

## Chapter 1. Genetics and epidemiology

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### Section A. Introduction

This sub-group considered current and future research on the epidemiology and genetics of diabetes, not in isolation, but rather in the context of the potential utility of the information produced. Epidemiological studies, for example, can be descriptive, creating information about prevalence and incidence. Although estimates of these parameters are often said to be required as the foundation for healthcare planning, this is too simplistic a view of how such information may be used. Indeed, descriptive epidemiological data are rarely used in this way, and it is more common to see estimates of disease occurrence being used as political justification for increased resource allocation. However, this sub-group has attempted to place the acquisition of knowledge about the absolute levels of disease risk in a more realistic framework of how these data would be of use. In type 1 diabetes, for example, continued investment in surveillance systems to monitor the incidence of disease in a standardised way across populations may contribute to generating clues to the environmental risk factors that cause or trigger the condition. By contrast, this would be unlikely to be a useful strategy in type 2 diabetes where accurate estimation of disease incidence is complex because of the chronic nature of the condition and definitional issues about the point of disease occurrence. However, information about prevalence and the association of all forms of diabetes and lesser degrees of hyperglycaemia with clinical outcomes is a necessary building block in the construction of a public health model of risk of diabetes and its complications. These models may play an important role in informing strategic choices about investment in alternative strategies that cannot readily be subjected to a randomised controlled trial. These examples serve to illustrate how the sub-group has defined the product of an epidemiological study (i.e. the estimate of incidence or prevalence) not as the end in itself, but rather as a component of a larger scientific endeavour.

Epidemiological studies, including those focussed on genetic factors, play an important role in understanding the aetiology and pathogenesis of diabetes and also have predictive or prognostic utility. Although these goals may often be addressed by analyses of the same studies, the sub-group has sought to make a clear distinction between them in this report, as the aetiological importance of an association with a given risk factor is measured by different metrics to those that allow assessment of its predictive utility. The current wave of discovery from the genome-wide association approach has, for example, been criticised for not contributing to the prediction of disease beyond conventional risk factors. However, this criticism ignores the utility of such studies in identifying novel associations whose importance lies in the basic mechanistic knowledge that results rather than in the measure of effect size and thus predictive capacity. It is the view of this sub-group that placing epidemiological and genetic studies in the context of how the information will be used leads to better study design, more informative analyses and eventually enhanced research translation.

Finally, the sub-group has considered issues of the contribution of epidemiology to the prevention of type 2 diabetes by providing a structure that facilitates integration of public health approaches with those focussed on individual preventive efforts aimed at high-risk individuals. In this context, diabetes is a salient example of a generic public health problem in which evidence is strongest for the individualistic prevention approaches, but potential public health gain is greatest for strategies that recognise the total societal nature of the problem. The framework provided for integration of epidemiological information into a public health strategy may be a model for other similar health issues.

## Section B. Scientific advances and major challenges

### Understanding the aetiology and prediction of type 1 diabetes

The peak age of incidence of type 1 diabetes is seen in childhood, but the disease may also occur at any stage of life, indicating the variation in the rapidity of the progression of the immune-mediated damage to the pancreatic beta cells that characterises this condition. There is marked geographic and temporal variation in the incidence of type 1 diabetes, but as yet this has not given rise to clear aetiological hypotheses that have been supported by studies with individual-level measures of exposure.

Although it is widely proposed that type 1 diabetes originates from an interaction between environmental and genetic factors, there has been little progress in identifying the environmental agents that lead to disease. By contrast, there has been rapid progress in understanding the genetic basis of the condition. The predominant genetic loci are *HLA DQ8* and *DQ2*, which are found in 80 percent of children with type 1 diabetes in Scandinavia. The development of large consortia to recruit both family and population-based case-control studies and the rapid advancements in mass genotyping technology have allowed progress in defining the non-HLA genetic determinants of type 1 diabetes.

It is estimated that the loci detected by these genome-wide association studies account for 40 percent of the heritability of type 1 diabetes. The detection of the association of these loci with type 1 diabetes is only the first step in the process of identification of the causal variant underlying the association signal through fine mapping and physiological studies linking genetic variation to a dysfunctional pathophysiological process. Such studies will enhance understanding of the pathophysiology of type 1 diabetes and may provide clues to help identify the environmental triggers.

Although theoretically enhanced understanding of the genetic and environmental aetiology of type 1 diabetes could lead to studies investigating the interaction between these factors, the study of interaction requires very large numbers of incident cases within a prospective cohort design. As the incidence of type 1 diabetes is relatively low, such an investigation would not be feasible in a general population-based cohort even in a high-risk area without some degree of enrichment of the selected cohort. It is more plausible to envisage the study of the combination of genetic and environmental factors on the development of early markers of type

1 diabetes risk rather than on the incidence of the clinical condition itself. However, such a study design would be dependent upon the development of sensitive and specific markers of the early disease process. Currently, most studies use autoantibodies against glutamic acid decarboxylase (GAD65), islet antigen-2, ZnT8 transporter or insulin as markers of the autoimmune processes underlying the beta cell destruction.

In addition to contributing to understanding the aetiology and pathogenesis of type 1 diabetes, genetics research has the potential to contribute to the development of prediction tools for quantifying type 1 diabetes risk, which is a necessary prerequisite for enriching cohorts with high-risk individuals to facilitate the study of gene-environment interaction and also, theoretically, as a step in the identification of suitable individuals for prevention trials. Previous trials of nicotinamide and insulin to prevent type 1 diabetes have not been successful, and it is likely that future trials will be based to a greater extent on enhanced understanding of the underlying disease process. Although there has been some success in slowing the disease process with treatments that modulate the immune process, there are considerable ethical challenges in considering such therapies in children for whom prevention could have the greatest lifetime impact since the complications of diabetes are mostly duration dependent.

### Prevention strategies for type 2 diabetes

The last decade has seen a number of key randomised clinical trials that have unequivocally demonstrated that type 2 diabetes can be prevented either by lifestyle change or by glucose-lowering therapies. The Finnish Prevention Study and United States NIH Diabetes Prevention Program both demonstrate that in high-risk individuals with impaired glucose tolerance (IGT), the risk of progression to diabetes can be approximately halved by a lifestyle intervention focussed on weight loss, dietary change and increased physical activity. These trials demonstrate how much could be achieved in theory to prevent type 2 diabetes, although to date none of these trials has been sufficiently large to demonstrate an impact on the clinical outcome of the complications of diabetes as well as on the risk of development of the condition itself. Future trials will need to investigate this long-term impact.

A major current challenge is to convert these effective interventions into real-life pragmatic prevention strategies. This necessitates the development of pragmatic approaches for defining

sub-groups of the population at risk of type 2 diabetes as approaches based on identification of people with IGT are not practical in everyday clinical practice. In addition, the intensive lifestyle interventions, which were successful in the trial setting, may not be deliverable in the real-life setting, and thus the development of pragmatic individual-level lifestyle behaviour change programmes is a key priority. In the Finnish study, a combination of five behavioural targets was strongly related to the likelihood of progression to type 2 diabetes among the high-risk group with IGT. However, it has also been demonstrated that the same targets predict risk of progression to diabetes at the population level. While the high-risk targeted prevention strategy is demonstrably effective, its focus on a relatively small proportion of the total population at risk means that it has a relatively small impact on the population-attributable fraction, the proportion of cases avoided by the prevention strategy.

