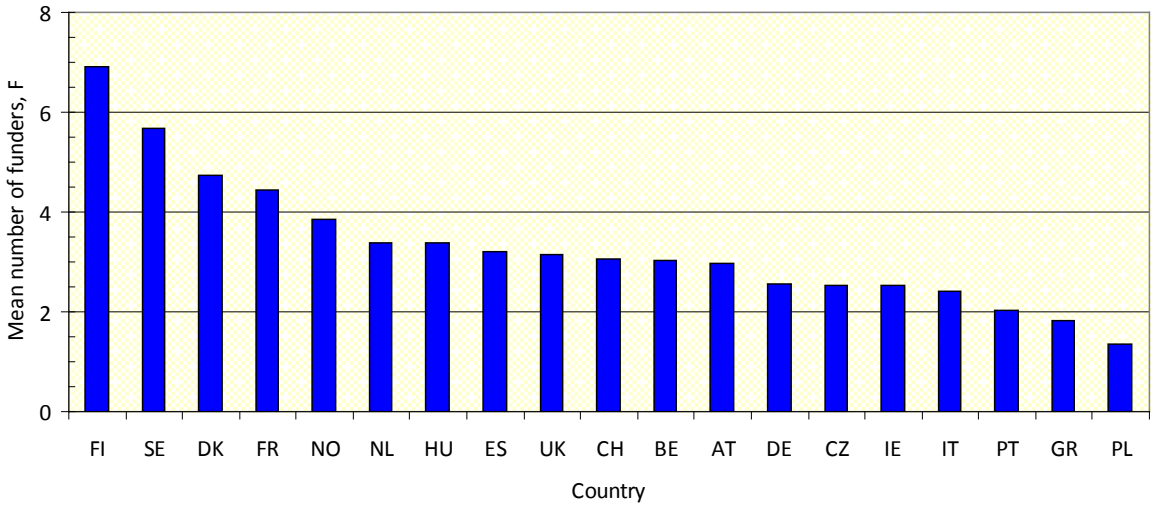
The analysis of diabetes included 40,547 papers, of which 20,015 were published during the last five years, 2009-13. Of these, 1,161 (5.8%) had a conflict of interest statement, and needed to be examined individually in order to check the funding bodies listed in the FU column of the spreadsheet, and redact them if necessary. Some papers originally crediting funding bodies were found not to be funded explicitly, and others displayed sharply reduced numbers; a very few resulted to have additional funders. After the redaction, 13,718 papers had one or more funders (69%) and the remaining 31% had none.
Figure 81 shows the percentages of papers with given numbers of funders or more.

Figure 81 Cumulative percentage of numbers of DIABE papers with different numbers of funders, 2009-13



The analysis on the mean number of funders showed considerable variation among countries, with Scandinavian countries exhibiting the highest values, while Poland and Greece had lower averages (Figure 82).

Figure 82 Mean number of funders per paper for DIABE papers, 2009-13, fractional count basis, for countries with at least 200 papers

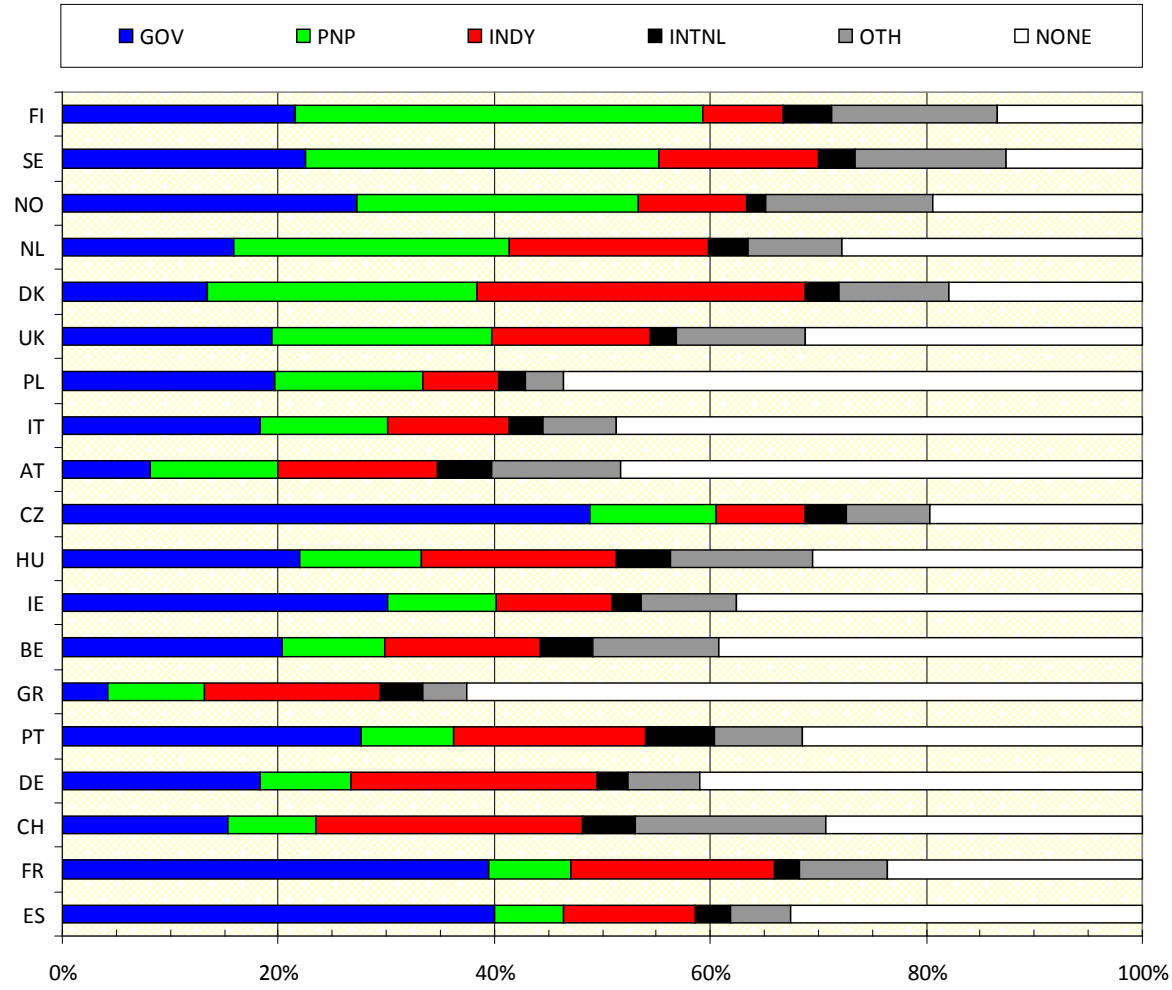


The number of funders has been calculated on a fractional count basis. The analysis by main sector of reference, using fractional counts of sectors for each paper and fractional country counts, is shown in Figure 83. This chart reveals that the Scandinavian countries have more private-non-profit sources, especially endowed foundations. Rather few of their DIABE papers do not report a funding acknowledgement, explicit or implicit. Czech Republic, France and Spain are notable for the high percentage of their papers explicitly funded by the public sector. This percentage is very low in Greece and Austria, where many papers are "unfunded", *i.e.* supported by higher education funds or the national health service.

For most countries the percentage of internationally-funded papers is quite low and mainly refers to funding from the EU. Such proportion is considerable for Latvia (63% on a fractional count basis) and Estonia (37%). The major countries in terms of DIABE research are also the major recipients of EU financial support: UK 200 papers on a fractional count basis with CEC funding, ES 149 papers, DE 143 papers, FR 118 papers and IT 108 papers, although the percentages are below 10%.

The DIABE database was divided up by 14 disease areas and *sequelae* of diabetes, as listed in Table 11.

Figure 83 Funding sources for DIABE papers from 19 leading European countries, 2009-13, based on fractional country counts and also on fractional funding counts for each paper.



The countries are ranked by the percentage of private-non-profit funded papers.[26]

Table 11 List of diabetes research subject areas, with codes used for the tables and figures that follow. N = number of DIABE papers in 2002-13

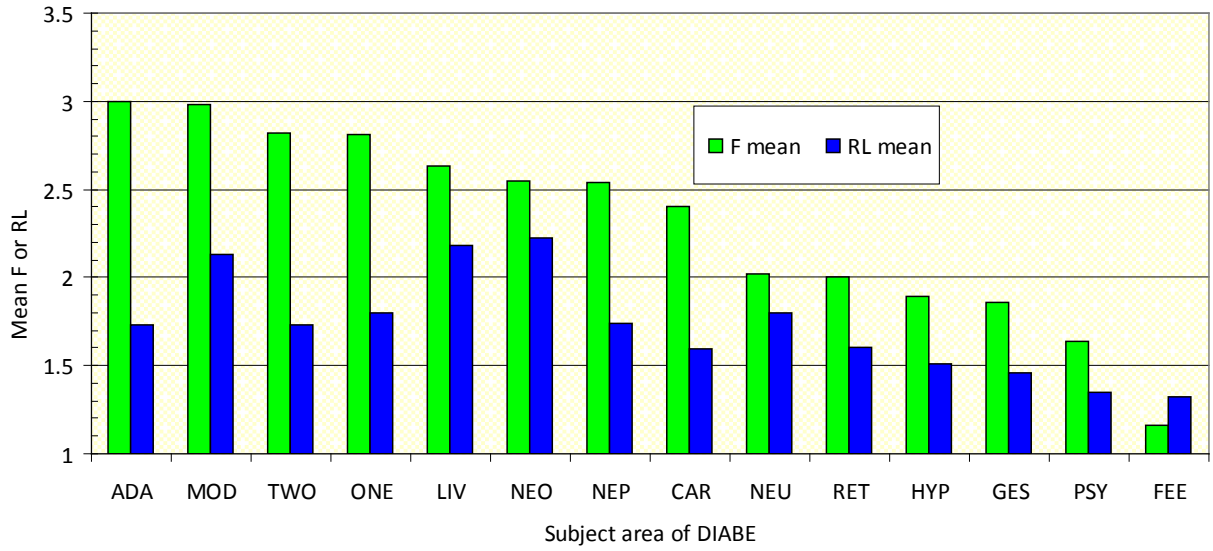
Code	*Subject area*	*N*	*%*		*Code*	*Complications*	*N*	*%*
ONE	Type I	5543	13.7		FEE	Feet	918	2.3
TWO	Type II	13310	32.8		CAR	Cardiovascular	5720	14.1
GES	Gestational diabetes	828	2.0		NEP	Nephropathy	2740	6.8
NEO	Neonatal diabetes	206	0.5		NEU	Neuropathy	1573	3.9
MOD	Maturity Onset Diabetes of the Young	346	0.9		LIV	Liver	1017	2.5
ADA	Latent Autoimmune Diabetes of Adults	76	0.2		HYP	Hypoglycaemia	638	1.6
RET	Complications: Retinopathy	1646	4.1		PSY	Psychosocial	730	1.8

Figure 84 shows the numbers of funders and the mean research level of the papers in each area. The two are fairly well correlated, with $r^2 = 0.53$, meaning that subject areas that are more basic

[26] Iceland is not shown as it has too few papers, but it would rank third in this chart, between Sweden and Norway.

tend to receive more funding. Complications involving the feet is the most clinical subject area, and receives much less funding than any other area. Type I and type II diabetes appear to be treated almost equally in terms of funding.

Figure 84 Mean number of funders per paper (F) and mean research level (RL) on a scale from 1 = clinical to 4 = basic research for all DIABE papers in 14 subject areas, 2009-13



Overall, papers in clinical journals tend to give fewer funding acknowledgements than ones in basic journals. This also holds true for papers with clinical title words compared with ones containing basic title words, see Table 12.

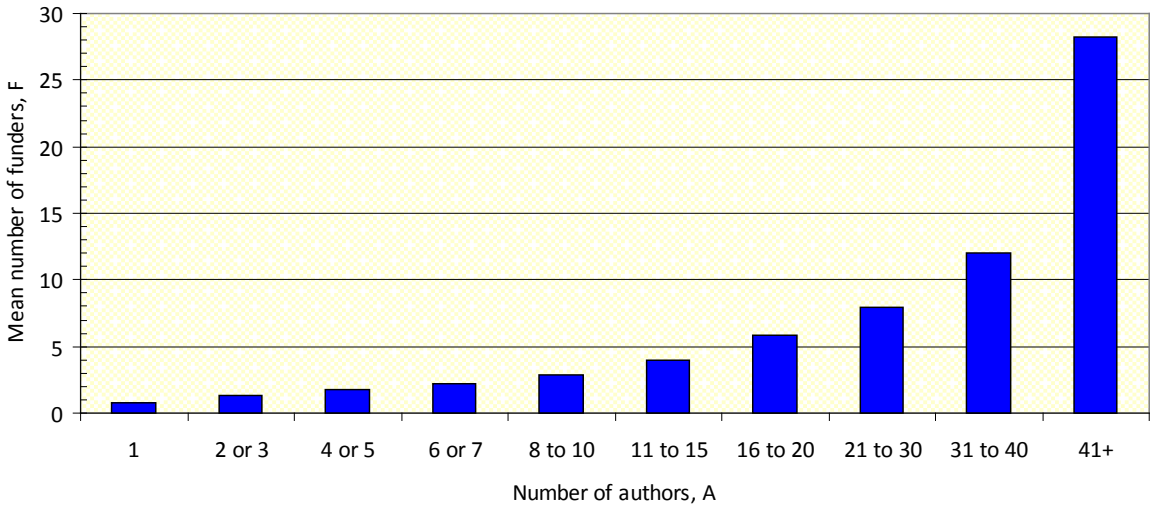
Table 12 Numbers of funding bodies per paper for DIABE papers, 2009-13, in journals of different RL (RL 1 is clinical; RL4 is basic) and containing clinical and/or basic title words

RL (J)	*F*	*N*	*F = 0*	*% fund*		*Title words*	*F*	*N*	*F = 0*	*% fund*
1.0 to 1.5	1.91	6895	2871	58.4		Clinical not basic	2.14	12008	4374	63.6
1.5 to 2.0	1.94	3529	1317	62.7		All clinical	2.33	14507	4877	66.4
2.0 to 2.5	3.31	1760	358	79.7		Clinical and basic	3.28	2510	503	80.0
2.5 to 3.0	3.86	1780	288	83.8		All basic	3.58	4643	789	83.0
3.0 to 3 .5	3.34	1057	176	83.3		Basic not clinical	3.94	2133	286	86.6
3.5 to 4 .0	4.35	541	44	91.7						

N = total number of papers in each group; F = 0 is number with no funding acknowledgements.

It is not surprising that the average number of funders per paper rises with the number of authors, as the additional authors may be expected to be able to tap extra funding sources, and papers with many authors are likely to have an international team and attract funding from different countries. Nevertheless the correlation is striking, see Figure 85.

Figure 85 Mean number of funding bodies per paper for DIABE papers, 2009-13, as a function of the numbers of authors.



Papers acknowledging the support of the leading European funders were also examined. Their numbers are are shown in Table 13. The European Union is the largest single source of support in terms of the numbers of papers funded, with the second largest being the Danish company Novo Nordisk A/S. The remaining are mainly government agencies, with the exception of the Juvenile Diabetes Research Foundation, the Wellcome Trust and Diabetes UK. Table 14 shows their relative concentration on the different aspects of diabetes research, relative to the European average.
The latter table confirms that the JDRF concentrates, as it states in its mission statement, on type I diabetes (although 12% of its papers were on type II), and that Novo Nordisk, along with the UK Department of Health, the Wellcome Trust and Diabetes UK, also relatively prioritize type I diabetes over other areas but support more papers on the study of type II than type I diabetes.

Table 13 Eleven of the leading European funders of diabetes research, 2009-13, and the numbers and percentages of their papers, and their division by subject area (where this has 500 papers or more), integer counts

Funding body	*COD*	*ALL*	*%*	*TWO*	*CAR*	*ONE*	*NEP*	*NEU*	*RET*	*LIV*
European Union	CEC	1578	*7.9*	548	202	250	93	46	32	53
DK Novo Nordisk A/S	NOV	1201	*6.0*	477	118	227	84	26	23	24
FR INSERM	INS	928	*4.6*	334	142	108	45	28	19	43
UK Dept of Health	DOH	736	*3.7*	253	100	138	28	17	29	9
Juvenile Diabetes Res Fdn	JDB	734	*3.7*	90	39	340	48	31	39	10
UK Med. Res. Council	MRC	631	*3.2*	269	87	66	15	15	10	19
ES Inst. Carlos III	ESS	556	*2.8*	241	89	49	28	18	22	29
DE Deutsche Forsch.	DFG	530	*2.6*	159	70	63	37	16	15	28
UK Wellcome Trust	WEL	517	*2.6*	160	50	104	18	10	12	9
DE Ministry Science	BEW	408	*2.0*	159	58	66	20	12	9	15

Diabetes UK	BDA	389	*1.9*	109	39	77	32	10	10	8
	Total	20015		6808	2958	2613	1221	829	806	533

For subject area codes, see Table 5.

Table 14 Eleven leading European funders of diabetes research, 2009-13, and the ratio of numbers of supported papers observed compared with those expected on the basis of the European average in each of 14 subject areas, integer counts

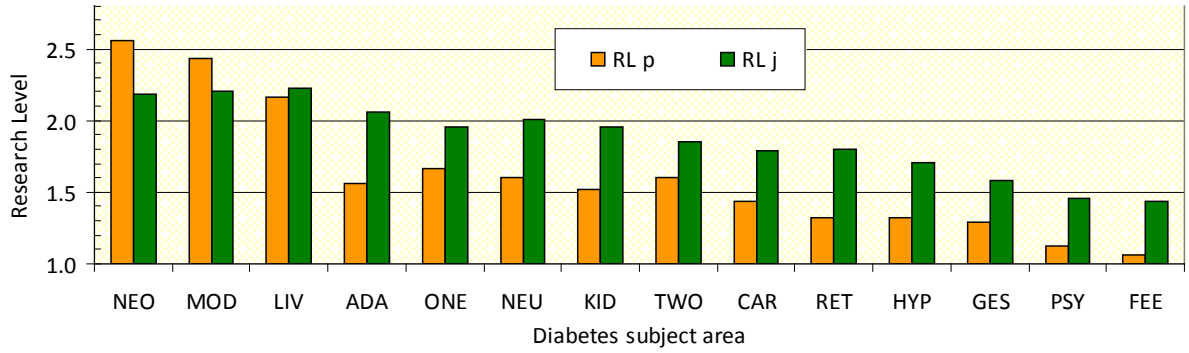
	TWO	*CAR*	*ONE*	*NEP*	*NEU*	*RET*	*LIV*	*GES*	*FEE*	*PSY*	*HYP*	*MOD*	*NEO*	*ADA*
CEC	1.02	0.87	1.21	0.97	0.70	0.50	1.26	0.82	0.38	0.42	0.49	2.46	2.64	1.88
NOV	1.17	0.66	1.45	1.15	0.52	0.48	0.75	0.54	0.25	0.76	2.14	1.15	0.66	0.62
INS	1.06	1.04	0.89	0.79	0.73	0.51	1.74	0.52	0.59	0.51	0.42	0.67	0.85	0.00
DOH	1.01	0.92	1.44	0.62	0.56	0.98	0.46	0.60	0.98	0.91	1.40	3.40	2.69	2.01
JDB	0.36	0.36	3.55	1.07	1.02	1.32	0.51	0.28	0.23	0.26	1.40	0.85	0.81	1.01
MRC	1.25	0.93	0.80	0.39	0.57	0.39	1.13	0.96	0.47	1.44	0.82	1.98	1.57	0.00
ESS	1.27	1.08	0.68	0.83	0.78	0.98	1.96	1.02	0.23	0.77	0.69	1.12	3.56	0.00
DFG	0.88	0.89	0.91	1.14	0.73	0.70	1.98	0.99	0.32	0.72	0.73	1.42	1.87	0.00
WEL	0.91	0.65	1.54	0.57	0.47	0.58	0.65	1.02	0.41	0.55	1.12	2.66	7.67	0.00
BEW	1.15	0.96	1.24	0.80	0.71	0.55	1.38	1.39	0.10	1.64	0.95	1.23	0.49	1.82
BDA	0.82	0.68	1.52	1.35	0.62	0.64	0.77	1.25	1.31	0.86	0.50	4.50	2.04	0.00

For funding body codes, see Table 7. Cells with values > 2.0 tinted green; > 1.41 tinted pale green; < 0.71 tinted yellow; < 0.5 tinted pink.

