Summary description of project context and main objectives:

The primary aim of PREDICTION-ADR is to develop genetic risk assessment and diagnostic tools for the prediction of adverse drug reactions in two commonly prescribed drug classes that are used to manage cardiovascular risk, namely statins and ACE inhibitors/Angiotensin Receptor Blockers. Drug intolerance is a major factor in lack of adherence and efficacy in both classes of drugs. The ultimate goal is to optimise the management of CVD with currently used medications. Particularly, we aim to develop tools that will identify (i) patients with likelihood of experiencing severe adverse reactions to drugs, and (ii) patients who may discontinue drugs due to milder intolerance. The application of such drug response prediction tools is expected to directly improve patient care through individualized management of both cardiovascular risk and disease in addition to reducing health care cost. This work will be achieved through integrating expertise from leading European groups in the fields of cardiovascular pharmacology, pharmacoepidemiology and molecular genetics, with clinical medicine.

The development of genetic drug response prediction tools will involve a clearly defined process of (a) discovery of novel genetic biomarkers by next generation sequencing, (b) using sophisticated statistical analysis to define massively multi-allelic genetic interaction models to predict adverse drug reactions with a high specificity and sensitivity, (c) validation of these markers in population-based data samples and clinical trials, (d) development of a novel diagnostic incorporating the validated drug response prediction tools, and finally, (e) dissemination through engagement with stakeholders, patient groups and exploitation through commercialization by ASPER-Biotech a leading EU genetic diagnostic provider.

The principle basis for the concept of PREDICTION-ADR is clinical need. With the ageing population in the developed and developing world, drug therapy to manage cardiovascular disease (CVD) is steadily increasing. Although the incidence of the most severe adverse reactions is rare, given the number of prescriptions of CVD drugs globally, the absolute number of adverse drug reactions (ADRs) is substantial. Studies have shown that ADRs are one of the most common reasons for hospitalisation in the adult population. It has been proposed that ADRs are the fourth to sixth leading cause of death in hospitalised patients. ADRs also commonly lead to poor compliance and discontinuation of vital therapies and therefore negatively affect the burden of CVD in health care systems worldwide. The current knowledge about possible genetic causes of ADRs is limited. Studying the genetic basis of susceptibility to ADRs may provide possibilities for identification of susceptible individuals through pharmacogenetic testing.

Understanding the molecular basis of ADRs may also make it possible to design safer drugs. Statins primarily reduce the risk of coronary artery disease (CAD) by lowering blood cholesterol through inhibition of the HMG-CoA reductase enzyme. Large clinical trials show a 27% average relative risk reduction of major coronary events. However there is large variability in benefits from statin therapy. This variability can be partially explained by factors such as adherence, gender, age, diet, concomitant drug use and environmental factors, with drug intolerance being a major factor in adherence and concomitant drug use also being a major factor in determining intolerance. Therapy with statins has become relatively cheap because most statins are out of patent which means that even more patients will be treated with them. Next to that, the dosages used in the treatment of patients are increasing, because it has been shown that higher doses are more effective. With more patients being treated with increasing doses the burden of adverse events becomes ever greater.
Description of work performed and main results:

The PREDICTION-ADR research activity covers discovery and validation of genetic markers of statin induced myopathy and ACE Inhibitor induced angioedema. Identification of variants is achieved by whole exome sequencing of cases and controls. It is of vital importance that the clinical definitions of such side effects are clear and precise to minimize misclassification which would greatly reduce the power of such genomic discovery experiments. To this end PREDICTION-ADR has coordinated an international workshop on phenotype standardisation for both adverse reactions and has published a consensus phenotype in Clinical Pharmacology and Therapeutics. PREDICTION-ADR has used collaborative networks and electronic medical records to identify and recruit individuals who have had drug reactions that fit the consensus criteria. Over 250 cases of angioedema have been recruited for our discovery sequence analysis (100% of the target cohort size). Over 220 cases of statin induced myopathy have been recruited which is 80% of the target recruitment. 500 controls will be used who have been treated with both statins and ACE inhibitors consistently without any evidence of drug intolerance. This will provide a 2:1 control to case ratio for optimal statistical power in the association analysis. Whole exome sequencing is being harmonized between the three centres, Uppsala, Liverpool and Dundee, with a common agreed exome capture panel, and a set of 8 common controls are being sequenced in all three centres. This will allow for pipelines to be established for harmonised sequence data analysis to provide robust association analysis. Work has begun in population cohorts from Scotland (GoDARTS/GoSHARE) and Holland (Rotterdam Study) where extensive Electronic Medical Records exist allowing us to define models of common intolerance to statins and ACE inhibitors that is much more common than the ADRs mentioned above. For statins we have used a combination of CK measures and drug discontinuation or switching to act as a proxy for intolerance. This has been validated with the main statin myopathy gene \( SLC01B1 \), which we have shown to be associated with statin discontinuation, both in the Scottish population cohorts and in the Dutch cohorts. As part of PREDICTION-ADR we have also shown that genes associated with high levels creatinine kinase activity in the serum (our definition of myopathy) may be unrelated to statin treatment. Specifically we have shown that a missense mutation in the \( CKM \) gene encoding a substitution of a Glycine for the ancestral Glutamic acid at codon 83 is associated with low serum CK levels. Individuals with the Glycine 83 variant appear to be strongly protected from having raised CK levels either due to statin exposures or other muscle insults such as trauma, but our population data suggests that this variant does not protect from statin related intolerance.

Discontinuation from ACEI inhibitors is common (10-20%) and is largely due to intolerance, We have performed a case review study in the Rotterdam cohort to determine the main causes of ACEI discontinuation. We have shown that the major cause of discontinuation is the occurrence of dry cough (80%), with angioedema being a minor component (2%). We have performed a discovery Genome Wide Association Analysis using 1000 Genomes imputed data (4 Million SNPs) in the GoDARTS and Rotterdam Study comprising over 5000 study subjects and have revealed four novel loci to be associated with this phenotype, each with an association statistic exceeding genome wide significance \((p<5\times10^{-8})\). These are currently being further replicated in Swedish and US cohorts of individuals with established ACE induced cough and we are also examining the potential role of these loci in determining predisposition to angioedema. This is being performed using in pre-existing GWAS data in our Swedish angioedema discovery cohort.
Expected final results and potential impacts:

Adverse drug reactions are a significant cause of morbidity and mortality in modern society. Studies have shown that adverse drug reactions (ADRs) are one of the most common reasons for hospitalisation in the adult population. It has also been proposed that ADRs are the fourth to sixth leading cause of death in hospitalised patients. The economic burden of ADRs is therefore significant. It has been estimated that the cost of ADRs of society exceeds that of direct drug costs. PREDICTION-ADR should yield great economic benefits as well as great reductions in patients suffering by producing methods to predict which patients are at risk of ADRs. Methods of this kind are currently unavailable. As there is good reason to believe that a significant part of an individual’s risk of developing ADRs resides in the genetic make-up, there is great interest in the development of genetic testing to predict who is at risk of ADRs for a given drug, so that a different drug treatment can be given instead, thereby avoiding the ADRs. A race is currently taking place to be the first to develop such genetic testing methodologies. This is not an easy task as such tests need to be highly specific, reliable, cheap, quick and easy to perform in order to be useful, and PREDICTION-ADR with its commercial partner, ASPER Biotech, is well placed to deliver such a test to the marketplace. The market for a method fulfilling these criteria is enormous and currently unprospected. From a business point-of-view, PREDICTION-ADR taking a lead within this field promises great profit. From a societal point-of-view, the use of such tests promises vast cuts in health costs while concomitantly increasing health care quality. The development and establishment of such tests in routine health care is a purely win-win situation for all parties involved. With its high level of scientific competence and innovative skills, the European union (EU) has a golden opportunity to take the lead within this field and to set the standards for the future. PREDICTION-ADR aims to provide the EU with such a head start, focusing on two major and widely used drug groups within the field of cardiovascular disease (CVD).
Title: Personalisation of tREatment In Cardiovascular disease through next generation sequencing in Adverse Drug Reactions

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Duration: 01st September 2013 - 31st August 2016 (36 months)

Funding scheme: FP7-HEALTH-2013-INNOVATION-1

Budget: EU contribution: 2,999,952.00€

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The PREDICTION-ADR project has received funding from the European Community’s Seventh Framework Programme (FP7/2007-2013) UNDER Grant Agreement no. 602108

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