Conversely, a strategy focussed on small changes in key behaviours in the whole population makes little impact on each individual but has the largest potential impact on the total population burden of the disorder. Thus, to complement the individual-level prevention approach, there needs to be investment in understanding the societal determinants of physical activity and dietary behaviour and the development and evaluation of collective behaviour change programmes. While some of these may be developed specifically for health improvement, it is likely that many interventions that impact on population behaviour will be primarily designed for other purposes. For example, major public transportation infrastructure investments are likely to impact on physical activity behaviour but are not primarily designed for that purpose. Such investments are not amenable to the reductionist evaluative method of the randomised controlled trial. They are, by contrast, natural experiments, which can be evaluated, provided there is a system for early identification of opportunities for evaluation. It is unlikely that such evaluations will demonstrate an impact on diabetes risk, and the outcome is more likely to be change in the lifestyle factor. The public health impact of these interventions will therefore need to be modelled rather than measured directly.

A major challenge is how to balance investment between the high-risk and population-based strategies especially since the type of evidence that underpins each strategy is likely to be very different, being based in the former on large-scale clinical trials and in the latter on natural experiments and public health modelling. However, the production of an integrated public health

modelling that allows the combination of these strategies is a critical step in synergising disease prevention and health promotion approaches to diabetes prevention.

### **Aetiology and prediction of type 2 diabetes**

Type 2 diabetes is a heterogeneous collection of conditions rather than a single disorder. The aetiology and pathogenesis of some rare, predominantly monogenic, causes of diabetes, which would previously have been classified as type 2 diabetes, have been identified. These include not only the various sub-types of maturity-onset diabetes of the young (MODY), but also other mutations affecting insulin secretion, insulin resistance or obesity. However, for the majority of individuals who remain classified as type 2 diabetic, our diagnosis is based solely on raised glucose levels without a specific cause, and therapy is targeted at dealing with the hyperglycaemia rather than at an underlying causal pathway.

There has been considerable progress in identifying a number of common genetic variants that are associated with type 2 diabetes. These have emerged from traditional linkage and positional cloning approaches but predominantly from whole genome-wide association studies. The rapid acquisition of knowledge from genome-wide association studies has been driven by technological capability and a global collaborative effort to combine forces to increase sample size and statistical power, leading to rapid expansion of knowledge of the genetic architecture of type 2 diabetes. Novel technology and bioinformatic methods have also been applied to other forms of data to identify key regulatory pathways for oxidative phosphorylation in mitochondria. The proportion of the heritability of type 2 diabetes explained by the known loci is relatively small, and attention will be paid in the future to identifying explanations for the 'missing heritability'. These include the association of multiple rare variants, copy number variation, epigenetics and gene-environment interaction.

The association between low birth weight and rapidity of post-natal growth and type 2 diabetes originally proposed in 1991 has been replicated in multiple studies. The pathophysiological mechanisms underlying these associations remain unknown, and although epigenetic mechanisms have been proposed, progress in investigating these in population-level studies has been slow. This is largely due to the scarcity of cohort studies with sufficient duration of follow-up that also have appropriate samples collected and the challenge of studying phenomena which vary across time and which may be tissue specific.

The impact of the overall level of obesity and its regional distribution on type 2 diabetes risk is strong and consistent in observational studies and interventional clinical trials. As obesity is neither necessary nor sufficient to cause type 2 diabetes, there has been considerable interest in the identification of potential interactions between obesity and other risk factors, including family history, genetics and early life growth. The study of combined effects requires much greater sample sizes than individual risk factors and needs to be undertaken in the context of a prospective cohort since the presence of disease alters factors. As the incidence of type 2 diabetes is relatively high, the establishment of such cohort studies is more tractable than for type 1 diabetes.

Previous cohort studies have shown clear associations between low levels of physical activity and the development of type 2 diabetes. However, the questionnaire-based methods used to estimate physical activity in such studies are relatively imprecise and are not well suited to addressing the uncertainties about the specificity of the association, dose-response relationship, or the possibility of effect modification. The application of objective assessment methods will help these issues to be addressed and will also aid the study of the association between sedentary behaviour and type 2 diabetes. Some studies have suggested that sedentary behaviour may have specific adverse metabolic effects independent of the level of physical activity. There are marked differences in diabetes risk by ethnic group and social class. However, the underlying explanations for such differences are uncertain.

The integration of understanding of genetic, lifestyle and developmental determinants of type 2 diabetes has the potential to enhance understanding of the pathophysiological basis of the complex set of interactions that underlie disease risk. In turn, this may lead to the development of novel and more personalised preventive interventions. Such interventions would need to be linked to tools to predict type 2 diabetes and to sub-stratify the population.

There are a variety of current diabetes prediction tools, ranging from those that predict risk based on existing data or questionnaires to those more clinical models incorporating biochemical and genetic information. The further development of this suite of tools designed to be 'fit-for-purpose' will require inclusion of information from on-going large-scale prospective studies that can investigate stratum-specific risk. An important aspect of the likely future effectiveness of personalised preventive interventions is the perception of risk by

the target individual. Currently, too little is known about how people at risk of diabetes perceive that risk, or how that perception of risk translates into intention to change behaviour and the achievement of that behaviour change.

### **The epidemiological investigation of the complications of type 2 diabetes**

Randomised controlled trials, including the UK Prospective Diabetes Study and the Heart Protection Study, have demonstrated that close control of key metabolic pathways can reduce the occurrence of the complications of diabetes. In the Steno 2 trial, the overall impact of simultaneous intervention on these multiple pathways has been shown to be effective in reducing cardiovascular outcomes in high-risk individuals with microalbuminuria. It is uncertain whether such multi-factorial intervention will be effective earlier in the disease process. Quantifying the benefit associated with this form of intervention in people with screen-detected diabetes is one of the key uncertainties that impacts on the policy decision about whether or not to establish programmes for the early detection of type 2 diabetes.

Most public policy decision-making tools for determining whether or not to instigate such programmes also consider the appropriate balance between primary and secondary prevention. In the case of type 2 diabetes, there is the clear potential for the development of an informative public health model that allows evaluation of the appropriate balance between high-risk and population-based approaches to the prevention of the complications of diabetes. The input to such a model for the high-risk approach comes from randomised controlled trials. However, the population-level approach requires a model that assembles data from surveillance systems of the temporal trends in distributions of glycaemia in European populations with knowledge about the association of glycaemia with clinical outcomes.

Clinical outcomes not only include the well-established complications of diabetes (micro- and macrovascular disease) but also those less well established, including cancer and cognitive decline, for which additional epidemiological information may need to be collected in prospective cohort studies. These data can be assembled to construct a dynamic public health model that relates the changes in population-level glycaemia to morbidity and mortality. The impact of population preventive strategies on glycaemia can be incorporated into such models, giving rise to an integrated model of the impact of public health interventions on the complications of diabetes.