4.5 Citations of Research Papers

There was a substantial difference in research level between the different subject areas, with papers on neonatal diabetes (NEO) and MODY being the most basic (mean RL > 2.3) and ones on psychosocial and foot complications (PSY and FEE) the most clinical (mean RL < 1.3). The values of paper and journal RL are shown in chart form in Figure 86. The neonatal diabetes and MODY papers were more basic than the mean for papers in the journals in which they were published, but in all the other subject areas except liver complications the papers were more clinical than the average for their journals.

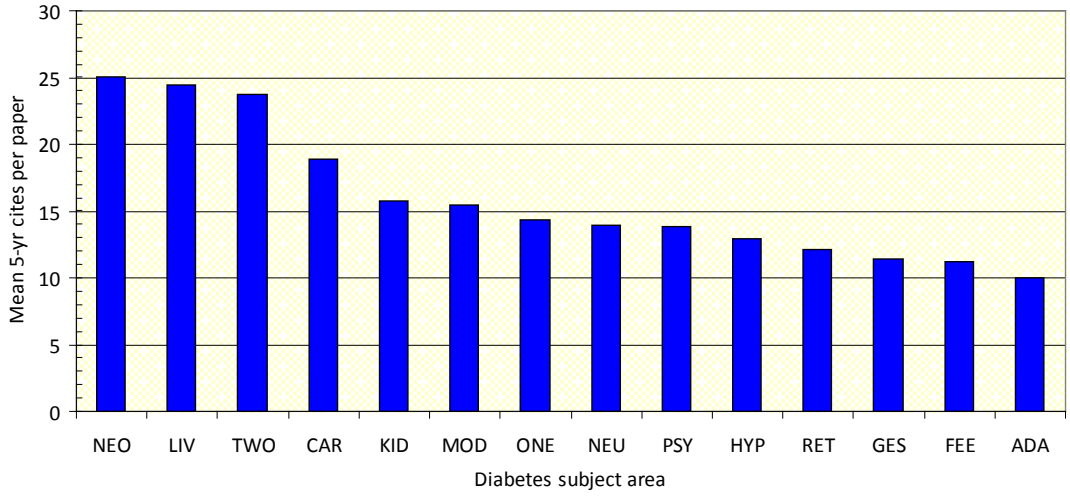
Figure 86 Chart of mean Research Level of papers and of journals in which they were published for DIABE papers of 14 subject areas



RL = 1.0 is clinical observation; RL = 4.0 is basic research.

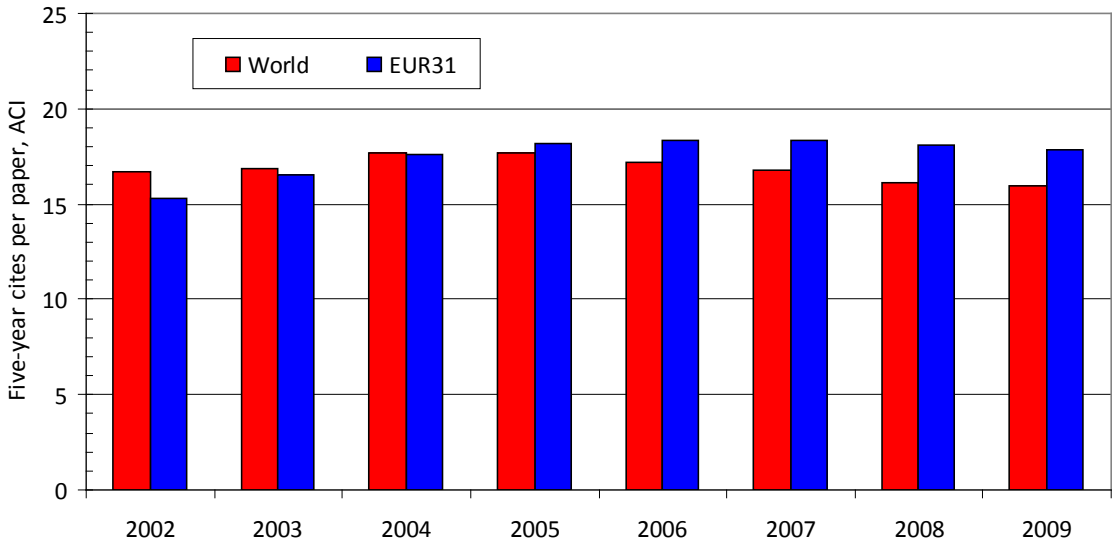
Neonatal diabetes, liver complications and Type II diabetes papers were much more highly cited than ones in most other subject areas. There is a striking difference between Type II and Type I diabetes papers: the former are much more numerous and are 66% more cited, on average.

Figure 87 Chart of mean five-year cites for DIABE papers in 14 subject areas published in 2002-09.



The most cited diabetes subject areas receive more cites in the five years following publication than any other sub-field or research type in the other four NCDs. Figure 88 shows that, in terms of citations, European papers on diabetes lagged behind the global average from 2002 to 2004, but have surpassed the world's average since 2005.

Figure 88 Chart showing the increase in mean citations per DIABE paper with publication year, 2002-09, for world and for EUR31 papers.



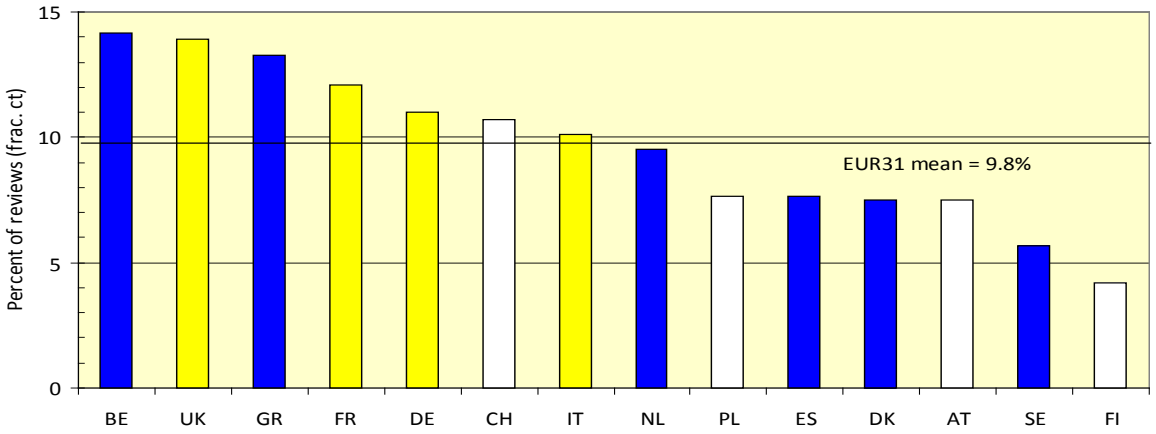
The citation performance of the individual countries is shown in Table 15 for countries with at least 100 citable papers. To be in the top 5% a paper on diabetes requires 58 citations – higher than the threshold needed for other disease areas such as ONCOL or CARDI.

Table 15 Citation performance of 20 EUR31 countries in DIABE in 2002-09 with at least 100 citable papers, ranked by the percent with 58 or more cites in the five years following publication (ACI) (Top 5%) rather than the mean value

ISO	*ACI*	*Top 5%*	*%*		*ISO*	*ACI*	*Top 5%*	*%*		*ISO*	*ACI*	*Top 5%*	*%*
FI	22.1	60.8	7.97		AT	14.5	21.5	5.00		IE	12.2	3.4	2.32
CH	19.3	32.6	6.70		IT	16.0	106.5	4.19		PT	12.1	2.3	2.13
DK	21.2	69.7	5.75		SE	17.9	58.8	4.05		HU	10.0	3.5	1.79
UK	19.6	234.5	5.56		DE	13.4	118.7	3.74		GR	10.5	3.8	0.88
BE	18.5	24.1	5.34		NO	16.2	8.5	3.19		PL	7.7	3.0	0.60
NL	18.1	66.3	5.15		ES	11.9	33.9	2.58		SK	7.0	0.5	0.41
FR	15.3	99.7	5.03		CZ	10.0	5.1	2.46					

Belgium, UK and Greece perform well on the indicator of percentages of reviews, while Austria, Sweden and Finland do less well than the EUR31 average.

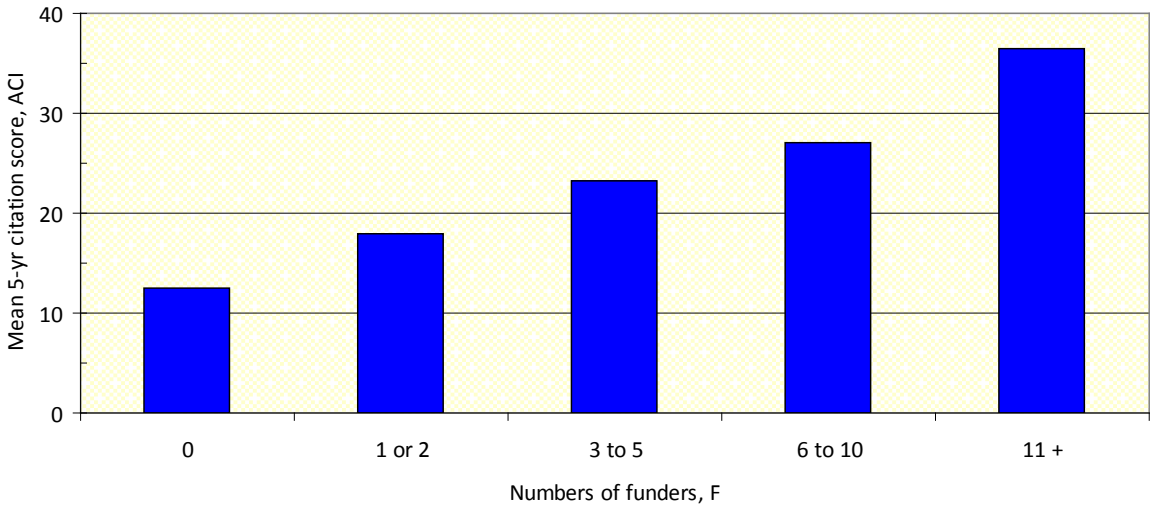
Figure 89 Chart showing the percentage of DIABE papers by 14 European countries with over 50 reviews that are classed as "reviews" in the WoS during 2002-13



Yellow bars: > 300 reviews; blue bars: > 100 reviews; white bars: < 100 reviews.

For 2009 papers, the numbers of funding bodies correlated positively with the mean citation score, see Figure 90. The increase in actual citation impact (ACI) for papers with several funding acknowledgements is very clear, and the relationship will be expected to hold even when account is taken of factors such as the papers tending to be basic and having more authors (Lewison & Dawson, 1998; Roe *et al.*, 2010).

Figure 90 Mean five-year citation count (ACI) for groups of 2009 DIABE papers with different numbers of funding acknowledgements



4.6 Clinical Guidelines

This measure of impact has been used previously both to evaluate the research being cited, and to describe the evidence base for recommendations regarding clinical practice. However, the mere presence of such guidelines is no guarantee that they will be effective at improving healthcare (Schrader et al., 2006). The first study, on a small scale, examined the cited papers on a sample of 15 UK clinical guidelines (Grant et al., 2000). It found that they were very clinical and that UK research was over-cited by 2.5 times. A subsequent study of 43 cancer clinical guidelines in the UK (Lewison et al., 2008) reached similar conclusions, and showed that they could also be used as a means to evaluate research in other countries, for example six Swedish universities. This work was subsequently updated (Pallari and Lewison, 2014) and showed that surgery featured strongly among the cited references (over 25% of the total). It also showed a big variation in whether a country's papers were over- or under-cited relative to its presence in cancer research. Thus UK research was over-cited by almost four, Danish, Dutch and Swedish research by more than two, but that from the "accession" States (Poland, Czech Republic and Romania) by half or less.

We investigated the clinical guidelines currently available in the different European States in order to extend the work to other countries. Although many countries had a set of national guidelines, some had regional ones as well, and there were yet others published by European societies of professionals in various branches of medicine. We even learned that in Sweden, each of the 21 counties had their own clinical guidelines. Clearly, it would have been impossible for us to collect the references on all of these, and so we decided to limit the study to national guidelines.

In the earlier studies on UK guidelines, the identification of the references with papers processed for the Web of Science involved much labour as each one had to be sought individually. It would not have been practical in the scope of this project to continue in this way for guidelines for the other NCDs and for all the other European countries, but we were able to semi-automate the process by means of a visual basic macro, written by Dr Philip Roe of Evaluametrics Ltd. This worked as follows: first, the references section of a guideline in PDF format were copied and pasted to an Excel spreadsheet; second, these were slightly tidied by removal of page numbers, document running heads, etc; and thirdly, the macro was then operated, and it generated sets of search statements, eight at a time, ready for copying and pasting into the search panel of the WoS. An example is given below:

((AU=(Anderson AND Pottier AND Strachan) AND TI=concurrent AND SO=(T*) AND PY=1992) OR (AU=(Heaney AND Conway AND Kelly AND Johnston AND English AND Stevenson) AND TI=Predictors AND SO=(T*) AND PY=2003) OR (AU=(Martin AND McLennan AND Landau AND Phelan) AND TI=childhood AND SO=(B*) AND PY=1980) OR (AU=Roorda,R AND TI=adolescence AND SO=(T*) AND PY=1996) OR (AU=(Remes AND Pekkanen AND Remes AND Salonen AND Korppi) AND TI=hyperresponsiveness AND SO=(T*) AND PY=2002) OR (AU=(Brouwer AND Roorda AND Brand) AND TI=spirometry AND SO=(E*) AND PY=2006) OR (AU=(Pellegrino AND Viegi AND Brusasco AND Crapo AND Burgos AND Casaburi) AND TI=Interpretative AND SO=(E*) AND PY=2005) OR (AU=(Dundas AND Chan AND Bridge AND McKenzie) AND TI=bronchodilator AND SO=(T*) AND PY=2005))

The limit of eight individual papers was set so as to keep within the limits for the number of terms allowed by the WoS. Author names (AU) up to six in number were given without initials as sometimes they were given incorrectly by the guideline although if there was only one author the first initial was given. [In the WoS, Jones or Jones,A will find papers by Jones, AT but Jones,PR will NOT find papers by Jones, PRT.] The title word (TI) was selected to be the longest in the paper title. The journal name (source, SO) was given by just its initial letter as the guidelines usually gave an abbreviated name and this would have needed to be substituted by its full name, which would have had to be researched and entered into the macro. Finally, the publication year (PY) was given for completeness.

This process worked well, and even though the search statements needed to be inspected individually (to remove author names with non-Roman characters which are not recognized by the WoS and to delete any punctuation marks attached to title words), it was possible to identify and download over 860 references from one guideline in about 3 1/2 hours. The macro also listed references that did not satisfy its specific requirements so that any errors could be corrected manually and the macro then run again.

The results of this element for DIABE will be reported in the Bibliometrics Work Package of Mapping NCDS.

4.7 Newspaper Stories

There is abundant evidence that politicians are unduly sensitive to stories in the media. Some of these are based on individual cases, in which it is reported that named patients do not have access to particular means of therapy (expensive drugs, for example). Ministers react by making special provision for them, but this can distort the overall health-care system as with the Cancer Drugs Fund in the UK (Thornton, 2011; Knapton, 2014). Senior officials can use the stories to bring news of research to their ministers; most will not have the time to read the literature extensively and need help to learn about interesting developments. The same is true for health-care administrators in hospitals and clinics, who may learn about new methods of health-care delivery that offer potential cost savings. Medical personnel will also benefit, though the media can also provide misinformation that can cause doctors to misdiagnose (Schmidt *et al.*, 2014). They can also influence researchers, and there is evidence that media coverage increases modestly the numbers of citations (Phillips *et al*., 1991; Lewison *et al*., 2008). The print media may even be a source in their own right (Hicks & Wang, 2013). The biggest influence may be on ordinary people, and could assist the public to choose healthier life styles (Nishtar *et al*., 2004; Caburnay *et al*., 2008; Hellyer & Haddock-Fraser, 2011), including enrolment for vaccinations (Olufowote, 2011; Robbins, Pang & Leask, 2012), although sensational press coverage of supposed links between MMR (measles, mumps, rubella) vaccination and autism has had a negative effect (Holton *et al*., 2012).

They may also add to the political pressure for public investment in medical research, particularly if own-country papers are well-cited. In some countries, commentators on the significance of the research often come from medical research charities, which thereby gain exposure (Lewison et al., 2012). Print newspapers are in decline in many countries, but many have a strong web presence and are still important despite the growing influence of social websites such as Twitter and Facebook.

This part of the project was intended to show the effects of European NCD research on six groups of people:

- politicians and other decision-makers;
- senior officials and advisers;
- health-care administrators;
- medical personnel (doctors, other professionals);
- researchers;
- the general public.

It embarked on an ambitious programme of study on the coverage of research in the five NCDs during the 12-year period, 2002-13, in a large number of European newspapers. Some of these have their own searchable websites; others can be searched through full-text databases such as Factiva ©Dow Jones, to which KCL subscribes.

The results of this element of the project span the five NCD disease areas. For this reason, they will be reported in the Bibliometrics Work Package of Mapping NCDS.