### **Personalising diabetes treatment strategies**

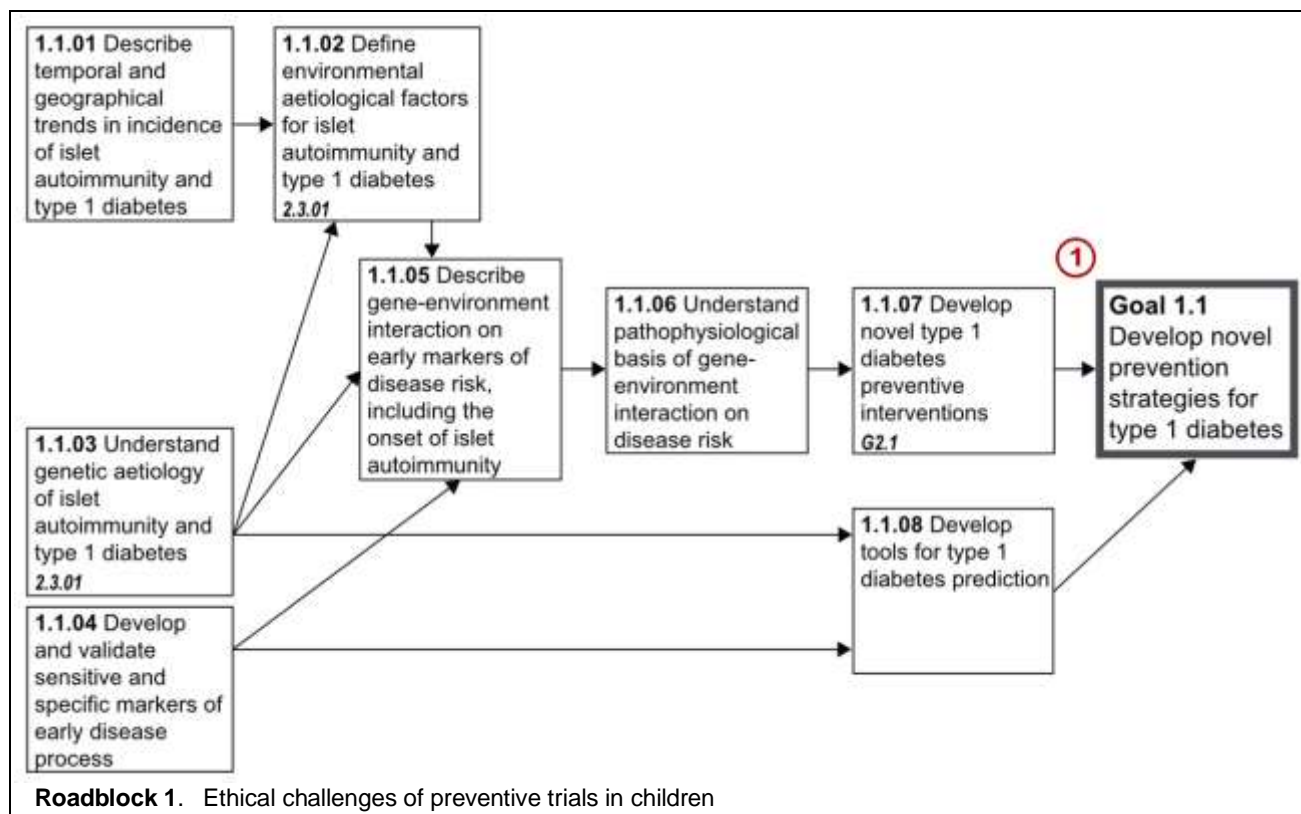
Although there is considerable between-person heterogeneity in the likelihood of developing the complications of diabetes, there has been relatively little investigation into explanations for these differences, which may include gene-lifestyle interactions and ethnic diversity. The study of these factors in the context of longitudinal studies and clinical trials would allow the development of

individually focussed tools for the prediction of the complications of diabetes and the potential personalisation of diabetes treatment strategies. Genetic studies have led to some key illustrations of the potential of this approach with the specification of therapy for people with individual forms of MODY and persistent neonatal diabetes.

## Section C. Road map reports

Links between Goals and Milestones in the DIAMAP report are noted within the text and also in the diagrams in *italics*. Roadblocks are shown in red circles, listed below the diagrams, and described at the end of the chapter. Goals and Milestones considered a priority are indicated with a broken green line.

### Goal 1.1. Develop novel prevention strategies for type 1 diabetes



#### Introduction and background

Patients with type 1 diabetes present acutely and at the time of clinical presentation already have such marked destruction of the insulin-producing beta cells that intervention at this point in the disease process is unlikely to modify the underlying causal disorders including most specifically islet autoimmunity. In order to target early interventions to appropriate individuals and on appropriate pathophysiological pathways, we need to develop better understanding of these pathways. Achieving this Goal requires the development and validation of novel biomarkers of the type 1 diabetes process and islet autoimmunity, with better proxy outcomes to facilitate the study of pathogenesis. This topic is clearly of relevance to Chapter 2. Islets (Goals 2.0-2.4), which discusses islet cell research in greater detail.

From an epidemiological perspective, such biomarkers would not only include immunological factors/markers reflecting islet autoimmunity but also novel techniques for imaging the disease process in islet cells. If sufficiently sensitive methods for measuring beta cell mass or function could be developed, it would be possible to test to what extent autoimmune markers – often present years before onset of disease – reflect beta cell destruction and, consequently, beta cell loss. Furthermore, this could potentially clarify the natural history of disease in those with antibodies who do or do not end up developing type 1 diabetes. Greater understanding of how the early stages of the autoimmune process are initiated will create opportunities for the development of potential interventions that can be aimed at stopping the occurrence of immune-mediated beta cell destruction before it starts. The early Milestones in this map therefore focus on both islet autoimmunity and type 1 diabetes.

There has been considerable progress in understanding the genetic basis of type 1 diabetes, yet the descriptive epidemiology of the condition suggests that major environmental factors must play a key role in determining why the incidence of the disease is rising on the background of stable genetic predisposition. These environmental factors remain unclear, and enhanced understanding is a necessary prerequisite for the design of future primary prevention strategies. The design of studies to investigate how genetic, epigenetic and environmental factors operate together to bring about disease will require multi-disciplinary large-scale prospective studies.

**Milestone 1.1.01. Describe temporal and geographical trends in incidence of islet autoimmunity and type 1 diabetes**

The epidemiological study of temporal and geographical variation in estimates of the incidence of islet autoimmunity and type 1 diabetes across different European countries may provide clues to the environmental factors that drive the occurrence of disease in susceptible individuals. Such studies need to be based on combined analyses of population-based registers established using existing or newly improved standardised methods for defining incident type 1 diabetes and islet autoimmunity.

**Milestone 1.1.02. Define environmental aetiological factors for islet autoimmunity and type 1 diabetes**

The environmental factors that drive the occurrence of islet autoimmunity and type 1 diabetes in susceptible individuals are largely unknown. Enhanced understanding of these factors is a key prerequisite for the development of preventive strategies. Clues to the environmental aetiology of type 1 diabetes may emerge from studies of temporal or geographical trends in disease incidence or from enhanced understanding of the pathophysiological processes leading to disease. Case-control studies with accurate measurement of possible environmental factors (including viruses and foods, and the gut microbiome) may be appropriate in the situation where assessment of the environmental exposure after the onset of disease is not biased by the occurrence of the disease. The alternative strategy of prospective assessment of the association between environmental exposure and disease risk may be possible where undertaken in an appropriately high-risk sub-group.

**Milestone 1.1.03. Understand genetic aetiology of islet autoimmunity and type 1 diabetes**

Considerable progress has been made in defining the role of HLA and other common genetic variation

in determining risk of type 1 diabetes. Future studies are needed to investigate the impact of HLA and multiple common variants on risk, including the possibility of epistasis. The study of the role of rare variants is also required, necessitating large-scale collaborative efforts. Remaining challenges include elucidating the pathways through which known variants are associated with disease and understanding the genetics of older onset type 1 diabetes.

**Milestone 1.1.04. Develop and validate sensitive and specific markers of early disease process**

Progression to clinically diagnosed type 1 diabetes is a relatively late stage in the disease process. The development of sensitive and specific early markers of the underlying disease process is important as it would allow the identification of a pre-disease stage in which preventive therapeutic interventions may be effective. Such markers would not only need to be predictive of future clinical type 1 diabetes but also be demonstrably linked to the stage of the pathophysiological process as opposed to being aetiologically linked to disease. The definition of a pre-disease stage using early markers of disease risk would also be important for the study of the combined impact of genetic and environmental factors.

**Milestone 1.1.05. Describe gene-environment interaction on early markers of disease risk, including the onset of islet autoimmunity**

Although it is likely that risk of progression to type 1 diabetes is a result of the impact of environmental factors on innate susceptibility, the relatively low incidence of type 1 diabetes makes the study of the combined effect of these factors on disease risk extremely difficult. Therefore, once the environmental factors have been defined with greater precision, it may be more tractable to study the interaction between genetic and environmental factors on the development of early markers of type 1 diabetes, including the onset of islet autoimmunity.

**Milestone 1.1.06. Understand the pathophysiological basis of gene-environment interaction on disease risk**

If a model of how genetic and environmental factors interact is developed in the context of studies of early markers of disease risk, then it may be possible to follow up these studies up with an investigation of how such factors combine to determine risk of progression to clinical type 1 diabetes in sub-groups of the population defined to be at high risk for type 1 diabetes.

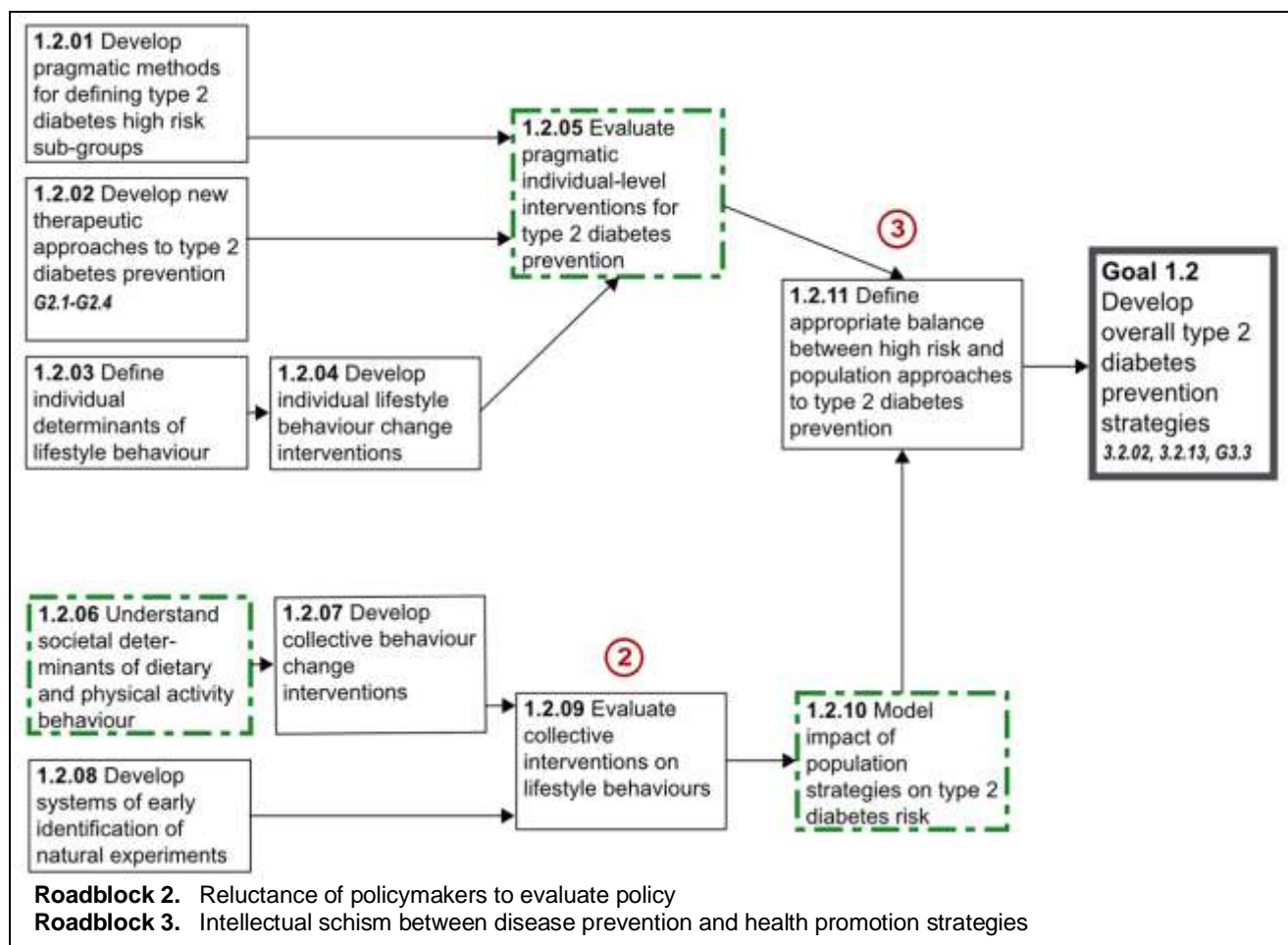
**Milestone 1.1.07. Develop novel type 1 diabetes preventive interventions**

Enhanced understanding of the combined impact of genetic and environmental factors in the aetiology of type 1 diabetes will lead to the development of novel preventive interventions, the efficacy of which will need to be evaluated in trials in high-risk individuals. Such trials are therefore dependent upon parallel progress in developing tools for accurate prediction of type 1 diabetes risk. As with all preventive interventions, the outcome of such trials should not only consider the degree to which interventions delay the onset of disease, but also impact more broadly on quality of life and the occurrence of complications of diabetes.

**Milestone 1.1.08. Develop tools for type 1 diabetes prediction**

Risk prediction models for type 1 diabetes are necessary in order to be able to identify individuals to whom preventive interventions may be targeted. The development of such prediction models may include aetiological factors (e.g. genetic variants) and/or early markers of disease process. The validation of prediction models in populations distinct from those in which the models were developed is important. Advantage should be taken of specific informative models or studies for gene environment interactions available in Europe, such as the maternal diabetes protection model (lower incidence of the disease in children of mothers than fathers with type 1 diabetes) and migration studies.

## Goal 1.2. Develop overall type 2 diabetes prevention strategies



### Introduction and background

The rising prevalence of type 2 diabetes is a major public health problem. Although individually focussed approaches to prevention in high-risk sub-groups are effective, these need to be balanced by the development of strategies aimed at tackling this problem at a population level. Developing greater understanding of the determinants of population-level dietary and physical activity behaviour will change the focus away from individual approaches to prevention towards more integrated strategies that acknowledge the wider societal determinants of these lifestyles. This public health focus requires a multi-disciplinary approach bringing together strategies for understanding population behaviour together with the evaluation of planned and natural experiments and enhanced disease surveillance. Many of the issues prominent in these Milestones are also of relevance to Chapters 3, 4 and 7 (see also Milestones 3.2.02, 3.2.13, Goal 3.3).

### Milestone 1.2.01. Develop pragmatic methods for defining type 2 diabetes high-risk sub-groups

The identification of people at high risk of progression to type 2 diabetes is the first step in individualistic approaches to disease prevention. Multiple potential approaches have been developed, using information that ranges from simple routinely available data to more complicated risk prediction models that require the acquisition of different levels of data from individuals identified as potentially at risk. The trade-off between enhanced prediction from the collection of more detailed information and the proportion of the target population in whom information is available has not been adequately defined. This is a particular issue when sub-groups of the population at high risk are over-represented among the non-responders. Future studies should compare the programmatic characteristics of risk prediction strategies as used in real-life population settings rather than simply the test performance among those who respond.