4.8 Conclusion

The Bibliometric tool provides a methodology to assess the impact of research funding in the field of diabetes in terms of production of scientific publications, as well as level of influence via citation analysis. It has allowed the identification of specific peculiarities related to volume, geography and type of funding institutions.

The volume of diabetes research as a proportion of biomedical scientific production has increased over the years, both on a global scale and at European level, although our continent has seen a decline in relative terms to the rest of the world when considering outputs of diabetes research papers (Europe accounted for 43.9% of world total in 2002 with 2.368 papers and for 35.7% in 2013 with 4.404 articles). There is however heterogeneity across States, with most Scandinavian countries (Denmark, Sweden and Finland) exhibiting higher scientific production than expected. Instead countries like Norway and Romania are producing less publications than their GDP would suggest.

When looking at the burden of disease in different countries (in terms of DALYs), Mediterranean and Southern European countries (except Greece) appear to suffer more from diabetes. The link between the burden and overall production of articles is still to be further explored: countries such as the UK are less affected by the disease in terms of prevalence and DALYs but still publish a considerable number of papers (DALYs are actually lower than what the prevalence would suggest, possibly due to large investments in research).

In terms of type of research, the analysis shows that articles tend to be published mostly in clinical journals, as research levels are equal to 1.70 (RL=1 for clinical journals, RL=4 for basic journals).
There is a tendency for the northern European countries, especially Estonia and Finland, to devote relatively more attention to Type I diabetes, while the contrary holds true for Southern Europe. The Scandinavian countries (Denmark being an exception) under-research the issue of complications.
With respect to RFOs, papers in clinical journals tend to give fewer funding acknowledgements than ones in basic journals. There is a striking difference between Type II and Type I diabetes papers: the former are much more numerous and are 66% more cited, on average. The most cited diabetes subject areas receive more cites in the five years following publication than any other sub-field or research type in the other four NCDs.
The analysis of the mean number of funders shows heterogeneity among states, with Scandinavian countries displaying higher averages per paper (7 for Finland, around 5.5 FOR Sweden and around 4.5 for Denmark), while in Poland and Greece there are less than 2 funders per paper. In terms of the mix of funding institutions, Scandinavian countries have more private-non-profit sources, especially endowed foundations. Rather few of their DIABE papers do not report a funding acknowledgement, explicit or implicit. Czech Republic, France and Spain are notable for the high percentage of their papers explicitly funded by the public sector. This percentage is very low in Greece and Austria, where many papers are "unfunded". For most countries the percentage of internationally-funded papers is quite low and mainly refers to funding from the EU. The European Union is the largest single source of support in terms of the numbers of papers funded, with the second largest being the Danish company Novo Nordisk A/S. The remaining are mainly government

agencies, with the exception of the Juvenile Diabetes Research Foundation, the Wellcome Trust and Diabetes UK.

5 Conclusion

According to various and credited source, diabetes ranks in the top 10 causes of disability worldwide with more than 4.5 million annual deaths. After the UN High-Level Summit on Non-communicable Diseases (NCDs) in 2011, diabetes, together with the other NCDs, registered an increase in importance in the health agenda (IDF, 2011). Consequently, policy makers and other stakeholders started to become more aware of the fact that investing in diabetes prevention and care can improve the quality of life of people affected, hinder diabetes-related complications and save lives.

In this report, the analysis of European research projects has highlighted areas of research where action has been taken to foster knowledge creation and sharing through funding of relevant projects. Diabetes Type I and Type II as classified by ICD-10 are a major focus of funding, which is mirrored by the result of the bibliometric analysis. Among the complications, cardiovascular complications are the most commonly studied in the projects funded by the European programmes, as well as other national and international RFOs. Their scientific production is also considerable (14.1% of total DIABE papers). It emerges that major projects tend to focus less on the study of patient-disease management, as well as on the analysis of policies related to diabetes prevention and treatment. A particularly crucial issue in this respect concerns the promotion of effective engagement with the general public to raise awareness on prevention of type II diabetes. Another area where investments are needed is the study of systems to share biological samples through bio-banks, registry data and research findings across Europe. This theme is also recurrent in the stakeholders interview data.

Over the period 2011-2014, the European pharmaceutical sector has generally increased its R&D expenditures, however with few exceptions. The most substantial increase was registered by smaller pharmaceutical companies. In terms of R&D intensity (a measure that allows to capture the relative importance of R&D among firms in the same industry), current findings suggest that US pharmaceutical companies generally allocate more resources in research and development activities than European firms. However, when focusing specifically on research pipelines for diabetes, US companies loose their role of leaders, with 26 molecules under development compared to 40 for EUR firms. These are mainly aimed at treating type 1 and type 2 diabetes mellitus, with a minority dedicated to diabetes complications.
Over the period 2011-2014, the medical device sector commitment to R&D investments has been highly heterogeneous. As regards R&D intensity, US firms generally record higher levels of R&D ratio on sales than European companies, meaning that US medical devices companies allocate more resources in research and development activities than EUR firms. Diabetes medical devices consist of a wide range of products: from insulin pumps to blood glucose meters and infusion sets. Despite being one of the top 10 causes of disability worldwide, few companies in the sector have developed any diabetes relevant medical devices in recent years.

The themes emerged from the stakeholders interviews were organized in six major areas: i) challenges in diabetes research, ii) duplication in diabetes research, iii) research gaps, iv) impact of research and priority-setting, v) partnerships and vi) the role of the EU. According to the informants, the challenges faced by researchers and RFOs in diabetes research are financial and organizational.

Heterogeneity of funding bodies was perceived to be an opportunity to preserve and develop through structured forms of cooperation. A general broader view on the impact of research as impact on diagnostic and therapeutic practice, patient outcomes and health services was supported. In terms of research gaps or unmet need, informants pointed out the broad area of aetiology (i.e. pathogenesis of hypo/hyperglycaemic events, pathogenesis of chronic complications), prevention (i.e. genetic factors linked to the adult development of T2DM) or treatment (i.e. adjunct therapies, artificial pancreas, beta-cell transplantation, cell line conversion). Many of these topics were also emerging through the bibliometric and research programs analysis. Similarly, bio-banks development was the most recommended suggestion to speed up genetic-based studies. Another probably unexpected topic suggested for future research was on the social and health related quality of life aspects of people living with the disease, how it is possible to make patients and families more engaged with the treatment and how to get them to use the treatment much more effectively. Finally, and in addition to what can be captured through other methodologies, the role attributed to the EU is one of coordination and leadership, with recommendations on fruitful engagement in discussion with all stakeholders or wider net casts to involve experts in drafting programs calls.

The Bibliometric analysis provides a quantitative methodology to assess the impact of research funding in the field of diabetes in terms of production of scientific publications, as well as level of influence via citation analysis. It has allowed the identification of specific peculiarities related to volume, geography and type of funding institutions. Overall, the volume of diabetes research as a proportion of biomedical scientific production has increased over the years, with geographic heterogeneity across countries in terms of GDP- productivity link. When looking at the burden of disease, countries such as the UK publish more than what prevalence and DALYs of the disease would suggest. There is a tendency for the Northern European countries to devote relatively more attention to Type I diabetes, while the contrary holds true for Southern Europe. Type II diabetes papers are much more numerous and 66% more cited, on average, than Type I diabetes papers. Scandinavian countries display higher number of funders per paper and more private-non-profit sources, especially endowed foundations. For most countries the percentage of internationally-funded papers is quite low and mainly refers to funding from the EU. The European Union is the largest single source of support in terms of the numbers of papers funded, with the second largest being the Danish company Novo Nordisk A/S.

There are numerous discussion points that start to surface by the combined considerations of findings from different analyses in this report. In the next and final evidence synthesis deliverable, we will illustrate the triangulation of the various outputs from the MAPPING_NCD within each disease categories to contrast, reinforce or discuss emerging directives to guide the future research funding strategies across NCDs in Europe.

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Annex 1:

RFO	Project funded
Association Française des Diabétiques	En 2010, l'AFD soutenait le projet de recherche du Pr Pierre Cattan : la greffe d'îlots de Langerhans (partie du pancréas contenant les cellules béta qui produisent l'insuline) et qui permet de rétablir un équilibre glycémique normal
Association Française des Diabétiques	E2F1 et réplication de la cellule ß : Identification des mécanismes moléculaires
Association Française des Diabétiques	Effets périphériques de la Spadine dans le contrôle de l'homéostasie glucidique
Association Française des Diabétiques	L'hypoxie et ses conséquences : modulation de la voie de l'oxygène et génération des cellules ß pancréatiques
Association Française des Diabétiques	Propriétés pharmacologiques et biologiques des analogues d'insuline employés en clinique dans le traitement du diabète. Utilisation de la technique de BRET pour étudier spécifiquement les récepteurs hybrides Insuline/IGF1
Association Française des Diabétiques	Rôle protecteur de la molécule HLA-G contre les dommages immuns portés aux îlots de Langherans : physiologie et applications pour le traitement du diabète de type I.
Association Française des Diabétiques	Hétérogénéité des cellules ß pancréatiques, conséquences pour la pathologie auto-immune
Association Française des Diabétiques	Le déficit de l'exocytose de l'insuline au cours du diabète de Type II. Mécanismes moléculaires et Pathogenèse
Association Française des Diabétiques	Impact de la maladie parodontale sur le diabète
Association Française des Diabétiques	Inhibition des prolyl-hydroxylases et efficacité des thérapies cellulaires pro-angiogéniques dans l'ischémie critique du membre inférieur chez le patient diabétique
Association Française des Diabétiques	Rôle de la molécule de co-stimulation CD28 dans le développement de l'état inflammatoire et de la résistance à l'insuline associés à l'obésité : Nouvelle frontière entre immunologie et maladies métaboliques
Association Française des Diabétiques	Méthylation de l'ADN dans le foie et diabète de Type II : une étude préliminaire
Association Française des Diabétiques	Apport de la génétique dans le diagnostic, la prise en charge initiale et le suivi des diabètes rares monogéniques de la petite enfance/diabète «néonatal » - GENEODIA -
Association Française des Diabétiques	Le diabète de Type II et les complications vasculaires associées entraînent-ils des anomalies chromosomiques clonales en mosaïque (qui prédisent un risque de cancer)
Association Française des Diabétiques	Titre du projet : Exposition à des Question de santé Recherche polluants organiques persistants (POP) et risque de diabète de Type II, d'augmentation de l'adiposité et de dyslipidémie dans la cohorte française DESIR.
Association Française des Diabétiques	Titre du projet : Microbiote de la muqueuse intestinale et biomarqueur des maladies métaboliques.
Diabetes Ireland Research Alliance	"What influences self-care in young adults with Type I diabet
Diabetes Ireland Research Alliance	Adipocyte Size and Type II Diabetes in Obesity - A Study of Patients undergoing Bariatric Surgery More
Diabetes Ireland Research Alliance	Autoimmunity and Prevention study
Diabetes Ireland Research Alliance	Autoimmunity and Prevention study
Diabetes Ireland Research Alliance	Nano Versus Micro Enscapsulation for Islet Transplantation

Diabetes Ireland Research Alliance	The Galway Diabetic Foot Study: Epidemiology, Cost, Feasibility,
Diabetes Ireland Research Alliance	Topically Applied Mesenchymal Stem Cell Therapy for Non-healing
Diabetes UK	A diet drink to burn fat in the muscles
Diabetes UK	A gut feeling about Type I
Diabetes UK	A new vision for neuropathy?
Diabetes UK	Alzheimer's drugs of use in Type II?
Diabetes UK	An artificial pancreas for Type II inpati
Diabetes UK	An eye for diabetes complications
Diabetes UK	Balancing Type I lows and Type II highs
Diabetes UK	Banking on retinopathy research
Diabetes UK	Beta cell damage in Type II
Diabetes UK	Brain glucokinase - a new treatment targ
Diabetes UK	BRITE future for stem cells in Type II
Diabetes UK	Building muscle to treat Type II
Diabetes UK	Can frogs spawn a new treatment for Type
Diabetes UK	Changing behaviours to improve diabetes
Diabetes UK	Control of insulin secretion, beta cell
Diabetes UK	CTLA-4, the immune system and Type I
Diabetes UK	Exploring the role of PASK in Type II
Diabetes UK	Extending the reach of diabetes educatio
Diabetes UK	Extending the reach of diabetes educatio
Diabetes UK	Family history and physical inactivity i
Diabetes UK	Fishing for an answer to kidney disease
Diabetes UK	Glucagon production in Type I and Type II
Diabetes UK	Improving knowledge of hypo unawareness
Diabetes UK	Improving recovery after amputation
Diabetes UK	Islet transplants and liver regeneration
Diabetes UK	Joining the dots between obesity and Typ
Diabetes UK	Leptin, the brain and Type II
Diabetes UK	Limiting damage in diabetic eyes
Diabetes UK	Making the most of metformin
Diabetes UK	Markers to reduce MODY misdiagnosis
Diabetes UK	Mechanisms behind GLUT4 movement
Diabetes UK	Obese pregnant mothers and metformin
Diabetes UK	Poring over the details of islet functio
Diabetes UK	Protecting nerve cells in retinopathy
Diabetes UK	Racking our brains on energy balance
Diabetes UK	Real-time analysis of fatty acids in the
Diabetes UK	Sex hormones and Type II
Diabetes UK	Solving the mystery of metformin mechani
Diabetes UK	Sorcin to save the islet cells in Type II
Diabetes UK	Statins and ACE inhibitors for teens wit
Diabetes UK	Superior screening for gestational diabe
Diabetes UK	Tailored diabetes education for people w
Diabetes UK	Taking account of ACC1 in beta cells
Diabetes UK	Targeting the trigger of diabetic neurop

Diabetes UK	The brain and hypo unawareness
Diabetes UK	The DiRECT route to Type II remission?
Diabetes UK	The interactions of islet cells
Diabetes UK	The role of adiponectin in Type II
Diabetes UK	The role of glycation in diabetes and de
Diabetes UK	The trafficking of glucose transporters
Diabetes UK	Thinking outside the BOX
Diabetes UK	Time-efficient exercise for Type II
Diabetes UK	Tracking hypos to the hypothalamus
Diabetes UK	Understanding immune targets in Type I
Diabetes UK	Understanding progression to Type I
Diabetes UK	Understanding the impact of iNKT cells
Diabetes UK	Understanding the role of muscle in Type
Diabetes UK	Understanding the Type I autoimmune atta
Dutch Diabetes Research Foundation	A longitudinal study on prognostic factors for the development of microvascular complications in IDDM patients
Dutch Diabetes Research Foundation	Adipose tissue hypoxia in the pathogenesis of insulin resistance: a novel approach for the continuous monitoring of oxygen tension in human subcutaneous adipose tissue by microdialysis
Dutch Diabetes Research Foundation	After the health check in vulnerable groups: a individually tailored self management intervention led by community health workers
Dutch Diabetes Research Foundation	An autofluorescence reader for advanced glycation end products (AGE's) in diabetes mellitus
Dutch Diabetes Research Foundation	An integrated approach from basic research to clinical intervention in Type I diabetes
Dutch Diabetes Research Foundation	Assessment of health-related quality of life in adolescents with Type I diabetes prior to periodic outpatient consultation: impact on psychosocial adaptation, satisfaction with care and glycaemic control. A randomised controlled cross-over study
Dutch Diabetes Research Foundation	Assessment of the heredity risk of several aspects of the beta-cell function in normal-glycaemic monozygotic and heterozygotic twins
Dutch Diabetes Research Foundation	Auto-antigens and the origin of diabetes Type I
Dutch Diabetes Research Foundation	Beyond Good Intentions: The effectiveness of a proactive self-management intervention in patients with screen-detected Type II diabetes
Dutch Diabetes Research Foundation	Bile acids regulate insulin sensitivity and postprandial glucose and lipid metabolism in healthy humans and patients with Type II diabetes mellitus
Dutch Diabetes Research Foundation	Biomarkers for the Prediction and Early Diagnosis of Diabetes and Diabetes-related Cardiovascular Complications (PREDICCt)
Dutch Diabetes Research Foundation	Blood coagulation disorders in diabetes mellitus
Dutch Diabetes Research Foundation	Cell-camouflage in grafting Islets of Langerhans
Dutch Diabetes Research Foundation	Characterization of vascular function of the human fetal-placental circulation in patients with diabetes mellitus
Dutch Diabetes Research Foundation	Children of mothers with Type I diabetes: a follow-up study
Dutch Diabetes Research Foundation	CML (Carboxy Methyl Lysine) and the production of adipocytokines

Dutch Diabetes Research Foundation	Cognitive behaviour therapy for chronic fatigue in Type I Diabetes: a randomized controlled trial
Dutch Diabetes Research Foundation	Colon baceria in relation with diabets Type I
Dutch Diabetes Research Foundation	Combatting diabetes with the support of fellow-sufferers
Dutch Diabetes Research Foundation	Control of metabolic flux by nutrient sensors
Dutch Diabetes Research Foundation	DCTI: An implantable islet cell replacement device for controlled insulin release in diabetes
Dutch Diabetes Research Foundation	Deciphering mitochondrial and molecular pathology in Type II Diabetes Mellitus
Dutch Diabetes Research Foundation	Defective endothelial progenitor cell development in diabetes: microRNA profile as biomarker for skewed myeloid differentiation
Dutch Diabetes Research Foundation	DESTINY: Developmental study in youth with Type I diabetes
Dutch Diabetes Research Foundation	Development of a Dutch diabetes risk score
Dutch Diabetes Research Foundation	Diabetes and brain damage
Dutch Diabetes Research Foundation	Diabetes and islet neogenesis
Dutch Diabetes Research Foundation	Diabetes and retinopathy
Dutch Diabetes Research Foundation	Diabetes and the Heart
Dutch Diabetes Research Foundation	Diabetes educations that fits cultural needs: what does the immigrant patient think?
Dutch Diabetes Research Foundation	Diabetic nephropathy: mechanistic insight in the role of Protease activated receptor-1
Dutch Diabetes Research Foundation	Diabetic retinopathy screening
Dutch Diabetes Research Foundation	DiAlert, effects of a lifestyle intervention in Dutch and Turkish Dutch 1st degree relatives of persons with Type II diabetes. A pragmatic randomised controlled trial
Dutch Diabetes Research Foundation	Diseasemanagement Chronisch Zieken - bijdrage deelprogramma Comorbiditeit (NL)
Dutch Diabetes Research Foundation	Driving advices for diabetes patients
Dutch Diabetes Research Foundation	Early environmental and genetic risk factors on foetal growth, insulin resistance and overweight: a prospective cohort study from foetal age to young adulthood
Dutch Diabetes Research Foundation	Effect of folic acid supplementation on endothelial function in type II diabetes mellitus
Dutch Diabetes Research Foundation	Endocrine-Disrupting Chemicals and Type II diabetes: what is their relationship?
Dutch Diabetes Research Foundation	Enhanced glucose clearance via bone morphogenetic protein 9 (BMP9) mediated activation of human brown adipose tissue metabolism in Type II diabetes
Dutch Diabetes Research Foundation	Exploration of human ductal cells for beta-cell replacement therapy
Dutch Diabetes	Exploring the role of cross-presenting dendritic cells in diet-induced obesity

Research Foundation	
Dutch Diabetes Research Foundation	Family matters in diabetes prevention. Communication about familial risk of Type II diabetes
Dutch Diabetes Research Foundation	Fat consumption and insulin resistance
Dutch Diabetes Research Foundation	Fibroblast Growth Factor 1: a novel regulator of glucose homeostasis and insulin sensitivity
Dutch Diabetes Research Foundation	Fish oil research
Dutch Diabetes Research Foundation	Friction in blood vessels and plaques
Dutch Diabetes Research Foundation	Generic methods for quantitative profiling of peptides and their posttranslational modifications in body fluids and cells/tissues: development and application in disease model systems
Dutch Diabetes Research Foundation	Genomic approaches to understanding the relations between nutrition, toxicity and disease
Dutch Diabetes Research Foundation	Glucose metabolism in the brain and the development of 'hypoglycaemia unawareness' in Type I diabetes
Dutch Diabetes Research Foundation	Health checks in vulnerable groups: the role of beliefs and expectations
Dutch Diabetes Research Foundation	How leads movement to the reception of glucose?
Dutch Diabetes Research Foundation	How to cope with your diabetic teenager. Development of an internet course for parents of diabetic teenagers.
Dutch Diabetes Research Foundation	Human fetal and adult progenitor cells as a source for insulin producing cells
Dutch Diabetes Research Foundation	Hyperoxic exercise training as an innovative therapy to improve endothelial dysfunction, metabolic control and physical fitness in deconditioned Type II diabetes patients
Dutch Diabetes Research Foundation	Hypothalamic neural networks in control of glucose homeostasis
Dutch Diabetes Research Foundation	Implementatie Very Low Calorie Diet bij mensen met diabetes Type II en overgewicht
Dutch Diabetes Research Foundation	Implementation and (cost)effectiveness of diabetes prevention in the Dutch Gelre-IJssel region: from SLIM to SLIMMER
Dutch Diabetes Research Foundation	Improving care for sexual problems in persons with Type II diabetes
Dutch Diabetes Research Foundation	Improving coping with diabetes: efficacy of a cognitive behavioural group training for Type I DM patients in fair to poor control. A randomized controlled trial
Dutch Diabetes Research Foundation	Improving health risk communication for cardiovascular diseases, diabetes and kidney disease by taking into account people's prior beliefs and cognitive abilities; a mental model approach
Dutch Diabetes Research Foundation	Improving the technique for the transplantation of the Islets of Langerhans in patients with Type I diabetes
Dutch Diabetes Research Foundation	In vivo functionality of autoreactive and regulatory human T cells
Dutch Diabetes Research Foundation	Information on the inheritance of Type II diabetes
Dutch Diabetes Research Foundation	Inhibition of adenine nucleotide translocators by long-chain fatty acyl-CoA esters and features of the insulin resistance syndrome

Dutch Diabetes Research Foundation	Insulin production at the mitochondrial level
Dutch Diabetes Research Foundation	Insulin resistance and mitochondrial function; a mitocentric view
Dutch Diabetes Research Foundation	Internet-therapy in the treatment of depression in diabetic patients
Dutch Diabetes Research Foundation	Is adipose tissue the cause of chronic inflammation?
Dutch Diabetes Research Foundation	Is inflammasome activation in adipose tissue an important mediator of obesity-induced insulin resistance?
Dutch Diabetes Research Foundation	Islets of Langerhans: the protective role of stem cells
Dutch Diabetes Research Foundation	Lifestyle intervention-induced effects on disturbed skeletal muscle fatty acid utilization in impaired glucose tolerance: role of fatty acid transport proteins
Dutch Diabetes Research Foundation	Metabolism in the obese
Dutch Diabetes Research Foundation	MicroRNA regulation of skeletal muscle mitochondrial oxidative capacity: implications for Type II diabetes mellitus
Dutch Diabetes Research Foundation	Mimicking the onset of autoimmune Type I diabetes: Enterovirus-infected pancreatic β-cells, primary human dendritic cells and innate lymphocytes
Dutch Diabetes Research Foundation	Molecular basis of fish-oil induced Type II diabetes prevention: shift of the balance between PPAR-alpha and LXR-alpha controlled pathways of glucose and fat metabolism in the liver
Dutch Diabetes Research Foundation	New insulin cells from stem cells or bone marrow cells
Dutch Diabetes Research Foundation	Obese, but with a fat deficiency?
Dutch Diabetes Research Foundation	Omgaan met diabetes in het dagelijkse leven: effectiviteit van zelfmanagement ondersteuning (SMS) uitgevoerd door praktijkondersteuners in de huisartsenpraktijk (NL)
Dutch Diabetes Research Foundation	Optimizing the beneficial health effect of exercise for diabetes: focus on the liver!
Dutch Diabetes Research Foundation	Optimizing the beneficial health effects of exercise for diabetes: focus on the liver
Dutch Diabetes Research Foundation	Pathophysiology of heart diseases in Type II diabetes: the association between diet-related changes in heart metabolism, insulin signals and modified contractile function
Dutch Diabetes Research Foundation	PKA signaling and its role in the protection of pancreatic ß-cell mass
Dutch Diabetes Research Foundation	Postprandial hyperglycaemia versus dyslipidaemia in relation to cardiovascular disease and different markers of vascular dysfunction in persons with Type II diabetes and in normoglycaemic subjects
Dutch Diabetes Research Foundation	Prevention and treatment of ketoacidosis in Type I diabetes via the inhibition of hepatic beta-oxydation
Dutch Diabetes Research Foundation	Prevention of diabetes in schizofrenics
Dutch Diabetes Research Foundation	Probing the role of fatty acids and the peroxisome proliferator activated receptor alpha in the regulation of hepatic glucose metabolism
Dutch Diabetes Research Foundation	Pro-inflammatory programming of macrophages through C-type Lectin receptors: increasing the risk for atherosclerosis in patients with diabetes
Dutch Diabetes	Protection of transplanted beta-cells from autoimmunity and allo-reactive T cells through

Research Foundation	viral immune evasion strategies
Dutch Diabetes Research Foundation	Regulatory enzymes of mitochondrial ß-oxidation as targets for treatment of the metabolic syndrome
Dutch Diabetes Research Foundation	Regulatory T cells: key players in nasal tolerance
Dutch Diabetes Research Foundation	Relevance of genetic predisposition and life-style factors in the pathogenesis of Type II diabetes mellitus and cardiovascular complications
Dutch Diabetes Research Foundation	Role of nNOS derived nitric oxide in the onset of hyperfiltration in diabetes
Dutch Diabetes Research Foundation	Role of the central nervous system in the regulation of triglyceride metabolism in plasma and adipose tissue
Dutch Diabetes Research Foundation	Role of the nervous system in controlling the glucose production in the liver
Dutch Diabetes Research Foundation	Role of viral infections in the induction of Type I diabetes mellitus. An experimental study
Dutch Diabetes Research Foundation	SCD-1: A moleacular target to prevent Type II diabetes mellitus?
Dutch Diabetes Research Foundation	Screening and focussed intervention for comorbid anxiety and depression in patients with diabetes by trained nurses - a pilot study
Dutch Diabetes Research Foundation	Screening for depression in diabetes outpatient clinics: point-prevalence of major depression and the impact of case-finding on the course of depression and glycaemic control
Dutch Diabetes Research Foundation	Selective insulin resistance in microcirculation: a new concept in the understanding of the relations between microvascular function, insulin sensitivity and tension
Dutch Diabetes Research Foundation	Sensitization of blood platelets by insulin/glucose imbalance
Dutch Diabetes Research Foundation	Signal Transduction and Ageing
Dutch Diabetes Research Foundation	Skeletal muscle lipid metabolism and insulin sensitivity: Can dietary fatty acid composition modulate muscle lipid storage?
Dutch Diabetes Research Foundation	Sleep duration: a determinant of intra-individual variations in glucoregulation in patients with Type I diabetes mellitus
Dutch Diabetes Research Foundation	Stroke prevention versus decreased blood supply of the brain - the therapeutic dilemma
Dutch Diabetes Research Foundation	Substrate metabolism in Type II diabetes
Dutch Diabetes Research Foundation	Tailoring an existing lifestyle intervention to reduce metabolic syndrome in individuals with low SES from different ethnic origins
Dutch Diabetes Research Foundation	Targeting mitochondrial function in pre-diabetic subjects: a role for SIRT1 activation by resveratrol?
Dutch Diabetes Research Foundation	Targetting glycosphingolipids in the pathophysiology of Type II diabetes
Dutch Diabetes Research Foundation	The basis of 'metabolism programming' in relation with perinatal feeding and its influence on the Type II diabetes susceptability in adulthood
Dutch Diabetes Research Foundation	The biological clock and its control of glucose homeostasis. Central and peripheral mechanisms involving glucose counter-regulation and insulin resistance
Dutch Diabetes Research Foundation	The cause of vascular problems in diabetes
Dutch Diabetes	The effect of dysregulation of the central clock on the development of obesity and insulin

Research Foundation	resistance
Dutch Diabetes Research Foundation	The effectiveness and cost-effectiveness of an integrated cardio-metabolic risk assessment and treatment program in primary care: the INTEGRATE study
Dutch Diabetes Research Foundation	The influence of candidate genes on lipid and carbohydrate metabolism using a twin study approach
Dutch Diabetes Research Foundation	The influence of hyperinsulinaemia and hyperglycaemia on the congenital immune response in bacterial infection
Dutch Diabetes Research Foundation	The mechanism of insulin mediated vasodilation and the effect of this insulin mediated vasodilation on glucose metabolism
Dutch Diabetes Research Foundation	The novel slit diaphragm-associated channel TRPC6 in the pathogenesis and treatment of diabetic nephropathy
Dutch Diabetes Research Foundation	The origin of cardiac disorders in diabetes patients
Dutch Diabetes Research Foundation	The replacement of beta-cells in Type I diabetes
Dutch Diabetes Research Foundation	The role of brain lactate in the pathogenesis of hypoglycemia unawareness in Type I diabetes
Dutch Diabetes Research Foundation	The role of cell-derived microparticles in atherogenesis in Type II diabetes mellitus
Dutch Diabetes Research Foundation	The role of genetic variations in the insulin-like growth factor-I system and renin-angiotensin-system in vascular complications in Type II diabetes mellitus
Dutch Diabetes Research Foundation	The role of macrophages in obesity induced Type II diabetes
Dutch Diabetes Research Foundation	The role of microRNAs in islet dysfunction in Type II diabetes mellitus
Dutch Diabetes Research Foundation	The role of T-cells in the origin of diabetes Type I
Dutch Diabetes Research Foundation	The role of the hexosamine pathway in insulin resistance and nutrient sensing
Dutch Diabetes Research Foundation	The Snuffie story book: guiding toddlers and pre-schoolers with diabetes mellitus to live a healthy life
Dutch Diabetes Research Foundation	Towards a personalized risk assessment and therapeutical strategy to prevent and treat macrovascular disease in Type II diabetes
Dutch Diabetes Research Foundation	Treatment of diabetic foot ulcers with cold plasma
Dutch Diabetes Research Foundation	Turning op the heat: role of brown adipose tissue in metabolic disease
Dutch Diabetes Research Foundation	Type II diabetes and cognition: Neuropsychological sequelae of vascular risk factors in the ageing brain
Dutch Diabetes Research Foundation	Van 't Hoff Program - Shared Research Program / Diabetes
Dutch Diabetes Research Foundation	Web-based cognitive behaviour therapy for depression in audults with Type I or Type II diabete
Dutch Diabetes Research Foundation	What is the working of fat in the muscles?
Dutch Diabetes Research Foundation	Whatever happens… Interventions to improve self-management and quality of life of patients with Type II diabetes mellitus through the course of illness
Dutch Diabetes Research Foundation	You are at risk: how health risk information can be made more meaningful for consumers

Juvenile Diabetes Research Fund	Project Title: Pancreatic enteroviral persistence - a molecular trigger for islet autoimmunity and Type I diabetes in humans?
Juvenile Diabetes Research Fund	Project Title: Harnessing vascular stem cells to model and treat diabetic retinopathy
Juvenile Diabetes Research Fund	Project Title: Targeting STAT3 for the management of diabetic retinopathy
Juvenile Diabetes Research Fund	Project Title: Tolerizing insulin-reactive CD8 T cells in Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: 7th Conference of the Immunology of Diabetes Society, March 28-30, 2004, Cambridge, England
Juvenile Diabetes Research Fund	Project Title: A DNA Resource to Facilitate the Identificaiton of Genetic Susceptibility Factors for Diabetic Nephropathy in Type I Diabetes Mellitus
Juvenile Diabetes Research Fund	Project Title: A new model of extensive retinal ischemia in diabetic rodents
Juvenile Diabetes Research Fund	Project Title: A study of the Epigenetics of Type I diabetes using identical twins
Juvenile Diabetes Research Fund	Project Title: Activation of insulin-reactive CD8 T cells in autoimmune diabetes
Juvenile Diabetes Research Fund	Project Title: adAPT (autoimmune diabetes ACCELERATOR PREVENTION TRIAL) – Setup
Juvenile Diabetes Research Fund	Project Title: adAPT (autoimmune diabetes ACCELERATOR PREVENTION TRIAL) - Stage 1 pilot
Juvenile Diabetes Research Fund	Project Title: Adenosine protection of islet beta cells
Juvenile Diabetes Research Fund	Project Title: Adolescent Type I Diabetes Cardio-Renal Protection Study
Juvenile Diabetes Research Fund	Project Title: AMPK and the control of electrical excitability of pancreatic islet cells
Juvenile Diabetes Research Fund	Project Title: An incident and high risk Type I diabetes research cohort
Juvenile Diabetes Research Fund	Project Title: An incident and high risk Type I diabetes research cohort - ADDRESS-2 - After Diabetes Diagnosis REsearch Support System-2
Juvenile Diabetes Research Fund	Project Title: An Investigation of the Potential of Human Embryonic Germ Cells as a Resource for the In Vitro Generation of Insulin-producing Cells: Towards a Curative Strategy for Type I Diabetes Mellitus
Juvenile Diabetes Research Fund	Project Title: Analysing how infection prevents onset of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Association of cellular phenotypes with genes causing human Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Blood glucose, recurrent hypoglycemia and memory; an fMRI study
Juvenile Diabetes Research Fund	Project Title: Brain K ATP Channels: Role in brain glucose-sensing and novel therapeutic target for restoring hormonal counterregulation against hypoglycemia in diabetes
Juvenile Diabetes Research Fund	Project Title: Central mechanisms of glucose metabolism: brain activation by hypoglycemia and glucose ingestion in humans
Juvenile Diabetes Research Fund	Project Title: Central Mechanisms of Hypoglycemia Unawareness: a failing primary inducer?
Juvenile Diabetes Research Fund	Project Title: Central Pain Processing in Diabetic Neuropathy

Juvenile Diabetes Research Fund	Project Title: Centre for Stem Cell Biology and Medicine
Juvenile Diabetes Research Fund	Project Title: Centre for Stem Cell Research
Juvenile Diabetes Research Fund	Project Title: Characterisation of new human ES cells derived in novel serum free conditions
Juvenile Diabetes Research Fund	Project Title: Characterizing ongoing B lymphocyte autoimmunity and beta cell function
Juvenile Diabetes Research Fund	Project Title: Closing the loop in children and adolescents
Juvenile Diabetes Research Fund	Project Title: Closing the loop in children and adolescents
Juvenile Diabetes Research Fund	Project Title: Conference Grant, Medical Research Council 2002 Conference on 'Stem Cells: Shaping the Future', 9/15 to 9/16/2003, London
Juvenile Diabetes Research Fund	Project Title: Corneal confocal microscopy: A non-invasive surrogate for small fibre damage and repair in human diabetic neuropathy
Juvenile Diabetes Research Fund	Project Title: Creating a tolerogenic environment in the skin for peptide immunotherapy
Juvenile Diabetes Research Fund	Project Title: Deciphering the epigenome of human beta cells during development and in pathology for novel regenerative strategies in diabetes
Juvenile Diabetes Research Fund	Project Title: Derivation and self-renewal of human pluripotent stem cells-the investigation of human embryonic germ cells
Juvenile Diabetes Research Fund	Project Title: Derivation, maintenance and characterization of insulin secreting cells and cell lines from human stem cells
Juvenile Diabetes Research Fund	Project Title: Detection and characterization of autoreactive CD8 T cells in T1D
Juvenile Diabetes Research Fund	Project Title: Developing and optimizing pHLA multimers as a biomarker for T1D
Juvenile Diabetes Research Fund	Project Title: Developing corneal confocal microscopy for human diabetic neuropathy
Juvenile Diabetes Research Fund	Project Title: Development of thiol specific chemical sensors for the near-patient monitoring of oxidative stress in diabetic patients
Juvenile Diabetes Research Fund	Project Title: Discovery, fine-mapping and allele specific expression analysis of T1D loci
Juvenile Diabetes Research Fund	Project Title: Do sulfonylureas preserve cortical function during hypoglycemia?
Juvenile Diabetes Research Fund	Project Title: Does Inhibition of Brain Glucokinase Restore Defences against Hypoglycemia?
Juvenile Diabetes Research Fund	Project Title: Does Omega-1 induce regulatory T cells to prevent Type I diabetes?
Juvenile Diabetes Research Fund	Project Title: Endothelial MicroRNA 126 as Biomarker Candidate for Diabetic Retinopathy
Juvenile Diabetes Research Fund	Project Title: Endothelial Progenitors and Therapeutic Angiogenesis in the Ischemic Retina
Juvenile Diabetes Research Fund	Project Title: Epitope discovery and peptide-based therapeutics'
Juvenile Diabetes Research Fund	Project Title: EU Collaboration- EuroStemCell
Juvenile Diabetes	Project Title: Evaluation of Methylglyoxal Derived Protein Glycation Adducts as Medium