**Milestone 1.2.02. Develop new therapeutic approaches to type 2 diabetes prevention**

Future preventive interventions aimed at individuals at high risk for type 2 diabetes may include lifestyle change as well as pharmaceutical agents that target specific pathways in the disease process. These interventions will not be a product of epidemiological investigations but rather those based on basic science and are thus described elsewhere in this strategic plan (see also Goals 2.1-2.4). However, these new interventions provide an important input into the development of future individualised prevention strategies.

**Milestone 1.2.03. Define individual determinants of lifestyle behaviour**

There are diverse models that explain differences in lifestyle behaviour between individuals, but the extent to which such models form an appropriate theoretical framework on which to base interventions is unclear. Future studies of determinants of lifestyle behaviours, such as physical activity and dietary intake, should combine prospective designs, objective assessment of behaviour and a mix of potential psychological, social and biological determinants.

**Milestone 1.2.04. Develop individual lifestyle behaviour change interventions**

The efficacy of lifestyle behaviour change interventions in the prevention of type 2 diabetes has previously been demonstrated. The development of intervention programmes that are cheap and feasible in everyday clinical practice along with appropriate training and implementation strategies is a critical next step. The effectiveness of these programmes will need to be demonstrated in a real-life setting (see also Milestone 4.2.04).

**Milestone 1.2.05. Evaluate pragmatic individual-level interventions for type 2 diabetes prevention**

Previous studies have demonstrated the efficacy of individually focussed lifestyle and pharmacological therapy on risk of progression to diabetes. There is a need for studies of the effectiveness of pragmatic interventions that can be applied in real-life settings in high-risk population sub-groups defined using methods that are feasible in clinical practice. Such studies should not only investigate the impact of preventive interventions on risk of progression to type 2 diabetes but also should evaluate impact on the major clinical complications of type 2 diabetes, particularly the occurrence of cardiovascular disease events.

**Milestone 1.2.06. Understand societal determinants of dietary and physical activity behaviour**

The development of broader models of dietary and physical activity behaviour taking into account not only individually focussed factors but also wider societal determinants is an important step in understanding behaviour at the population level as the foundation for appropriate public health strategies. Information on these wider determinants is available in the United States and Australia but is sparse in Europe. Studies that overlay information about potential collective factors on information about objectively assessed individual behaviour will be efficient but need to include large numbers of participants to be appropriately powered and to have sufficient heterogeneity in the wider societal determinants.

**Milestone 1.2.07. Develop collective behaviour change interventions**

The acquisition of information about the wider determinants of dietary and physical activity behaviour may produce opportunities for the development of interventions aimed at modifying these determinants. It is likely that such planned public health interventions would be developed with the aim of impacting on the proximal behaviours rather than the more distal clinical outcomes.

**Milestone 1.2.08. Develop systems of early identification of natural experiments**

Many relevant large-scale interventions that could impact on dietary and lifestyle behaviour are not developed specifically for that purpose, are implemented with a timetable that is driven by issues beyond the health sector and are thus not amenable to evaluation by the traditional medical model of the randomised controlled trial. However, these policy or infrastructure interventions are potentially highly relevant to type 2 diabetes prevention. This form of intervention is termed a natural experiment, and examples would include major transport infrastructure developments, which are designed for the purpose of influencing transportation behaviour but have much wider impacts on health-related behaviours. These natural experiments can be evaluated, but one critical issue is the early identification of the opportunity for evaluation so that there can be an appropriate period of study development and method testing, and pre-intervention data collection.

**Milestone 1.2.09. Evaluate collective interventions on lifestyle behaviours**

Information on the effectiveness of population approaches to change dietary and physical activity behaviour is limited. Studies aimed at evaluating planned developments of population-level

interventions or, alternatively, natural experiments should be encouraged. It is unlikely that such interventions will be amenable to evaluation by traditional randomised controlled designs so alternative approaches are required.

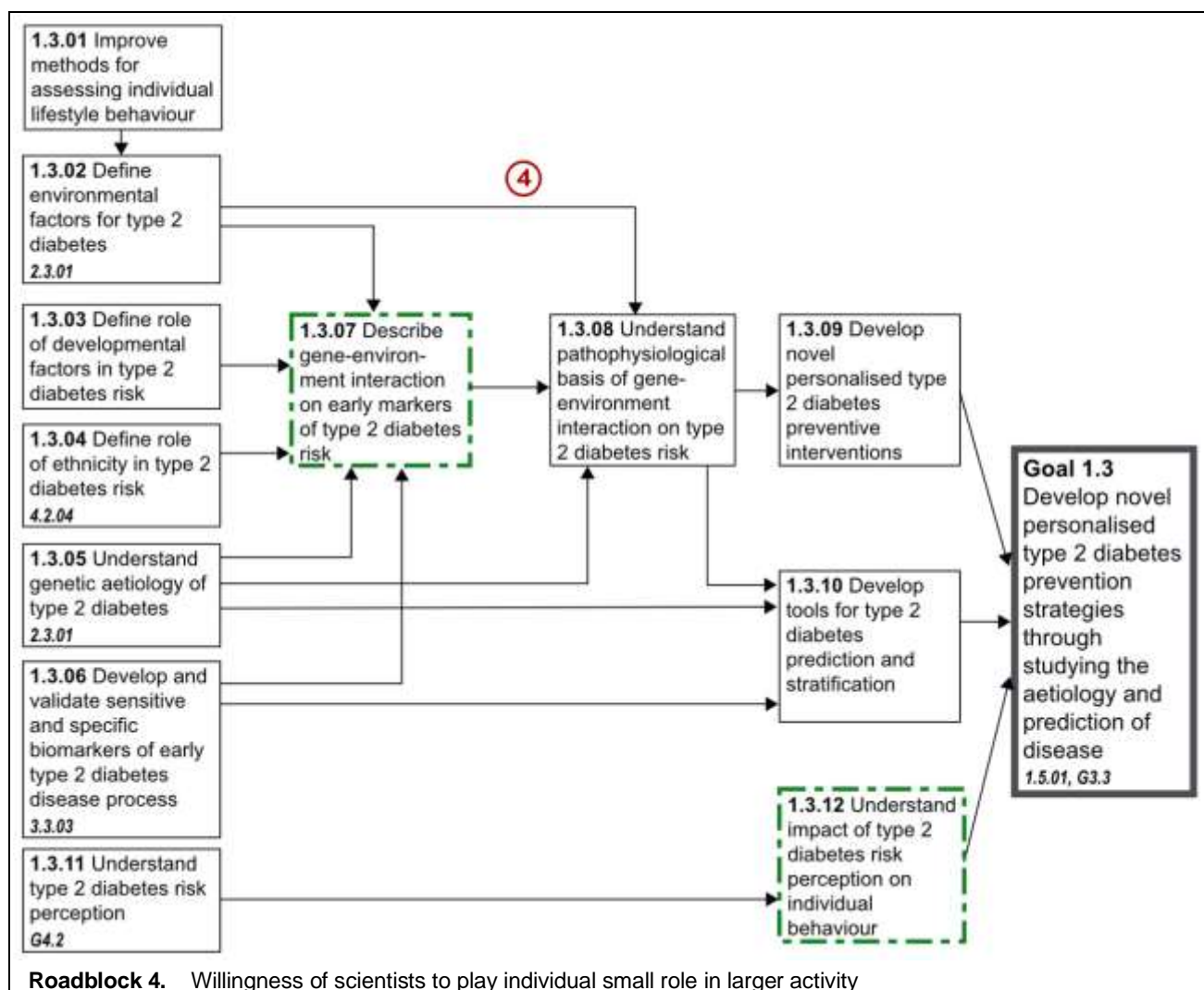
**Milestone 1.2.10. Model impact of population strategies on type 2 diabetes risk**

The outcome of interest in many evaluations of population-based interventions is likely to be the impact on the lifestyle behaviour rather than disease risk. In order to estimate the impact of such interventions on health outcomes, public health modelling will be required to quantify the extent to which such interventions will impact on the incidence of diabetes and its complications.