Research Fund	Term Indicators of Postprandial and Fasting Hyperglycemia in Type I Clinical Diabetes Mellitus
Juvenile Diabetes Research Fund	Project Title: Excreted Volatile Compounds as a Novel Method for Monitoring Blood Glucose
Juvenile Diabetes Research Fund	Project Title: Extracellular matrix glycation in diabetic neuropathy
Juvenile Diabetes Research Fund	Project Title: Extreme Phenotypes relevant to Diabetic Complications in Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: Fetal epigenetic programming and epigenetic risk of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Function of shared autoimmune disease T cell genetic risk variants.
Juvenile Diabetes Research Fund	Project Title: Generation of functional pancreatic B-cells from stem cell populations
Juvenile Diabetes Research Fund	Project Title: Genetically-modified T cells for the protection of regenerated Beta-cells in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Growth and Differentiation of Human Embryonic Beta Cells: An Investigation of Normal Development and In Vitro Cell Culture
Juvenile Diabetes Research Fund	Project Title: Haplotype-dependent pre-mRNA splicing of the human insulin gene
Juvenile Diabetes Research Fund	Project Title: HOVORKA Overview: Overnight closed-loop in young people Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Human B-cell Lines for Diabetes
Juvenile Diabetes Research Fund	Project Title: Human Embryonic Stem Cells for Diabetes (PPG)
Juvenile Diabetes Research Fund	Project Title: Iatrogenic immunization reveals the properties of islet destructive T-cells
Juvenile Diabetes Research Fund	Project Title: Identifying a signature for islet-specific IL-10 secreting (ISIS) Tregs
Juvenile Diabetes Research Fund	Project Title: Immunological markers of beta cell decline in new onset Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Improving recovery from hypoglycemia using Katp
Juvenile Diabetes Research Fund	Project Title: Induction of ARE linked gene expression to prevent vascular complications
Juvenile Diabetes Research Fund	Project Title: Integration of genome-wide association, exome array and exome sequence data for diabetic kidney disease from JDRF- and IMI-funded consortia
Juvenile Diabetes Research Fund	Project Title: International Stem Cell Forum Activities: Characterization of Human Embryonic Stem Cell Lines and Development of Forum Web site
Juvenile Diabetes Research Fund	Project Title: Investigation of the Genetic Basis of Endothelial Dysfunction in Type I Diabetic Patients with Microalbuminuria Using a Human Microvascular Endothelial Cell Culture System
Juvenile Diabetes Research Fund	Project Title: In-vivo evaluation of a novel genetic approach for antigen specific immunotargeting of diabetogenic CD8 T cells
Juvenile Diabetes Research Fund	Project Title: Ion Channel Dysfunction and the Pathogenesis of Diabetic Retinopathy
Juvenile Diabetes Research Fund	Project Title: Islet encapsulation for transplantation: nano- versus micro-encapsulation

Juvenile Diabetes Research Fund	Project Title: Islets For Research- JDRF funded Investigators
Juvenile Diabetes Research Fund	Project Title: Islet-specific T-cell response genes identified by microarray analysis
Juvenile Diabetes Research Fund	Project Title: JDRF International Clinical Sites - UK - Bingley
Juvenile Diabetes Research Fund	Project Title: JDRF UK Centre for Diabetes Genes, Autoimmunity and Prevention (D-GAP)
Juvenile Diabetes Research Fund	Project Title: JDRF/ Wellcome Trust Diabetes and Inflammation Laboratory
Juvenile Diabetes Research Fund	Project Title: JDRF/ Wellcome Trust Diabetes and Inflammation Laboratory
Juvenile Diabetes Research Fund	Project Title: JDRF/Wellcome Trust Partnership in Stem Cell Research
Juvenile Diabetes Research Fund	Project Title: Linkage and association analysis of Type I diabetes diagnosed under age 15 years in Finland
Juvenile Diabetes Research Fund	Project Title: Mechanism of Nitrergic Neuropathy in Diabetes
Juvenile Diabetes Research Fund	Project Title: Meeting Support: Medical Research Council 'Shaping the Future' September 15-16, 2003 (3000GBP) change dollar amount once I get information
Juvenile Diabetes Research Fund	Project Title: Memory function during, and recovery of cognitive function after, acute hypoglycemia in subjects with Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Metabolic and Vascular Mechanisms of Nerve Dysfunction in Experimental Models of Diabetes - Focus on Small Fibers
Juvenile Diabetes Research Fund	Project Title: Microneedle arrays to deliver antigen specific immunotherapy
Juvenile Diabetes Research Fund	Project Title: MicroRNAs and the p75NTR-mediated signature in endothelial cells
Juvenile Diabetes Research Fund	Project Title: Molecular Characterization of a Novel Candidate Gene for Diabetic Nephropathy: Caldesmon in Patients and Family Trios
Juvenile Diabetes Research Fund	Project Title: Molecular mechanism of ¿gkiss-and-run¿h exocytosis in pancreatic beta cells
Juvenile Diabetes Research Fund	Project Title: Molecular mechanisms of allele-specific pre-mRNA splicing at the INS locus
Juvenile Diabetes Research Fund	Project Title: Molecular Mechanisms of Glucose Sensing by Pancreatic Islet Alpha-Cells
Juvenile Diabetes Research Fund	Project Title: Molecular pathogenesis of Type I diabetes in man
Juvenile Diabetes Research Fund	Project Title: Monoclonal T cell receptor therapeutics in the treatment of type I diabetes
Juvenile Diabetes Research Fund	Project Title: MonoPepT1De trial
Juvenile Diabetes Research Fund	Project Title: MonoPepT1De trial
Juvenile Diabetes Research Fund	Project Title: MRC - International Stem Cell Forum Initiative
Juvenile Diabetes Research Fund	Project Title: NIDDK X (TrialNet UK - Bingley)
Juvenile Diabetes	Project Title: NIDDK X (TrialNet UK - Peakman)

Research Fund	
Juvenile Diabetes Research Fund	Project Title: Overnight closed loop in sub-optimally controlled Type I diabetes under free living conditions (APCam11)
Juvenile Diabetes Research Fund	Project Title: Peripheral Tolerance of CD8+ T Lymphocytes
Juvenile Diabetes Research Fund	Project Title: Phenotype, specificity, diversity and clonal spread of B cells in T1DM
Juvenile Diabetes Research Fund	Project Title: Potassium channel openers as a treatment for HAAF
Juvenile Diabetes Research Fund	Project Title: Potential mechanisms of persistent C-peptide in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Potential therapeutic agents to combat diabetic retinopathy
Juvenile Diabetes Research Fund	Project Title: Pre-Conditioning and the Development of Hypoglycemia Tolerance
Juvenile Diabetes Research Fund	Project Title: Prevention of Diabetic Nephropathy by Thiamine
Juvenile Diabetes Research Fund	Project Title: Promoting survival of porcine islet xenograft with graft specific immunotherapy
Juvenile Diabetes Research Fund	Project Title: Promotion of Neovascularization by Human Tissue Kallikrein Gene Therapy and Trasplantation of Endothelial Progenitor Cells for the Healing of Diabetic Ulcers.
Juvenile Diabetes Research Fund	Project Title: Protecting the brain from hypoglycaemic damage
Juvenile Diabetes Research Fund	Project Title: Rejuvenating ßcell antigen-specific regulatory T-cells for adoptive therapy
Juvenile Diabetes Research Fund	Project Title: Relationships between antibody and T-cell responses to the IA-2 autoantigen
Juvenile Diabetes Research Fund	Project Title: REMOVAL study: REducing with MetfOrmin Vascular Adverse Lesions in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Restoring Hypoglycemia Counterregulation in Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: Risk of Autoimmune Diseases and Human Self-Antigen expression
Juvenile Diabetes Research Fund	Project Title: Risk of type I diabetes and autoimmunity in twins: Combined analysis of British and American studies
Juvenile Diabetes Research Fund	Project Title: Role of CD28 and the PI3K p110delta in islet transplantation
Juvenile Diabetes Research Fund	Project Title: Role of follicular helper T cells in autoimmune diabetes
Juvenile Diabetes Research Fund	Project Title: Role of Mcl-1 in regulation of beta-cell apoptosis
Juvenile Diabetes Research Fund	Project Title: Role of PAS kinase as a glucose sensor in pancreatic beta cells
Juvenile Diabetes Research Fund	Project Title: Role of VMH BAD in hypoglycemia counterregulation
Juvenile Diabetes Research Fund	Project Title: Selective depletion of primed T cells: therapeutic potential in diabetes
Juvenile Diabetes Research Fund	Project Title: Skills and technology to isolate and define human early fetal beta cells

Juvenile Diabetes Research Fund	Project Title: Statistical methods for Type I Diabetes association studies
Juvenile Diabetes Research Fund	Project Title: Steering embryonic stem cells towards pancreatic lineages.
Juvenile Diabetes Research Fund	Project Title: Supplement to bridge existing ACC into the collaborative ACC Biomarker Study
Juvenile Diabetes Research Fund	Project Title: Targeting B-cell Transcriptional Dysfunction in NIDDM: Defining Critical Differences Between the Nutritional Regulation of the Human Insulin and IAPP Genes
Juvenile Diabetes Research Fund	Project Title: Targeting the IL-6/IL-6R signaling pathway in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: The cumulative role of hypoxia and hyperglycaemia on diabetic retinopathy
Juvenile Diabetes Research Fund	Project Title: The development of intravitreal plasma kallikrein inhibitors for DME
Juvenile Diabetes Research Fund	Project Title: The Effects of a Specific Growth Hormone Inhibitor (B2036-PEG) on Insulin Sensitivity in Subjects with Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: The European Nicotinamide Diabetes Intervention Trial (ENDIT) - Final Phase
Juvenile Diabetes Research Fund	Project Title: The influence of hypothalamic-pituitary-adrenal disease on the counter-regulatory response to recurrent hypoglycemia.
Juvenile Diabetes Research Fund	Project Title: The potential for nonheart beating donors (NHBD) as a source for human islet cells for transplantation'
Juvenile Diabetes Research Fund	Project Title: The Role of Aberrant Neurofilament Phosphorylation in the Pathogenesis of Diabetic Sensory Nueropathy
Juvenile Diabetes Research Fund	Project Title: The role of AGEs and RAGE in neural retina dysfunction during diabetes
Juvenile Diabetes Research Fund	Project Title: The role of AMPK in hypoglycemia detection and GABA regulation
Juvenile Diabetes Research Fund	Project Title: The Role of Associated Mesenchyme in Pancreatic Development: Identification of Factors Responsible for Controlling Pancreatic Growth and Differentiation
Juvenile Diabetes Research Fund	Project Title: The role of Class II MHC Expression on Islet Endothelium in the Selective Recruitment of Islet Autoantigen-specific T-cells; Effects on Diabetes Development of a Novel Therapy to Down-regulate MHC Class II Expression on Islet Vessels
Juvenile Diabetes Research Fund	Project Title: The Role of Hepatic and Portal Vein Glucose Sensing in Hypoglycaemia Recognition and Defence in Man
Juvenile Diabetes Research Fund	Project Title: The Role of Maternal Microchimerism in Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: The role of novel epigenetic regulators in beta cell development and growth
Juvenile Diabetes Research Fund	Project Title: The role of plasmacytoid dendritic cells in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: The UK International Clinical Site (UK Trials Group)
Juvenile Diabetes Research Fund	Project Title: The UK International Clinical Site (UK Trials Group)
Juvenile Diabetes Research Fund	Project Title: The Unseen Threat from Phagocytes to the Xenotransplantation of Pancreatic or Renal Tissue
Juvenile Diabetes Research Fund	Project Title: Tissue electrical fields and wound healing in diabetes

Juvenile Diabetes Research Fund	Project Title: To Support Postdoctoral Fellowship Awards to the Heat Shock Protein Consortium
Juvenile Diabetes Research Fund	Project Title: Understanding T cell migration via inflamed endothelium in Diabetes Type I
Juvenile Diabetes Research Fund	Project Title: United Kingdom Control Trio Collection for GoKinD Study
Juvenile Diabetes Research Fund	Project Title: Use of telomerase immortalisation to develop human islet b-cell lines safe for transplantation
Juvenile Diabetes Research Fund	Project Title: Using gene-phenotype studies to identify early disease biomarkers for T1D
Juvenile Diabetes Research Fund	Project Title: Validation of Novel and Candidate Biomarkers for Diabetic Kidney Disease in Large Cohorts of people with Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: Validation of Y receptors as targets for the maintenance of beta cell mass
Juvenile Diabetes Research Fund	Project Title: Wellcome Trust U.K.
Juvenile Diabetes Research Fund	Project Title: What protects islet antibody positive T1D relatives who do not progress?
Juvenile Diabetes Research Fund	Project Title: What protects islet autoantibody positive T1D relatives who do notprogress?
Juvenile Diabetes Research Fund	Project Title: Alterations in the Phosphoinositide 3-kinase Signaling Pathway in the diabetic Myocardium
Juvenile Diabetes Research Fund	Project Title: Antigen processing and presentation of GAD65
Juvenile Diabetes Research Fund	Project Title: AUTOANTIGEN TARGETING TO ANTIGEN PRESENTING CELLS TO PREVENT AND CURE T1D
Juvenile Diabetes Research Fund	Project Title: Autoreactive CD8+ T cell responses in T1D patients treated with anti-CD3
Juvenile Diabetes Research Fund	Project Title: Characterization and In Vitro Mass Propagation of Human Pancreatic Stem Cells
Juvenile Diabetes Research Fund	Project Title: Characterization of genels on distal mouse chromosome b conferring resistance to type I diabetes and their immunological correlates
Juvenile Diabetes Research Fund	Project Title: Clinical translation of beta cell imaging with GLP1 analogs
Juvenile Diabetes Research Fund	Project Title: Cloning and Engineering the IC2 Biomarker targeting functional beta cells
Juvenile Diabetes Research Fund	Project Title: Danish & French effort to dissect the genetics of diabetic nephropathy
Juvenile Diabetes Research Fund	Project Title: DiaZEpi: an epigenetic approach to Type I diabetes susceptibility
Juvenile Diabetes Research Fund	Project Title: Differentiation of human amniotic stem cells into beta cells
Juvenile Diabetes Research Fund	Project Title: ECIT Islets for Research
Juvenile Diabetes Research Fund	Project Title: Generating antibodies against human pancreatic beta cells
Juvenile Diabetes Research Fund	Project Title: Generation of functional ß-cells from alternative pancreatic cell subtypes
Juvenile Diabetes	Project Title: Generation of functional ß-cells from alternative pancreatic cell subtypes

Research Fund	
Juvenile Diabetes Research Fund	Project Title: Generation of HLA-tetramer reagents for the study of T cells recognizing IDDM autoantigens presented by HLA class II molecules predisposing for or protecting from IDDM
Juvenile Diabetes Research Fund	Project Title: Genetical genomics of the MHC in type I diabetes.
Juvenile Diabetes Research Fund	Project Title: Immune tolerance to pro-insulin and the role of pro-insulin in the development of Type I diabetes in the NOD mouse
Juvenile Diabetes Research Fund	Project Title: Inducing alpha-cell-mediated beta-cell regeneration
Juvenile Diabetes Research Fund	Project Title: INSERM (Institut National de la Sante et de la Recherche Medicale)
Juvenile Diabetes Research Fund	Project Title: INSERM- Stem Cell Research
Juvenile Diabetes Research Fund	Project Title: Islets For Research- Lille University Hospital
Juvenile Diabetes Research Fund	Project Title: Mechanism of protection from Type I diabetes by insulinase deficiency
Juvenile Diabetes Research Fund	Project Title: Modulation of diabetogenic response by beta cells via antimicrobial peptide
Juvenile Diabetes Research Fund	Project Title: Monitoring of autoantigen-specific CD8 T cell responses in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Pancreatic beta-cell Specific Intracellular Delivery of Drugs by Peptide Vectors
Juvenile Diabetes Research Fund	Project Title: Physiopathology and therapeutics of T1D: role of CD4CD25 regulatory T cells
Juvenile Diabetes Research Fund	Project Title: Reprogramming Mouse Pancreatic Cells in vivo
Juvenile Diabetes Research Fund	Project Title: Revisiting tolerance induction to beta cells in a novel preclinical model
Juvenile Diabetes Research Fund	Project Title: Role of dendritic cell subsets in G-CSF-mediated protection against T1D
Juvenile Diabetes Research Fund	Project Title: Role of insulin-degrading enzyme in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Role of nitric oxide synthase 2 (NOS2) in murine type I diabetes
Juvenile Diabetes Research Fund	Project Title: Role of Toll-like Receptor Signaling Pathways in the Pathogenesis of Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: T cell assays for T1D: application to disease staging and immunotherapy
Juvenile Diabetes Research Fund	Project Title: T1D prevention by induction of dermal tolerogenic dendritic cells
Juvenile Diabetes Research Fund	Project Title: Thymus specific serine protease, a new target to control Type I diabetes?
Juvenile Diabetes Research Fund	Project Title: BETA-CELL NEO-EPITOPES GENERATED BY ALTERNATIVE SPLICING: NOVEL T-CELL BIOMARKERS OF AUTOIMMUNE PROGRESSION IN T1D
Juvenile Diabetes Research Fund	Project Title: A Search for Novel Post-Transplant Allo-graft 'autoantigens' Relevant for Islet and Pancreas Graft Survival
Juvenile Diabetes Research Fund	Project Title: Accomplishing Type I diabetes immune regulation in the pancreas

Juvenile Diabetes Research Fund	Project Title: Analysis of the immune regulatory cells in the gut of T1D patients
Juvenile Diabetes Research Fund	Project Title: Anti-CD38 (ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase) autoimmunity: Relevance to human type I diabetes and islet function
Juvenile Diabetes Research Fund	Project Title: Autoreactive memory stem T cells generation and expansion post islet transplantation
Juvenile Diabetes Research Fund	Project Title: Axxam-Fast Forward: Identification of Kv1.3 blockers for the treatment of Type I diabetes and multiple sclerosis
Juvenile Diabetes Research Fund	Project Title: Axxam-Fast Forward-JDRF: Discovery research of innovative immunosuppressant far prevention of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Beta cell specific aptamers as targeting and imaging agents in diabetes
Juvenile Diabetes Research Fund	Project Title: BetaSel2 – Therapeutic efficacy of novel cytokines and growth factors selected in vivo to improve beta cell mass
Juvenile Diabetes Research Fund	Project Title: BETASEL-In vivo selection of novel genes and miRNAs improving betacell mass
Juvenile Diabetes Research Fund	Project Title: Combined immunotherapy for islet transplantation and the role of viruses
Juvenile Diabetes Research Fund	Project Title: Control of Autoimmune Diabetes Via Small-Molecular-Weight Compound
Juvenile Diabetes Research Fund	Project Title: De novo generation of human nephrons for the treatment of experimental DN
Juvenile Diabetes Research Fund	Project Title: Diabetes-related Impairment of Angiogenesis by Intramuscular Adenovirus-mediated Human Tissue Kallikrein Gene Delivery
Juvenile Diabetes Research Fund	Project Title: Dissection of the Genetic Bases of Type I Diabetes in the Isolated Founder Population of Sardinia
Juvenile Diabetes Research Fund	Project Title: ECIT Clinical Trial
Juvenile Diabetes Research Fund	Project Title: ECIT Islets for Research
Juvenile Diabetes Research Fund	Project Title: Endothelial progenitor cells and vascular disease in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Exploiting the therapeutic potential of Treg cell-inducing Clostridia in T1D
Juvenile Diabetes Research Fund	Project Title: HARNESSING THE TRANS-DIFFERENTIATION CAPACITY OF STEM CELLS: TURNING NEURAL STEM CELLS INTO BETA-PANCREATIC CELLS
Juvenile Diabetes Research Fund	Project Title: Human pancreatic islets produce and release MCP-1: implications for islet engraftment
Juvenile Diabetes Research Fund	Project Title: Immune Cells Assay to predict C-peptide Loss
Juvenile Diabetes Research Fund	Project Title: In Vitro Expression Cloning of the Type I Diabetes Autoantigen Glima 38 and other ICAs
Juvenile Diabetes Research Fund	Project Title: In Vivo Imaging of Infiltrating Activated T-Lymphocytes in the Pancreas by 99mTc-Interleukin-2 Scintigraphy
Juvenile Diabetes Research Fund	Project Title: In vivo imaging of insulitis by 18F-interleukin-2
Juvenile Diabetes Research Fund	Project Title: Islets For Research
Juvenile Diabetes	Project Title: Italy JDRF International site: ongoing and proposed studies

Research Fund	
Juvenile Diabetes Research Fund	Project Title: JDRF European Consortium for Human Islet Transplantation
Juvenile Diabetes Research Fund	Project Title: JDRF International Clinical Sites - Italy - Bosi
Juvenile Diabetes Research Fund	Project Title: JDRF International TrialNet Clinical Center in Italy
Juvenile Diabetes Research Fund	Project Title: Langerhans Islet Transplantation as a cellular replacement therapy for diabetes: Evaluation of new in vitro parameters predictive of graft function
Juvenile Diabetes Research Fund	Project Title: Liver-Mediated Ag-specific tolerance to cure T1D
Juvenile Diabetes Research Fund	Project Title: MHC Class I and II regulation by glucose
Juvenile Diabetes Research Fund	Project Title: Modulation of TIMP3/ADAM17 dyad to block Diabetic Nephropathy
Juvenile Diabetes Research Fund	Project Title: Negative vaccination with tolerogenic dendritic cells in the NOD mouse
Juvenile Diabetes Research Fund	Project Title: New HLA-G-related biomarkers of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: NIDDK X (TrialNet Italy/Germany - Bosi)
Juvenile Diabetes Research Fund	Project Title: Novel vascular actions for adiponectin
Juvenile Diabetes Research Fund	Project Title: Postprandial Glucose Counterregulation to Hypoglycemia: Physiology and Recovery of Glucagon Response in Type I Diabetes Mellitus
Juvenile Diabetes Research Fund	Project Title: Post-transcriptional regulation of pancreas-targeting nTreg cells
Juvenile Diabetes Research Fund	Project Title: Posttranslationally modified insulin as target for therapy in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Provide Islet for Research
Juvenile Diabetes Research Fund	Project Title: Re-establishment of secretion competence in insulin-secreting cells
Juvenile Diabetes Research Fund	Project Title: RESTORATION OF APPROPRIATE RESPONSES OF GLUCAGON TO HYPOGLYCEMIA IN T1DM
Juvenile Diabetes Research Fund	Project Title: Role of mast cells at different checkpoints in T1D progression.
Juvenile Diabetes Research Fund	Project Title: Role of Regulated Membrane Proteolysis in diabetes vascular complications
Juvenile Diabetes Research Fund	Project Title: Role of T1DM-associated CTLA-4 Polymorphisms on Protein Trafficking and Compartimentalization
Juvenile Diabetes Research Fund	Project Title: Synthetic tryptophan catabolites as immune regulators in NOD mice
Juvenile Diabetes Research Fund	Project Title: Telethon Italy
Juvenile Diabetes Research Fund	Project Title: The IL-7/IL7R axis in T cell memory in type I diabetes
Juvenile Diabetes Research Fund	Project Title: The Role of Tunnelling Nanotubes in Diabetic Nephropathy

Juvenile Diabetes Research Fund	Project Title: Therapeutic angiogenesis with NGF for the treatment of diabetic ulcers and peripheral ischemia
Juvenile Diabetes Research Fund	Project Title: A beta cell reporter system in the NOD model of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: BABYDIAB: prospective long-term follow-up from birth in at risk children
Juvenile Diabetes Research Fund	Project Title: Collaborative Research on BABYDIAB/BABYDIET Bio-bank and Database
Juvenile Diabetes Research Fund	Project Title: Collaborative Research on Munich cohort studies - Bio-bank and Database
Juvenile Diabetes Research Fund	Project Title: Consortium's aims are to support the study of diabetes throughout Europe, improve communication among diabetes research groups, and to be active in public advocacy and political lobbying in Europe.
Juvenile Diabetes Research Fund	Project Title: Development of novel therapeutic agents enhancing human beta cell survival
Juvenile Diabetes Research Fund	Project Title: Discovery and Development of Beta Cell Regeneration Drugs for Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: Dysregulation of TGF-beta Receptor Expression in Diabetic Nephropathy
Juvenile Diabetes Research Fund	Project Title: EFSD Novo Nordisk III
Juvenile Diabetes Research Fund	Project Title: EFSD Novo Nordisk IV
Juvenile Diabetes Research Fund	Project Title: EFSD/Novo-Nordisk/JDRF Partnership
Juvenile Diabetes Research Fund	Project Title: EFSD-Novo Nordisk II
Juvenile Diabetes Research Fund	Project Title: Five and 8 year follow-up evaluation of islet autoimmunity in offspring of parents with type I diabetes in the prospective German BABYDIAB study
Juvenile Diabetes Research Fund	Project Title: Generation of functional ß-cells from alternative pancreatic cell subtypes
Juvenile Diabetes Research Fund	Project Title: Generation of functional ß-cells from alternative pancreatic cell subtypes
Juvenile Diabetes Research Fund	Project Title: High resolution single cell definition of autoreactive CD4+ T cells
Juvenile Diabetes Research Fund	Project Title: Identification of proteomic patterns predictive for T1D progression rate
Juvenile Diabetes Research Fund	Project Title: Immune modulation and tolerance induction to human islets
Juvenile Diabetes Research Fund	Project Title: JDRF International Clinical Sites - Germany - Ziegler
Juvenile Diabetes Research Fund	Project Title: Ligands of Siglec-7 for the Treatment of Type I Diabetes: LiSTeD
Juvenile Diabetes Research Fund	Project Title: Mechanism of CD8 tolerance induction by Idd9.
Juvenile Diabetes Research Fund	Project Title: Mechanisms of Type I diabetes protection through maternal diabetes
Juvenile Diabetes Research Fund	Project Title: Memory CD4+ T cell expansion profiles and mechanisms post islet transplant

Juvenile Diabetes Research Fund	Project Title: Model Project Diabetes 2015: Early diagnosis and care of Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Molecular machinery for the biogenesis of insulin secretory granules
Juvenile Diabetes Research Fund	Project Title: MST1 as a target for beta-cell survival
Juvenile Diabetes Research Fund	Project Title: New mechanisms to protect the beta-cell from chemokine-induced cell death
Juvenile Diabetes Research Fund	Project Title: NIDDK X (TrialNet Italy/Germany - Ziegler)
Juvenile Diabetes Research Fund	Project Title: Peripheral Blood T Cell Transplantation (PBTCT) to Preserve Beta Cell Mass in Human Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: pre-POINT
Juvenile Diabetes Research Fund	Project Title: Prevention of Type I diabetes by Treg vaccination with an insulin mimetope
Juvenile Diabetes Research Fund	Project Title: Prospective determination and stratification of childhood Type I diabetes risk in offspring of affected parents: the German BABYDIAB study.
Juvenile Diabetes Research Fund	Project Title: Regulatory Mechanisms in the Re-vascularization of Transplanted Islets
Juvenile Diabetes Research Fund	Project Title: Role of ICA512 ectodomain in beta-cell signalling and proliferation
Juvenile Diabetes Research Fund	Project Title: Staging and monitoring pathogenesis and intervention in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Strategies to rescue the ß-cell from enterovirus-induced damage
Juvenile Diabetes Research Fund	Project Title: T cell features associated with preclinical disease remission or latency
Juvenile Diabetes Research Fund	Project Title: Targets of patient pancreatic lymph node IgG+ B lymphocyte
Juvenile Diabetes Research Fund	Project Title: The role of Th17 lineage T lymphocytes in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: The role of the susceptibility gene KIAA0350 in Type I diabetes
Juvenile Diabetes Research Fund	Project Title: Type I diabetes intervention studies in Germany
Juvenile Diabetes Research Fund	Project Title: Type I diabetes intervention studies in Germany
Juvenile Diabetes Research Fund	Project Title: VEGF-A driven beta cell expansion
Juvenile Diabetes Research Fund	Project Title: A Novel hnfl Alpha-Dependent Transcriptional Network Required to Maintain Terminal Differentiation of Pancreatic Beta-Cells
Juvenile Diabetes Research Fund	Project Title: Ex vivo generation of autologous insulin-specific CD4 TR1 regulatory cells
Juvenile Diabetes Research Fund	Project Title: Gene expression profile of human pancreas at the onset of T1D
Juvenile Diabetes Research Fund	Project Title: Induction of Central and Peripheral Tolerance in NOD and 8.3-NOD Mice by Antigen Presenting Cells Constitutively Expressing NRP and NRP-A7 Agonistic Mimetopes
Juvenile Diabetes	Project Title: Insulin-Octamers For The Detection Of Low Affinity Autoreactive B cells

Research Fund	
Juvenile Diabetes Research Fund	Project Title: LRH-1, a Novel Therapeutic Immunomodulator Implicated in beta Cell Health
Juvenile Diabetes Research Fund	Project Title: Nanomedicines to expand Type I diabetes-specific T-regulatory-1 type cells: mechanistic and translational studies
Juvenile Diabetes Research Fund	Project Title: Obtaining pancreatic beta cells from human embryonic stem cells.
Juvenile Diabetes Research Fund	Project Title: Prevention of Initial Beta-cell Death and Preservation of Beta-cell Mass in Islet Cell Transplantation
Juvenile Diabetes Research Fund	Project Title: Role of nervous system reactive-B-lymphocytes in the course of T1D
Juvenile Diabetes Research Fund	Project Title: Tracing Effector and Regulatory T Cell Populations in Type I Diabetes
Juvenile Diabetes Research Fund	Project Title: Biomarkers of heterogeneity: an integrated approach to clinical and metabolic phenotyping of individuals with established Type I diabetes.
Juvenile Diabetes Research Fund	Project Title: Autoimmunity to posttranslationally and posttranscriptionally modified islet autoantigens promoted by inflammatory assault
Juvenile Diabetes Research Fund	Project Title: Characterization of In-111-DTPA-Exendin
Juvenile Diabetes Research Fund	Project Title: Detection of islet autoreactive CD8 T-cells in insulitis versus periphery
Juvenile Diabetes Research Fund	Project Title: Dutch Partnership- JDRF/NWO/DFN (Netherlands Organization for Scientific Research and the Dutch Diabetes Research Foundation)
Juvenile Diabetes Research Fund	Project Title: Enterovirus, DC, and pancreatic islets; a dangerous triangle in T1D?
Juvenile Diabetes Research Fund	Project Title: Evaluating immune correlates of beta-cell function and stress
Juvenile Diabetes Research Fund	Project Title: HLA-DQ in Type I diabetes: defining and translating the immune mechanisms that underlie the highest genetic risk of disease
Juvenile Diabetes Research Fund	Project Title: Local pancreas precursors for dendritic cells and macrophages
Juvenile Diabetes Research Fund	Project Title: New islet encapsulation method for ideal masstransport and immunoprotection
Juvenile Diabetes Research Fund	Project Title: Pancreatic cell plasticity for the (re)generation of beta-cells in Diabetes
Juvenile Diabetes Research Fund	Project Title: Profiling islet-reactive CD8 T-cells for immune memory and activation
Juvenile Diabetes Research Fund	Project Title: Towards noninvasive imaging of residual beta cell mass
Juvenile Diabetes Research Fund	Project Title: Validation of In-111-exendin for the determination of the beta cell mass in humans
Juvenile Diabetes Research Fund	Project Title: Biomarkers of heterogeneity: an integrated approach to clinical and metabolic phenotyping of individuals with established Type I diabetes.
The Diabetes Research & Wellness Foundation	A role for C-peptide in alleviating diabetic nephropathy
The Diabetes Research & Wellness Foundation	Adapting the HOMA model to estimate insulin sensitivity and beta cell function in people with Type II diabetes mellitus treated with insulin
The Diabetes Research & Wellness Foundation	An investigation into the mechanisms of pathological bone resorption in acute Charcot osteoarthropathy

The Diabetes Research & Wellness Foundation	Analysis of tethering factors in the regulation of Glut4 spatial dynamics
The Diabetes Research & Wellness Foundation	Analysis of the role of Munc18c tyrosine phosphorylation in insulin-stimulated glucose transport
The Diabetes Research & Wellness Foundation	Application made for a B/G/R: L filter system in order to adapt this instrument for three colour operation
The Diabetes Research & Wellness Foundation	Are human SPARC isoforms suitable peripheral makers of insulin resistance and diabetes-related complications?
The Diabetes Research & Wellness Foundation	Bariatric surgery for diabetes: Does the GLP1 or GIP response predict who will respond?
The Diabetes Research & Wellness Foundation	Bile acid metabolism and recycling in improving Type II diabetes resolution after bariatric surgery
The Diabetes Research & Wellness Foundation	Can VEGFC rescue albuminuria in a experimental model of diabetic nephropathy?
The Diabetes Research & Wellness Foundation	Cerebral Insulin Resistance - a cause of dementia in diabetes?
The Diabetes Research & Wellness Foundation	DECS, Diabetic Eye disease in Children Study: incidence, detection/presentation, clinical characteristics and putcomes of diabetic eye disease in childhood in the UK
The Diabetes Research & Wellness Foundation	Defining the role of the indirect pathway in islet allograft and xenograft rejection
The Diabetes Research & Wellness Foundation	Development and biological characterisation of novel PEGylated GIP-receptor antagonists for the treatment of obesity-related Type II diabetes.
The Diabetes Research & Wellness Foundation	Development of a device to prevent or reverse diabetic retinopathy
The Diabetes Research & Wellness Foundation	Development of a robust clinically-relevant approach to antibody-medicated diabetes and hypoglycaemia
The Diabetes Research & Wellness Foundation	Development of High Field Magnetic Resonance Techniques for the non-invasive investigation of diabetic kidney disease
The Diabetes Research & Wellness Foundation	Development of regulatory B cell assay in Type I diabetes
The Diabetes Research & Wellness Foundation	Diabetic nephropathy
The Diabetes Research & Wellness Foundation	Diabetic retinopathy
The Diabetes Research & Wellness Foundation	Does Adiponectin influence the loss of T-Cell tolerance and the development of Type I diabetes?
The Diabetes Research & Wellness Foundation	Does low vitamin D cause adipose tissue inflammation and insulin resistance?
The Diabetes Research & Wellness Foundation	Does reorganisation of the Extracellular Matrix promote glucose induced fibrosis in Diabetic Nephropathy?
The Diabetes Research & Wellness Foundation	Endothelin receptor antagonism as a therapeutic target in diabetic nephropathy
The Diabetes Research & Wellness Foundation	Enhancement of beta-cell mass and function in human islets by physiological factors up-regulated in pregnancy.
The Diabetes Research & Wellness Foundation	Enteroviral infection as a causative factor in human Type I diabetes
The Diabetes Research & Wellness Foundation	Evaluating the role of the pancreatic beta-cell in the development of Cystic Fibrosis related diabetes
The Diabetes Research	Evaluation of a novel glucagon-incretin hybrid peptide for diabetes and obesity therapy

& Wellness Foundation	
The Diabetes Research & Wellness Foundation	Extending whole organ pancreas transplant function in Type I diabetics
The Diabetes Research & Wellness Foundation	Extra-cellular exosomal microRNA – a potential new class of urinary biomarker for diabetic kidney disease
The Diabetes Research & Wellness Foundation	Finding the genes in human adipose tissue that cause insulin resistance
The Diabetes Research & Wellness Foundation	Glucokinase in Specialised Glucose-Sensing Neurones in Brain Plays a Key Role in Controlling Blood Glucose
The Diabetes Research & Wellness Foundation	Glucose control in offspring of women with Type I diabetes (ODM)
The Diabetes Research & Wellness Foundation	Human Islet Isolation Facility
The Diabetes Research & Wellness Foundation	Humanin (and related bioactive peptides) - a novel treatment for diabetic nephropathy
The Diabetes Research & Wellness Foundation	Hypoglycaemia and cardiac arrhythmia in Type I diabetes - a study using ambulatory blood glucose and ECG monitoring
The Diabetes Research & Wellness Foundation	Identification of Caveolar Proteins Regulating Insulin-Stimulated Glut4 Translocation in Adipocytes
The Diabetes Research & Wellness Foundation	Identification of novel non-MHC susceptibility loci for Type I diabetes
The Diabetes Research & Wellness Foundation	Identifying Genetic Predictors of Graft Function to Enable Pancreas Transplantation to Become a Lifelong Cure for Type I Diabetes
The Diabetes Research & Wellness Foundation	Improvement in the prospects for successful islet transplantation by reduction of cell death during human islet isolation
The Diabetes Research & Wellness Foundation	Influence of n-3FA intake on high-fat diet induced changes in anabolic signalling in healthy adults
The Diabetes Research & Wellness Foundation	Insulin resistance
The Diabetes Research & Wellness Foundation	Insulin resistance and cardiovascular disease
The Diabetes Research & Wellness Foundation	Insulin secretion
The Diabetes Research & Wellness Foundation	Investigating inflammatory changes in human diabetic bladder dysfunction
The Diabetes Research & Wellness Foundation	Investigation of anti-insulin receptor antibodies as a potential therapy for human insulin receptoropathy.
The Diabetes Research & Wellness Foundation	Investigation of glucose sensing in the brain.
The Diabetes Research & Wellness Foundation	Investigation of the association between glucokinase and the pro-apoptotic protein BAD in pancreatic beta-cells
The Diabetes Research & Wellness Foundation	Investigation of the incretin pathway in Maturity onset diabetes of the young (MODY) secondary to heterozygous hepatocyte nuclear factor 1 alpha (HNF1A) gene mutations
The Diabetes Research & Wellness Foundation	Investigation of the role of newly identified Type II diabetes susceptibility genes in the pathogenesis of Type II diabetes
The Diabetes Research & Wellness Foundation	Is Charcot osteoarthropathy a Cytokine-Driven Disease?
The Diabetes Research & Wellness Foundation	Is high intensity interval training an efficient and effective form of exercise for people with Type I diabetes?