**Milestone 1.2.11. Define appropriate balance between high-risk and population approaches to type 2 diabetes prevention**

A balanced approach is required combining individually focussed high-risk approaches with collective population-based strategies. It is not known how to determine the balance between the investments in these two strategies. The evidence of the impact of individually focussed interventions is strong as such interventions are amenable to evaluation by randomised controlled trials. By contrast, the evidence for population-level approaches is relatively weak but these have the potential for the greater impact on the public health burden of diabetes. The development of public health models capable of synthesising data on cost-utility from individual and population approaches to prevention would be an important step in the process of informing health strategy.

## Goal 1.3. Develop novel personalised type 2 diabetes prevention strategies through studying the aetiology and prediction of disease



### Introduction and background

The variation in the prevalence of type 2 diabetes around the world suggests that this disease arises from an interaction between innate susceptibility (arising from genetic and/or early developmental programming) and potentially modifiable environmental factors which include diet and physical activity behaviours and socioeconomic position. Progress has been made in defining the association of common genetic variants with diabetes, but little is yet known about the interaction of these variants with lifestyle behavioural factors. Future work will determine the role of rare variants, copy number variation and epigenetic factors in determining diabetes risk. The use of this genetic and epigenetic understanding to describe the different pathways leading to disease will produce opportunities for sub-classifying this disorder and potentially for moving away from non-specific

strategies to a more individualised approach to prevention (see also Milestone 1.5.01, Goal 3.3).

### Milestone 1.3.01. Improve methods for assessing individual lifestyle behaviour

The traditional assessment of diet and physical activity in epidemiological studies by self-report has demonstrated that these factors are broadly important. However, these methods are not sufficiently precise to allow investigation of the details of association nor do they allow examination of gene-lifestyle interaction. The development and validation of novel and feasible objective methods for assessing these factors in large-scale epidemiological studies is a priority.

#### **Milestone 1.3.02. Define environmental factors for type 2 diabetes**

The overall association between dietary factors and physical activity with incident type 2 diabetes has been demonstrated in prospective studies. However, because of the imprecision of the measurement instruments used, there is much uncertainty about the detail of these associations, specifically concerning dose-response issues and the specification of which aspects of these complex exposures are most closely associated with diabetes risk. Future studies are needed to describe the detail of the association of objectively measured behavioural lifestyle factors with diabetes risk. This is of importance when converting epidemiological data into targets for either individual or public health prevention.

#### **Milestone 1.3.03. Define role of developmental factors in type 2 diabetes risk**

The overall association of early life factors with future risk of type 2 diabetes has been demonstrated. Epidemiological uncertainties remain about the timing of growth restriction in relation to birth and the role of rapid infant weight gain, and the mechanisms that underlie these associations.

#### **Milestone 1.3.04. Define role of ethnicity in type 2 diabetes risk**

There are clear and marked ethnic differences in risk of type 2 diabetes. However, the extent to which such variation is attributable to genetic, developmental or lifestyle behavioural differences between ethnic groups is unclear. It is also unclear whether ethnic differences in risk are affected by economic and social factors. Studies aimed at resolving these issues will need to utilise objective assessment of lifestyle behaviours because of between-population differences in bias using self-report methods. Migration leading to forced and rapid alterations in lifestyle behaviours must also be taken into account (see also Milestone 4.2.04).

#### **Milestone 1.3.05. Understand genetic aetiology of type 2 diabetes**

There has been considerable progress in identifying the association of common variants with type 2 diabetes. Future research is needed to determine the role of rare variants, copy number variation and epigenetic factors in determining diabetes risk.

#### **Milestone 1.3.06. Develop and validate sensitive and specific biomarkers of early type 2 diabetes disease process**

The ability to describe the interaction between different exogenous and innate factors in the aetiology of diabetes would be greatly enhanced by the availability of sensitive and specific biomarkers of the type 2 diabetes disease process. While there

are a variety of markers of insulin sensitivity, biomarkers of beta cell number, function and dysfunction are poorly specified, relatively imprecise, and difficult to apply in large-scale studies. The development and validation of new markers of this process are a priority. This Milestone is similar to that discussed in Goal 3.3, which focuses on type 2 diabetes risk prediction.

#### **Milestone 1.3.07. Describe gene-environment interaction on early markers of type 2 diabetes risk**

The identification of common genetic variants that are reproducibly associated with type 2 diabetes makes it possible to investigate how these variants are associated with disease risk. Such studies need to be large and ideally to employ objective assessment of important but difficult to measure lifestyle factors. It is possible that gene-lifestyle interaction may obscure the main genetic effects, and therefore as an alternative approach to starting with loci previously proven to be associated with diabetes, studies of gene-lifestyle interaction that utilise discovery approaches, such as genome-wide analysis, are desirable. Such studies need to be large and to employ strategies for a primary analysis and replication approach.

#### **Milestone 1.3.08. Understand pathophysiological basis of gene-environment interaction on type 2 diabetes risk**

The detection of combined effects of genetic and lifestyle factors may potentially lead to opportunities for disease prediction and targeted prevention. However, such knowledge may also lead to the investigation of the pathophysiological pathways underlying these interactions, which may, in turn, lead to the development of novel interventions.

#### **Milestone 1.3.09. Develop novel personalised type 2 diabetes preventive interventions**

Progress in understanding how genetic, developmental and lifestyle behavioural factors operate together to increase diabetes risk presents the potential for the development of novel personalised type 2 diabetes preventive interventions. The impact of these interventions not only on progression to diabetes but also on clinically relevant outcomes, such as cardiovascular events, should also be assessed. Particular attention should be given to the evaluation of the long-term impact of established and cheap glucose-lowering therapies that are unlikely to be assessed in industry-funded trials.

#### **Milestone 1.3.10. Develop tools for type 2 diabetes prediction and stratification**

Progress in understanding how genetic, developmental and lifestyle behavioural factors

operate together to increase diabetes risk also presents the potential for developing tools to better predict future type 2 diabetes and potentially to stratify at-risk individuals into sub-groups who might potentially benefit from different interventions. New or existing tools need to be evaluated in terms of their cost and performance (sensitivity and specificity) in the context of the programme in which they will be utilised, therefore taking into account the important issues of feasibility and the proportion of the at-risk population in whom information can be obtained.