The Diabetes Research & Wellness Foundation	Is the abnormal postprandial suppression of hepatic glucose production in Type II diabetes reversible by decreasing intrahepatic triglyceride stores?
The Diabetes Research & Wellness Foundation	Lifestyle intervention for reducing beta cell autoimmunity in Type I diabetes: a preliminary ex-vivo study Funding Type: Open Funding 2010
The Diabetes Research & Wellness Foundation	Manipulating the phenotype of endothelial progenitor cells from insulin resistant South Asian men: A pilot study towards cell based therapies
The Diabetes Research & Wellness Foundation	Mapping novel Type I diabetes genes in the major histocompatibility complex
The Diabetes Research & Wellness Foundation	Measuring the effects of kisspeptin on insulin secretion, and on the growth and survival of β-cells
The Diabetes Research & Wellness Foundation	Mechanism of action of Grb10, a negative regulator of insulin signalling & a potential drug target for treating Type II diabetes
The Diabetes Research & Wellness Foundation	Mechanisms of Schwann cell dysfunction under hyperglycaemia and in a mouse model of diabetic neuropathy.
The Diabetes Research & Wellness Foundation	Metabolic and molecular mechanisms for alleviation of diet-induced insulin resistance by dietary fish oils
The Diabetes Research & Wellness Foundation	Metformin improves Endothelial function, endothelial progenitor cells (EPCs) and cardiovascular Risk factors in Type I diabetes; MERIT study
The Diabetes Research & Wellness Foundation	Molecular mechanisms contributing to the pathogenesis of insulin resistance in skeletal muscle
The Diabetes Research & Wellness Foundation	Molecular mechanisms involved in the cytoprotective actions of mono-unsaturated fatty acids in pancreatic beta-cells
The Diabetes Research & Wellness Foundation	Nephrin phosphorylation & podocyte structure in diabetic rats - low birth weight study
The Diabetes Research & Wellness Foundation	Nogo-B in diabetic glomerulopathy: novel target for treatment?
The Diabetes Research & Wellness Foundation	Non-invasive live imaging of immune infiltration into islets of Langerhans
The Diabetes Research & Wellness Foundation	Novel signalling pathways regulating insulin secretion
The Diabetes Research & Wellness Foundation	Peripheral neuropathy and muscle weakness: how do they influence the safety of daily gait tasks for people with diabetes?
The Diabetes Research & Wellness Foundation	Plasma kisspeptin in pregnancy and gestational diabetes: a translational pilot study
The Diabetes Research & Wellness Foundation	Reducing fear of hypoglycaemia in families and Improving metabolic control in Children and young people with diabetes (RICHes): A feasibility pilot study
The Diabetes Research & Wellness Foundation	Refurbishment for EU Regulations compliance
The Diabetes Research & Wellness Foundation	Role of adipose tissue in age-dependent beneficial effects of PI 3-kinase pathway inactivation on glucose and lipid homeostasis
The Diabetes Research & Wellness Foundation	Skeletal muscle protein metabolism and insulin sensitivity in overweight individuals: Effects of meals with various fatty acid compositions
The Diabetes Research & Wellness Foundation	Substrate selection and metabolomics in the diabetic mouse heart: validating metabolic markers of disease progression
The Diabetes Research & Wellness Foundation	The expression and functionality of antimicrobial peptides in the gingival crevice in Type I diabetes
The Diabetes Research & Wellness Foundation	The Generation of functional islets of Langerhans from stem cells in vitro
The Diabetes Research	The identification of maturity onset diabetes of the young (MODY) and characterization of

& Wellness Foundation	diabetes subtype in a young multi-ethnic population to inform appropriate treatment
The Diabetes Research & Wellness Foundation	The influence of glucose tolerance status on the predisposition to ex vivo thrombus formation of flowing blood and the effect of improving glycaemic control
The Diabetes Research & Wellness Foundation	The prevalence and risk factors for non-alcoholic fatty liver disease in patients with Type II diabetes mellitus
The Diabetes Research & Wellness Foundation	The regulation of metalloproteinases and tissue inhibitors of metalloproteinases in adipose inflammation and Type II diabetes
The Diabetes Research & Wellness Foundation	The role of kisspeptin and its receptor GPR54 in pancreatic islet function
The Diabetes Research & Wellness Foundation	The role of long non-coding RNAs in regulating β-cell function and development
The Diabetes Research & Wellness Foundation	The role of Synaptotagmins in Insulin-stimulated Glucose Transport in the Adipocyte
The Diabetes Research & Wellness Foundation	The role of the transcriptional repressor CITED2 in endothelial cells as a mediator of impaired angiogenesis in insulin resistant conditions
The Diabetes Research & Wellness Foundation	To use Mendelian randomisation to understanding the causal relationship between circulating biomarkers and Type II Diabetes in the UK Bio-bank.
The Diabetes Research & Wellness Foundation	TUB expression and function in adipose tissue: implications for obesity and insulin resistance.
The Diabetes Research & Wellness Foundation	Young people with Type I diabetes (16 – 25 years old) with good and poor glycaemic control: adopting a resilience approach to enhance understanding of differences in this transitional group with generally poor clinical performance.
The Diabetes Research & Wellness Foundation	Zinc-alpha2-glycoprotein (ZAG): A 'friend or foe' in obesity-induced insulin resistance and non-alcoholic fatty liver disease (NAFLD)

Annex 2:

Table EU FP 6-7 projects on Diabetes 2006-2013 (139)

FP	Record number	Title	Last updated
FP7	105033	Unraveling the mechanism underlying the anti-diabetic action of leptin	29/06/2015 11:17
FP7	188118	Preclinical efficacy testing of hydrogen sulfide donors against diabetic complications	12/03/2015 06:57
FP7	185642	Dynamic signalling networks in Diabetic Nephropathy (DN) – New avenues to a personalized therapy.-	11/03/2015 22:00
FP7	105364	Repair of Diabetic Damage by Stromal Cell Administration	11/03/2015 02:34
FP7	104427	Joint European and Latin American Research Network on Diabetic Microangiopathy	10/03/2015 23:13
FP7	101250	Device for prophylaxis and treatment of diabetic foot ulcers for hospital and home use	10/03/2015 21:02
FP7	101158	Development of a new generation of DIABetic footwear using an integrated approach and SMART materials	10/03/2015 20:44
FP7	101813	Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In Type II diabetic patients with normoalbuminuria	10/03/2015 18:46
FP7	102516	European Consortium for the Early Treatment of Diabetic Retinopathy	10/03/2015 18:21
FP7	99729	Long-Term e-Health Evolution for Improving Diabetic Social and Behavioural Change Management	10/03/2015 17:30
FP7	99618	Regulation of obesity and fatty acid-induced inflammation by AMP-activated protein kinase in obese/Type II diabetic and inactive human skeletal muscle	10/03/2015 17:07
FP7	96061	The Diabetic Brain	10/03/2015 10:18
FP7	95162	Evaluation of Beneficial Role of Protein Phosphatases and KLF2 in Diabetic Endothelial and Progenitor Cell Repair	10/03/2015 09:57
FP7	90146	Natural antidiabetic & anti-hypertensive drugs	10/03/2015 00:24
FP7	192739	"Role of Nrf2 transcription factor in diabetic vasculopathy, oxidative stress and inflammation."	09/03/2015 22:38
FP7	88746	Molecular Mechanisms in Diabetic Embryopathy	09/03/2015 22:32
FP7	88559	Sensory and Biomechanical Markers in Diabetic Neuropathy of the Gut. Basic Investigations and New Approaches for Treatment	09/03/2015 22:28
FP6	72281	New healing footwear reducing problems with foot wounds among diabetic patients	17/10/2012 00:00
FP6	84713	Predictive diagnostics for diabetic nephropathy (DiaNa) - novel nanotechnology based test platforms	29/10/2010 00:00
FP6	79441	Development of an Implantable bio-sensor for continuous care and monitoring or diabetic patients	05/07/2010 10:11
FP6	78434	The Identification of Risk Factors for the Development of Diabetic Nephropathy: The PREDICTIONS Project	03/12/2009 00:00
FP6	83949	Joint development of novel anti-diabetic drugs from natural sources by strategic combination of pharmacology and chemistry	03/04/2009 00:00
FP6	86540	Development of a cost-effective adjustable damping sole based on magneto-rheological fluids to provide diabetics with a customizable	13/11/2008 00:00

		product-service which reduces foot stress and diseases	
FP6	82555	Role of the MCP-1/CCR2 system in the podocyte alterations of Diabetic Nephropathy: an in vivo and in vitro study	07/11/2007 00:00
FP6	82678	Development of parallel analytical strategies for the generation and interpretation of metabolic data of diabetic rats	02/07/2007 00:00
FP7	108786	Unravelling the unconventional processing and presentation of preproinsulin to the immune system in human Type I Diabetes: the role of intramembrane-cleaving proteases	11/03/2015 13:39
FP7	105859	Single-Port Insulin Infusion for Improved Diabetes Management	11/03/2015 02:27
FP7	103185	Bile acids targeting Retinoic Related Orphan Receptor gamma for the Treatment of Obesity associated Insulin Resistance and Type II Diabetes	11/03/2015 02:13
FP7	96798	Role of the Cullin7 E3 ubiquitin ligase in insulin signaling and diabetes	10/03/2015 10:51
FP7	94023	Role of pancreatic beta-cell regeneration in the pathofisiology and treatment of insulin resistance and Type II diabetes	10/03/2015 06:13
FP7	90727	Circadian regulation in the control of insulin and glucagon release and its role in Type II diabetes	10/03/2015 02:06
FP6	81753	Control of insulin sensitivity through transcriptional co-factors: implications for type II diabetes therapy	02/04/2009 00:00
FP6	83763	Molecular dissection of insulin signaling in Type II diabetes mellitus	01/04/2009 00:00
FP6	83071	The role of adipose tissue in insulin resistance and inflammation - the way to obesity and Type II diabetes	28/03/2008 00:00
FP6	82734	The role of insulin in the development of nociceptive dysfunctions in impaired glucose tolerance, the condition preceding Type II diabetes	02/07/2007 00:00
FP7	186141	Extracellular Matrix Remodeling and Muscle Insulin Resistance: Role of Hyaluronan-CD44 Interaction	12/03/2015 03:42
FP7	109474	Upscaling human insulin-producing beta cell production by efficient differentiation and expansion of endoderm progenitors	11/03/2015 18:02
FP7	106055	"The Physiological Control of Stem Cells: Obesity, Insulin, and Neural Stem Cell Dynamics."	11/03/2015 01:41
FP7	102571	Micro- and Macrocirculation Coupling: a cross sectional investigation of the cross-talk between the two circuits in insulin resistance states	11/03/2015 00:10
FP7	99744	Molecular mechanisms underlying the development of insulin resistance: role of betaine supplementation	10/03/2015 22:26
FP7	102113	Induction of Insulin-producing beta-cells Regeneration in vivo	10/03/2015 19:15
FP7	101810	Genetic and environmental factors of insulin resistance syndrome and its long-term complications in immigrant Mediterranean populations	10/03/2015 18:45
FP7	99730	FGF1: a novel metabolic regulator involved in insulin sensitization and glycemic control	10/03/2015 18:12
FP7	94470	Insulin/IGF-1 Signaling Regulates Novel Activities of the ER Stress Response Gene ire-1	10/03/2015 10:48
FP7	94603	Hepatocyte Growth Factor and Insulin Resistance	10/03/2015 10:33
FP7	95769	The highly calcium-sensitive pool of granules in biphasic insulin secretion: Experimental and theoretical investigations	10/03/2015 09:19
FP7	92381	Insulin resistance and diabetic nephropathy - development of novel in vivo models for drug discovery	10/03/2015 04:43
FP7	90771	The role of p16INK4a in the development of obesity and insulin resistance	10/03/2015 02:14
FP7	90222	"Metabolic control by the TGF-² superfamily receptor ALK7: A novel regulator of insulin secretion, fat accumulation and energy balance"	10/03/2015 01:00

FP7	88741	Role of the chylomicron and HDL pathways in the development of obesity and insulin resistance	09/03/2015 20:37
FP6	71227	Closed Loop INsulin Infusion for Critically Ill Patients	07/10/2014 17:03
FP7	185455	Personalized diagnosis and treatment of hyperinsulinemic hypoglycaemia caused by beta-cell pathology	08/08/2014 18:04
FP6	74044	Health benefits of exercise: identification of genes and signalling pathways involved in effects of exercise on insulin resistance, obesity and the metabolic syndrome	20/10/2010 00:00
FP6	73157	Insulin receptor-mediated modulation of nociceptor function. Characterisation of primary sensory neurones co-expressing VR1 and insulin receptors	02/07/2007 00:00
FP6	82149	Understanding the interplay of insulin/IGF signalling with endocrine hormones in ageing	02/07/2007 00:00
FP6	73235	Regulation of protein kinase B-mediated insulin signalling by atypical PKCs: implications for insulin resistance	02/07/2007 00:00
FP7	100589	DIAbetes Trans-national Research Advancement for INvestigators	08/07/2015 16:23
FP7	106271	A bioartificial pancreas to treat Type I diabetes: optimization of cell survival and function in preclinical and clinical phases	07/07/2015 17:45
FP7	101998	Early Prevention of Diabetes Complications in people with Hyperglycaemia in Europe	07/07/2015 17:35
FP7	105313	A Portable bihormonal Closed Loop for Diabetes	29/06/2015 10:45
FP7	101811	Mechanisms of prevention of Type II diabetes by lifestyle intervention in subjects with pre-diabetes or at high-risk for progression	01/06/2015 12:38
FP7	105252	Beta cell preservation via antigen-specific immunotherapy in Type I Diabetes: Enhanced Epidermal Antigen Delivery Systems	01/06/2015 12:00
FP7	105723	Application of the innovative data fusion based non-invasive approach for management of the diabetes mellitus	19/05/2015 19:05
FP7	102211	A RANDOMIZED CLINICAL TRIAL TO EVALUATE THE EFFECTIVENESS OF A MULTI-MODAL INTERVENTION IN OLDER PEOPLE WITH TYPE II DIABETES ON FRAILTY AND QUALITY OF LIFE: THE MID-FRAIL STUDY	12/03/2015 11:59
FP7	91220	Life Style and Genetic Factors in Prevention of Type II Diabetes (re-integration period)	12/03/2015 10:38
FP7	187900	The incretin system: From genetic determinants to impact on early development of Type II diabetes in the population	12/03/2015 03:36
FP7	187693	Beta-cell Receptors in Diabetes Therapy	12/03/2015 01:01
FP7	110112	Can metabolic states induced by diabetes and obesity promote cancer?	11/03/2015 22:12
FP7	188654	Metabolic actions of brain leptin receptors signaling in Type I diabetes	11/03/2015 21:36
FP7	110445	"Proposal to assess an innovative Immunotherapy, based on a thioredox peptide antigen, in a Phase I Trial for Type-1 Diabetes"	11/03/2015 17:56
FP7	109333	Global initiative on gene-environment interaction on diabetes/obesity risk	11/03/2015 17:47
FP7	108766	Macroencapsulated Porcine Pancreatic Islets to cure Diabetes Mellitus Type I/2	11/03/2015 17:45
FP7	110407	"Gut microbiota, innate immunity and endocannabinoid system interactions link metabolic inflammation with the hallmarks of obesity and Type II diabetes"	11/03/2015 16:16
FP7	109984	ß-cell Dysfunction in Diabetes: Elucidating the Role of Islet-Associated Mesenchymal Cells	11/03/2015 16:14
FP7	108506	Defining the molecular basis of Type II diabetes predisposition through	11/03/2015 14:11

		targeted sequencing of the CREBBP-interacting gene network	
FP7	107261	Personalised insoles via additive manufacture for the prevention of plantar ulceration in diabetes	11/03/2015 14:11
FP7	105270	Identification and validation of cerebral KCa3.1/KCa2.3 potassium channels a drug tragets for the prevention and treatment of cerebral ischemia associated with diabetes and Alzheimers disease	11/03/2015 11:38
FP7	106041	"Investigating the therapeutic potential of manipulating the IGF-IGFBP1 axis in the prevention and treatment of cardiovascular disease, diabetes and obesity."	11/03/2015 03:55
FP7	105861	Enhancing the (cost-)effectiveness of diabetes self-management education: A comparative assessment of different educational approaches and conditions for successful implementation	11/03/2015 02:45
FP7	105311	Ultra-low dose of IL-2 for the treatment of recently diagnosed Type I diabetes	11/03/2015 02:28
FP7	105829	"Concurrent Tuberculosis and Diabetes Mellitus; unraveling the causal link, and improving care"	11/03/2015 02:25
FP7	102299	Functional profiling and therapeutic tolerization of macrophages in Type I diabetes	11/03/2015 01:48
FP7	105305	"Obesity, Type II diabetes and the increased risk of cancer and cancer-related Mortality; the study of Molecular Mechanisms and potential therapeutic modalities."	11/03/2015 00:42
FP7	105825	Genetics and epigenetics of Type II Diabetes physiology	10/03/2015 23:01
FP7	100072	The effect of a sedentary lifestyle on Type II diabetes and its complications	10/03/2015 22:30
FP7	101407	European Training Network for Excellence in Molecular Imaging in Diabetes	10/03/2015 21:44
FP7	100244	Type I Diabetes Self-Management and Carbohydrate Counting: A Computer Vision based Approach	10/03/2015 20:54
FP7	101741	Biomarker Applications for Nanotechnology and Imaging in Diabetes	10/03/2015 20:53
FP7	101808	"Self-care Support for People with Long Term Conditions, Diabetes and Heart Disease: A Whole System Approach"	10/03/2015 18:43
FP7	102036	Genomic and lifestyle predictors of foetal outcome relevant to diabetes and obesity and their relevance to prevention strategies in South Asian peoples	10/03/2015 18:41
FP7	99305	Quality of chronic kidney disease management in people with diabetes in England after the introduction of new primary care policies for diabetes and renal disease	10/03/2015 18:06
FP7	98638	Effect of PTPN22 on Treg to Teff equilibrium in human and murine autoimmune diabetes	10/03/2015 17:50
FP7	98303	Helminth-induced regulatory mechanisms that prevent the onset of diabetes	10/03/2015 17:50
FP7	100057	The association between Type II diabetes diagnosis and diabetes medications with risk of cancer	10/03/2015 17:39
FP7	98878	General and targeted approaches to unravel the molecular causes of Type II diabetes	10/03/2015 15:31
FP7	98261	Using gene to phenotype studies to identify Type I diabetes genes and their functions	10/03/2015 15:17
FP7	96148	Wnt agonist Dickkopf 3 (DKK3) is a Type II diabetes susceptibility gene	10/03/2015 15:15
FP7	96145	The role of microRNAs in pancreatic islet dysfunction in Type II diabetes	10/03/2015 15:13

		mellitus	
FP7	97034	Siglecs as mediators of the pancreatic cellular crosstalk in diabetes	10/03/2015 11:43
FP7	96399	Immunomodulatory Effects of Exercise in Type I Diabetes	10/03/2015 06:00
FP7	93426	Beta Cell Therapy in Diabetes	10/03/2015 04:26
FP7	92853	Novel immunotherapies for Type I diabetes	10/03/2015 04:17
FP7	192779	MHC Class I Expression Level in Type I Diabetes	10/03/2015 03:15
FP7	91161	"A genome wide association study of the relationship between BMI, type II diabetes and recurrent depression"	10/03/2015 02:59
FP7	90652	"Trends in hospital admissions for lower extremity amputations in people with and without diabetes in England, 1996-2005"	10/03/2015 02:45
FP7	89155	Discovery of Type II Diabetes Targets	10/03/2015 01:07
FP7	88747	Adenosine receptors in diabetes	09/03/2015 22:33
FP7	107632	Development of a non-invasive hypoglycaemia sensor for diabetes patients	09/03/2015 22:02
FP7	88723	STUDY THE ROLE OF OXYGEN SENSORS PROLYL HYDROXYLASE DOMAIN (PHD) PROTEIN IN OBESITY AND TYPE II DIABETES	09/03/2015 21:46
FP7	88712	Genetical genomics of Type II diabetes and cardiovascular phenotypes in experimental systems	09/03/2015 21:35
FP7	88009	Life Style and Genetic Factors in Prevention of Type II Diabetes	09/03/2015 21:07
FP7	89608	IDENTIFICATION OF THE GENES REGULATED BY THE SIRT1 HISTONE DEACETYLASE AND THEIR CONTRIBUTION IN THE PATHOGENESIS OF TYPE II DIABETES AND OBESITY	09/03/2015 18:32
FP7	87463	Adipocyte Differentiation and Metabolic Functions in Obesity and Type II Diabetes	09/03/2015 18:21
FP7	89559	Role of the alpha4 integrin (CD49d) in Type-1 Diabetes mellitus prevention and treatment	09/03/2015 17:36
FP7	88149	Road Map for Diabetes Research in Europe	09/03/2015 17:33
FP7	85459	Personal Glucose Predictive Diabetes Advisor	07/10/2014 17:20
FP7	100711	Continuous Multi-parametric and Multi-layered analysis Of Diabetes Type I & 2	09/09/2014 15:39
FP7	108157	Remote Accessibility to Diabetes Management and Therapy in Operational healthcare Networks	09/09/2014 14:42
FP7	108366	Multiscale Immune System Simulator for the ONset of Type II Diabetes integrating genetic, metabolic and nutritional data	09/09/2014 14:28
FP7	106729	MOSAIC - MOdels and Simulation techniques for discovering diAbetes Influence faCtors	03/09/2014 13:27
FP6	79287	Genetic susceptibility for Type II diabetes and obesity among immigrants in Europe - prevention and treatment	26/03/2013 00:00
FP6	84940	An examination of the interaction of genetic and lifestyle factors on the incidence of Type II diabetes	21/11/2012 00:00
FP6	78694	Novel molecular drug targets for obesity and Type II diabetes	08/03/2012 00:00
FP6	80808	The role Of T Cell activation in Type I diabetes; T cell differentiation versus T cell tolerance	23/12/2010 00:00
FP6	74073	European network on functional genomics of Type II diabetes	25/10/2010 00:00
FP6	82239	Anti-CD3 systemic therapy in combination with antigen-specific intervention: A novel approach for treating Type I diabetes	18/10/2010 00:00
FP6	84717	Functional genomics of pancreatic beta cells and of tissues involved in control of the endocrine pancreas for prevention and treatment of Type II	31/08/2010 09:28

		diabetes	
FP6	84297	Molecular basis of atherosclerosis induced by hypercholesterolemia and Type II diabetes	17/12/2009 00:00
FP6	84929	Molecular pathways underlying decreased beta cell mass in diabetes mellitus	14/12/2009 00:00
FP6	75288	Coordination Action on the Aetiology, pathology and prediction of Type I diabetes in Europe	14/12/2009 00:00
FP6	81737	Development of a novel DNA vaccine and identification of an autoantigen relevant to type I diabetes	03/12/2009 00:00
FP6	75700	Beta cell programming for treatment of diabetes	02/12/2009 00:00
FP6	83896	B cells, splenic marginal zone, and complement -as opsonin and inflammatory mediator- in the immunopathogenesis of virally induced Type I Diabetes	21/11/2008 00:00
FP6	74865	Strengthening the European Research Area by Reinforcement of Romanian Research Competency in Genomics and Proteomics of Major Global Risk Diseases: Atherosclerosis, Diabetes and its Complications	16/06/2008 00:00
FP6	84550	The role of T Cell Activation in Type I Diabetes. T cell differentiation versus T Cell tolerance	28/03/2008 00:00
FP6	74396	Development of a bioartificial pancreas for type I diabetes therapy	02/07/2007 00:00
FP6	82095	Natural killer T cells (NK-T) immunoregulation by VIP: functional analysis, mechanisms of action and effects on Type I diabetes as a model of Th1 type autoimmnune disease	02/07/2007 00:00
FP6	72954	Regulation of DOR, a novel gene involved in diabetes	02/07/2007 00:00
FP6	82103	Characterisation of Pancreatic Beta-Cell Antiviral defence, providing a basis for the development of a novel preventative treatment for Type I Diabetes	02/07/2007 00:00

Annex 3:

Table EU Horizon 2020 projects on DIABE

Rcn	Title	Start Date	End Date	Total Cost	EC Max Contribution
194673	A Non-Invasive GLUCOse MONitoring device for diabetics based on Stimulated Raman Spectroscopy in a quick, cheap and painless method.	01/10/2014	01/04/2015	€ 71,429	€ 50,000
194647	DEVELOPMENT OF A SPIRAL LAMINAR FLOW INDUCING ENDOVASCULAR STENT FOR THE TREATMENT OF PERIPHERAL ARTERIAL DISEASE	01/10/2014	01/03/2015	€ 71,429	€ 50,000
194683	An innovative dental implant with osteoinductive properties by means of bioactive sol-gel coating	01/10/2014	01/04/2015	€ 71,429	€ 50,000
194094	Developing and implementing a community-based intervention to create a more supportive social and physical environment for lifestyle changes to prevent diabetes in vulnerable families across Europe	01/12/2014	01/09/2019	€ 2,997,405	€ 2,997,405
194100	Family-based intervention to improve healthy lifestyle and prevent Type II Diabetes amongst South Asians with central obesity and prediabetes	01/01/2015	01/01/2020	€ 3,614,084	€ 3,614,084
194091	A people-centred approach through Self-Management and Reciprocal learning for the prevention and management of Type-2-Diabetes	01/01/2015	01/04/2019	€ 3,344,981	€ 3,344,979
193983	Rapid Bioprocess Development	01/01/2015	01/01/2019	€ 4,038,972	€ 4,038,972
193810	Sequence-Enabled Single cEll Identification device	01/02/2015	01/08/2016	€ 150,000	€ 150,000
196290	Patented advanced low-cost multiwell cell-culture system for in-vitro physiologically relevant biomarker screening	01/02/2015	01/06/2015	€ 71,429	€ 50,000
196172	Predicting Response to Depression Treatment	01/02/2015	01/06/2015	€ 71,429	€ 50,000
196211	Emulsar: give the world appetite for health.	01/02/2015	01/08/2015	€ 71,429	€ 50,000
194102	Personal Assistant for healthy Lifestyle (PAL)	01/03/2015	01/03/2019	€ 4,515,460	€ 4,515,460
193337	Next-generation biopharmaceutical downstream process	01/03/2015	01/03/2019	€ 10,569,663	€ 8,366,433
196027	Deciphering central role of VMH circuits in regulating energy balance	01/04/2015	01/04/2017	€ 145,846	€ 145,846
193247	Understanding the dynamic determinants of glucose homeostasis and social capability to promote Healthy and active aging	01/04/2015	01/04/2019	€ 5,918,766	€ 5,917,266
195143	Functions of non-coding RNAs in protein synthesis and homeostasis during aging	01/04/2015	01/04/2017	€ 159,461	€ 159,461
193269	Novel Stromal Cell Therapy for Diabetic Kidney Disease	01/05/2015	01/05/2019	€ 5,994,374	€ 5,994,374
195837	Temporally controlled delivery of vascular therapeutics from a regenerative template for diabetic wound healing	01/05/2015	01/05/2017	€ 187,866	€ 187,866
193778	Exploring the Potential for Therapeutic Lineage	01/05/2015	01/11/2016	€ 150,000	€ 150,000

	Reprogramming of Diabetes				
193284	Elucidating Pathways of Steatohepatitis	01/05/2015	01/05/2019	€ 6,173,021	€ 5,985,521
193556	Elucidating Neuronal Susceptibility to Mitochondrial Disease	01/05/2015	01/05/2020	€ 1,500,000	€ 1,500,000
193506	Autonomous Cellular Computers for Diagnosis	01/05/2015	01/05/2020	€ 1,500,000	€ 1,500,000
193651	Circadian Regulation Of Brown Adipose Thermogenesis	01/05/2015	01/05/2020	€ 1,497,008	€ 1,497,008
195594	Developing next-generation tools for mitochondrial dissection with cell-specific resolution.	01/05/2015	01/05/2017	€ 170,122	€ 170,122
196486	Objective delirium detection with an innovative EEG-based spot monitor	01/05/2015	01/11/2015	€ 71,429	€ 50,000
196514	Clinical validation of retinal oximetry as a biomarker	01/05/2015	01/11/2015	€ 71,429	€ 50,000
196838	Diabetes Reversing Implants with enhanced Viability and long-term Efficacy	01/06/2015	01/06/2019	€ 8,832,063	€ 8,832,062
196840	Tailored Elastin-like Recombinamers as Advanced Systems for Cell Therapies in Diabetes Mellitus: a Synthetic Biology Approach towards a Bioeffective and Immunoisolated Biosimilar Islet/Cell Niche	01/06/2015	01/06/2019	€ 6,718,036	€ 6,214,495
195557	Analysis of tridimensional changes caused by Type II Diabetes-Associated varianTs	01/06/2015	01/06/2017	€ 158,122	€ 158,122
197116	Advanced Regional Translation of Excellence into Medical Innovations for Delayed Aging	01/06/2015	01/06/2016	€ 499,833	€ 499,833
195949	ALTERNATIVE SPLICING NETWORKS IN PANCREATIC BETA CELLS	01/06/2015	01/06/2017	€ 160,800	€ 160,800
197012	Low-Cost Diagnostics Monitoring Technology	01/06/2015	01/12/2015	€ 71,429	€ 50,000
197026	Empowered control of drugs's dosage in chronic diseases.	01/06/2015	01/12/2015	€ 71,429	€ 50,000
196692	World’s first complete motion-preservation 'Implant-less' surgical correction for Scoliosis	01/06/2015	01/12/2015	€ 71,429	€ 50,000
197053	DERMADROP - A COMPREHENSIVE TRANSDERMAL THERAPY CONCEPT FOR NON-HEALING WOUNDS AND OTHER SKIN DISORDERS	01/06/2015	01/12/2015	€ 71,429	€ 50,000
197087	BIOactive implantable CApsule for PANcreatic islets immunosuppression free therapy	01/06/2015	01/06/2019	€ 7,998,875	€ 7,998,875
197197	Innovative diagnostic device for the early detection of diabetic neuropathy in diabetes patients	01/07/2015	01/01/2016	€ 71,429	€ 50,000
197184	Moving to Efficient Diabetes care: Multimode Integrated CO-morbidity diagnostics platform	01/07/2015	01/01/2019	€ 4,487,525	€ 4,487,525
197320	The ERA Chair for Translational Genomics and Personalized Medicine	01/07/2015	01/07/2020	€ 2,677,500	€ 2,409,700
193488	Cholesterol and Sugar Uptake Mechanisms	01/07/2015	01/07/2020	€ 1,499,848	€ 1,499,848
195322	Does reducing β-cell glucotoxicity increase the hyperglycaemia-lowering effect of physical exercise in Type II diabetes?	01/07/2015	01/07/2017	€ 183,455	€ 183,455
193582	Mechanisms of Gene Silencing by the Glucocorticoid	01/08/2015	01/08/2020	€	€ 1,496,275

	Receptor			1,496,275	
195473	Omics Phenotyping of Endocrine Disease in the General Population	01/08/2015	01/08/2017	€ 200,195	€ 200,195
193232	Efficacy and safety of low-dose IL-2 (ld-IL-2) as a Treg enhancer for anti-neuroinflammatory therapy in newly diagnosed Amyotrophic Lateral Sclerosis (ALS) patients	01/09/2015	01/09/2019	€ 6,510,743	€ 5,980,435
196158	European Glaucoma Research Training Program	01/10/2015	01/10/2020	€ 2,092,800	€ 1,046,400
195137	Embryonic stem cell origin of the adipose tissue macrophages	01/10/2015	01/10/2017	€ 159,461	€ 159,461
196076	Creating an evaluation and research strategy and an evidence base for eHealth systems to improve the quality of data collection and care in low and middle income settings	01/05/2017	01/05/2017	€ 195,455	€ 195,455
195912	Delineation of a brain circuit regulating energy expenditure to impact body weight	01/05/2017	01/05/2017	€ 195,455	€ 195,455
195446	Information from Symbols and Illustrations: how to get it without vision	01/05/2017	01/05/2017	€ 183,455	€ 183,455
197115	Advanced Regional Translation of Excellence into Medical Innovations for Delayed Aging	01/06/2020	01/06/2020		
195312	ROLE OF THE TANYCYTIC BARRIER AT THE BLOOD-HYPOTHALAMUS INTERFACE DURING METABOLIC DISORDER DEVELOPMENT	01/05/2017	01/05/2017	€ 173,076	€ 173,076
195487	Characterization of the mechanism of inter-organ communication coordinating tissue growth and developmental timing	01/05/2017	01/05/2017	€ 173,076	€ 173,076

Annex 4:

Search strategy for MDs' clinical trials from www.clinicaltrials.gov

The search was performed according to top MD companies.

Search strategy:

1. Interventions: device
2. Sponsor (lead):
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Covidien plc
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Only ongoing/completed clinical trials between 2011 and 2015 have been considered. Moreover only MDs for non-communicable diseases have been included.

We excluded terminated clinical trials and those with unknown/not verified status.

Annex 5:

Search strategy for PMA (Premarket Approval) of medical devices at FDA

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Due to the level of risk associated with Class III devices, FDA has determined that a PMA is needed in order to obtain marketing clearance. PMA is the most stringent type of device marketing application required by FDA.

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

3. Date: 01/01/2011 – current date (June 2015)
4. Keywords:
    - ONCOL:
        - cancer
    - CARDI:
        - cardiovascular
        - stroke
    - DIABE:
        - diabetes
    - RESPI:
        - respiratory
        - pulmonary
        - pneumonia
        - pharyngitis
        - rhinitis
        - bronchitis
        - asthma
        - allergy
        - COPD
        - emphysema
        - lung
        - apnea
    - MENTH:
        - mental
        - depression
        - schizophrenia
        - dementia
        - alzheimer
        - brain
        - pain
        - epilepsy

- addiction
- smoke/smoking
- behavior/behavioral
- anxiety
- eating disorder
- sleep

Annex 6:

Search strategy for de novo medical devices at FDA

The FDA added the de novo classification option as an alternate pathway to classify novel devices of low to moderate risk that had automatically been placed in Class III after receiving a "not substantially equivalent" (NSE) determination in response to a premarket notification [510(k)] submission. Devices that are classified through the de novo process may be marketed and used as predicates for future 510(k) submissions.

The search was performed first according to top MD companies, but we did not find any result. The search strategy adopted was the following:

1. Decision date: 01/01/2011 – current date (June 2015)
2. Requester name:
    - Johnson & Johnson
    - General Electric Co.
    - Medtronic Inc
    - Covidien plc
    - Siemens AG
    - Baxter International Inc
    - Fresenius Medical Care AG & Co. KGAA
    - Koninklijke Philips NV
    - Cardinal Health Inc.
    - Novartis AG (Alcon)
    - Stryker Corp.
    - Becton, Dickinson and Co.
    - Boston Scientific Corp.
    - Essilor International SA
    - Allergan Inc. (Actavis)
    - St. Jude Medical Inc.

Then, we performed a second search using as filter only the decision date (from 01/01/2011 to June 2015). We included only MDs for non-communicable diseases and MDs which have not received 510(k) clearance yet.

Annex 7:

Search strategy for EuroScan medical devices

The search was performed according to indication in the five NCD areas (cancer, respiratory disease, cardiovascular disease, diabetes, mental health) and not according to top MD companies.

Search strategy:

1. Technology–type: device
2. Specialty:
    - ONCOL: Oncology & radiotherapy
    - CARDI: Cardiovascular disease & vascular surgery
    - DIABE: Endocrine, nutritional and metabolic
    - RESPI: Respiratory disease & thoracic surgery
    - MENTH: Mental health, addiction & learning difficulties

Only MDs approved between 2011 and 2015 have been considered.

Annex 8:

Interview guidance

Mapping Chronic Non-Communicable Diseases Research Activities and their Impact

EC/FP7/602536

WP 4
Interview guide

Name: **Organization:** **Date:**
Past and Existing Funding Strategies and Programmes for Diabetes/NCD: ➢ Can you describe some of the impacts of these programmes and strategies? ➢ In what ways have the impacts been positive? Can this be quantified? How? ➢ In what ways have the impacts been negative? Can this be quantified? How?
The Challenges for the Future: ➢ Can you describe some of the challenges for future Diabetes/NCD research? (probe into funding sources, staff availability, incentives, intellectual property issues, cross-border collaborations, among others) ➢ Can you describe some of the funding challenges for Diabetes/NCD research?
Recommendations for Future EC Activity on Diabetes/NCD: ➢ How would you describe the current research gaps for Diabetes/NCDs (probe into how these have been identified? who identified them? is it about basic research? developmental research? more focused research? What about the interface between pharmacological research/cell-based research / health system delivery research? Etc) ➢ How would you describe the future priorities for Diabetes/NCD research funding (probe into areas of unmet need, own areas of research, how governmental bodies prioritise areas of research, how NGOs prioritise areas of research, etc). ➢ What do you think the EU should be doing with regard to Diabetes/NCD funding and research on NCDs? ➢ Can you tell me about areas beyond financing that the Diabetes/EU should be looking at (e.g. probe into areas such as incentives, policies around Foundations, charitable giving encouragement, etc.)

- Can you tell me about the ways in which research in Diabetes/NCDs is funded delivers the best possible results or can be improved upon? If the latter, in which way(s)?
- Can you tell me about ways that Diabetes/NCD research might suffer from a significant/a certain degree of duplication of effort? If so, in what way(s) can we avoid duplication(s) in the research effort in Diabetes/NCDs?

Any other Relevant Information:

- Can you recommend any other key stakeholder to who we should speak?