#### **Milestone 1.3.11. Understand type 2 diabetes risk perception**

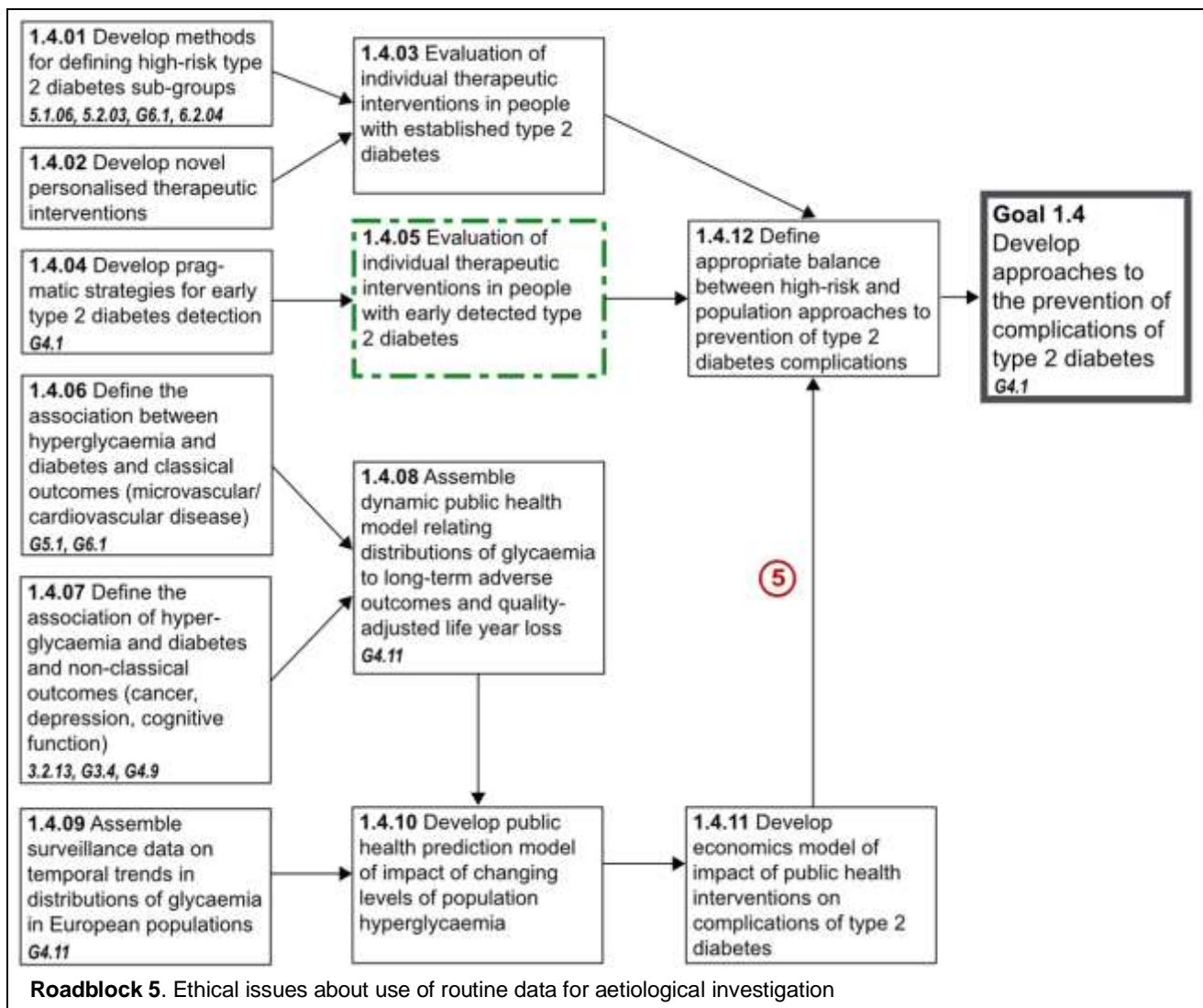
The quantification of risk is only one step in the process of using that information in a preventive setting. Greater understanding is required about

how individuals at risk of diabetes in different cultural and social settings throughout Europe perceive risk of diabetes (see also Goal 4.2).

#### **Milestone 1.3.12. Understand impact of type 2 diabetes risk perception on individual behaviour**

The impact of presenting individuals who are at risk of diabetes and who perceive that risk differently with different forms of information about the quantitative nature of their risk (relative or absolute) and the degree to which that risk is modifiable or fixed is unknown. Ideally, studies would go beyond the impact of changing risk perception on theoretical intention to change behaviour to the use of objectively assessed lifestyle change as the outcome.

## Goal 1.4. Develop approaches to the prevention of the complications of type 2 diabetes



### Introduction and background

Previous randomised controlled trials in people with type 2 diabetes have demonstrated that many of the complications of diabetes are preventable. However, all such therapies are generally applied to all people with diabetes with no current understanding about how interventions might be tailored to the individual.

Developments in understanding the genetic basis of complications and the response to therapy will increase ability to tailor therapeutic interventions. While understanding of the role of diabetes and the underlying state of hyperglycaemia in determining risk of micro- and macrovascular risk is reasonably well established, the role of these factors in other clinical outcomes, such as cancer and cognitive function, is less clear. The development of public

health models that estimate the likely impact on all health outcomes of changes in the population distribution of glucose levels is important as it will inform the development of public health strategies to deal with this issue. Such strategies need to create a balanced view of the impact of approaches that target interventions only on people with established disease with alternative ones aimed at the entire population. This necessitates public health modelling as such information will not be obtained from individual clinical trials. In turn, this may require the use of routinely collected clinical, demographic and other data, and the possibility of linkage of databases established for other purposes (see also Goal 4.1).

**Milestone 1.4.01. Develop methods for defining high-risk type 2 diabetes sub-groups**

There are a number of different methods for defining individuals and groups at high risk of the development of the complications of type 2 diabetes. Research to understand the genetics of the specific complications of diabetes and response to therapy would allow stratification of risk (see *also* Milestones 5.1.06, 5.2.03, 6.2.04 Goal 6.1)

**Milestone 1.4.02. Develop novel personalised therapeutic interventions**

Enhanced understanding of the pathophysiological processes underlying the development of complications and the differential response to interventions between individuals would lead to the development of novel personalised therapeutic interventions that can be applied to specific sub-groups of people at risk of the complications of type 2 diabetes.

**Milestone 1.4.03. Evaluation of individual therapeutic interventions in people with established type 2 diabetes**

Newly developed individual therapeutic interventions will need to be evaluated in clinical trials that employ these interventions in settings where people are sub-stratified prior to the delivery of the intervention. Such trials should use the occurrence of clinical disease as the endpoint or proxy outcomes that have been demonstrably shown to be acceptable intermediaries.

**Milestone 1.4.04. Develop pragmatic strategies for early type 2 diabetes detection**

Approximately 50 percent of people with detectable type 2 diabetes are clinically unrecognised. This has led for calls for diabetes early detection strategies to be implemented. There is a continuing need for the development of pragmatic strategies for the early detection of type 2 diabetes, including evaluation of approaches using routinely available data and those collected by direct approach to individuals (see *also* Goal 4.1).

**Milestone 1.4.05. Evaluation of individual therapeutic interventions in people with early detected type 2 diabetes**

The demonstration of the efficacy of therapeutic interventions to prevent complications applied to people with established diabetes cannot necessarily be generalised to those individuals whose diabetes is detected early by screening. It is possible that therapy may be more effective if implemented early, but the assessment of this possibility needs to take account of issues such as lead and length time bias. Trials of different approaches to reduction of complication risk in people with screen-detected diabetes are a priority.

**Milestone 1.4.06. Define the association between hyperglycaemia and diabetes and classical outcomes (microvascular /cardiovascular disease)**

Although much is known about the association of diabetes and hyperglycaemia with micro- and macrovascular risk, there are still uncertainties about the shape of the risk curves and the existence or otherwise of thresholds. Resolution of these uncertainties by meta-analysis of existing datasets is to be encouraged (see *also* Goals 5.1 and 6.1).

**Milestone 1.4.07. Define the association between hyperglycaemia and diabetes and non-classical outcomes (cancer, depression, cognitive function)**

It is increasingly apparent that hyperglycaemia and diabetes are associated with other disease endpoints beyond micro- and macrovascular disease. The association of glucose-related traits with cancer, depression, cognitive function (see *also* Milestones, 3.2.13 and Goals 3.4 and 4.9) and other disorders is of considerable interest and there are uncertainties about the magnitude of the association, the specificity (with specific cancer sub-groups), dose-response issue, direction of causality (particularly for affective disorders) and confounding by disease treatment. Analyses of observational cohort studies and trials to address these issues are a priority.

**Milestone 1.4.08. Assemble dynamic public health model relating distributions of glycaemia to long-term adverse outcomes and quality-adjusted life years (QALY) loss**

The collection of information about the association of hyperglycaemia with health outcomes of all causes and of measures of health utility (such as QALYs) provides the opportunity to create a universal public health model that can predict the total health impact of shifts in population glucose levels. Such a model needs to be based on population-level information about distributions of glycaemia in European populations (see *also* Goal 4.11).

**Milestone 1.4.09. Assemble surveillance data on temporal trends in distributions of glycaemia in European populations**

Although there are population estimates of the prevalence of diagnosed and undiagnosed diabetes in Europe, the use of these data in simulation models to estimate impact of glucose on health will underestimate that impact as it would not take account of the morbidity associated with moderate degrees of hyperglycaemia. Simulation modelling requires population estimates of the distribution of glucose levels in European populations and the

temporal trends in those estimates over time. Knowledge of the association of the impact on glucose levels of age, sex and body mass index (BMI) would allow projection of population distributions in the future.

**Milestone 1.4.10. Develop public health prediction model of impact of changing levels of population hyperglycaemia**

Fed by information about current and estimated future population distributions of glucose and the epidemiological associations of glucose levels with health outcomes, a public health prediction model could be developed to allow estimation of the likely impact of population shifts in glucose levels on longer term health outcomes.

**Milestone 1.4.11. Develop economics model of impact of public health interventions on complications of type 2 diabetes**

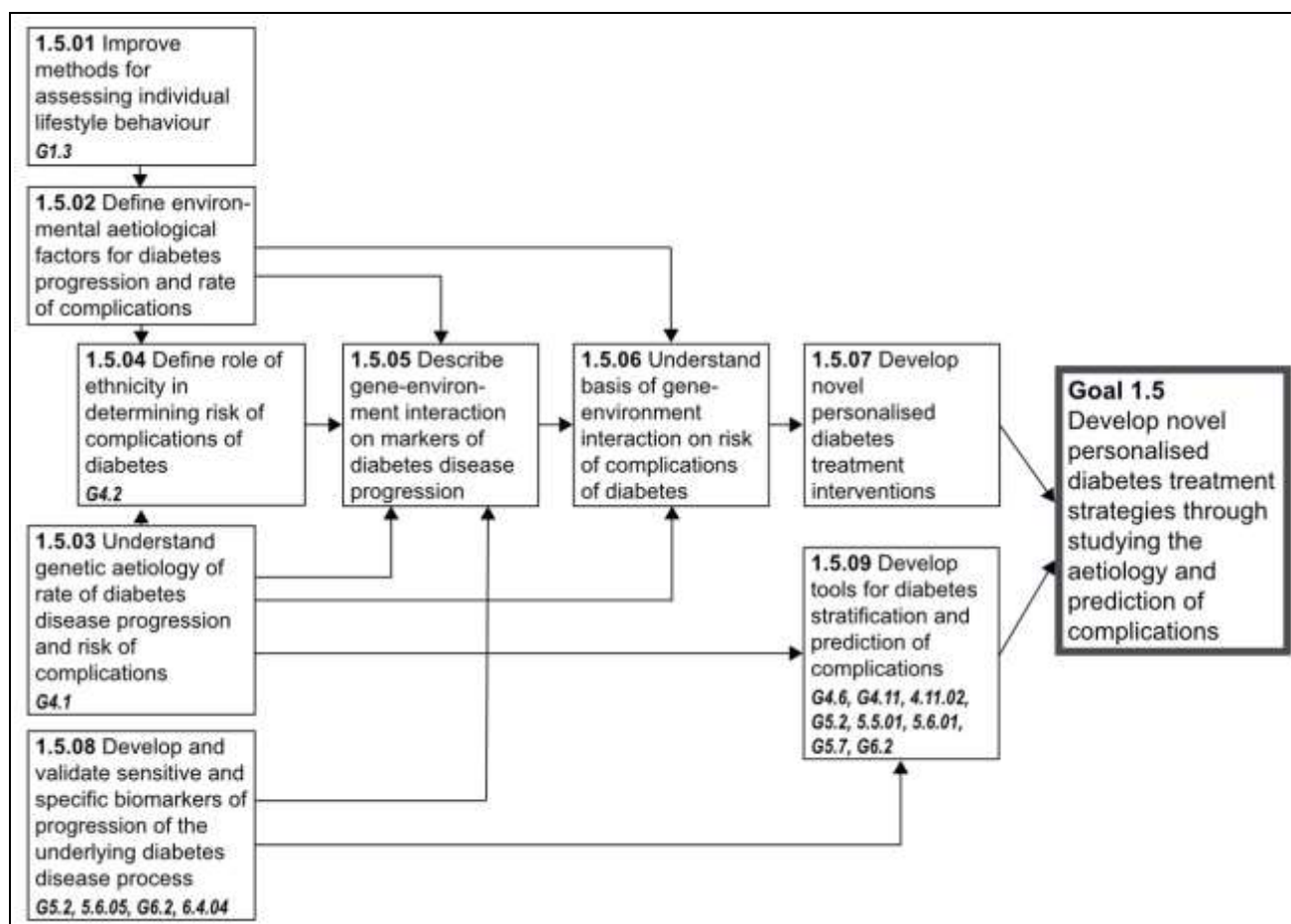
A public health prediction model could be further developed to allow for the estimation of the impact

of health outcomes of population-level strategies to shift glucose levels. Such a modelling exercise needs to include information about the costs of such population interventions to allow for the calculation of expected cost-utility.

**Milestone 1.4.12. Define appropriate balance between high-risk and population approaches to prevention of type 2 diabetes complications**

Health strategists in European countries require cost-utility public health models developed under Milestone 1.4.11 alongside more traditional cost-effectiveness analyses from clinical trials in people with established and early-detected diabetes. This will inform strategic decisions about relative investment in population and high-risk approaches to prevention of the complications of diabetes. The use of such models, including deterministic and probabilistic sensitivity analyses, not only informs immediate health strategy decisions but can inform future research priorities as it identifies information that is currently uncertain or unknown.

## Goal 1.5. Develop novel personalised diabetes treatment strategies through studying the aetiology and prediction of complications



### Introduction and background

There is heterogeneity in the rate of change in the underlying pathophysiological processes that are driving hyperglycaemia among people with established diabetes. This heterogeneity may be explained by genetic, developmental and environmental factors. Understanding these factors could lead to targeting of therapy at these specific pathways, to individualised treatment and improved health outcomes.

### Milestone 1.5.01. Improve methods for assessing individual lifestyle behaviour

As in the study of gene-lifestyle interaction on risk of progression to diabetes (see also Goal 1.3), the study of factors impacting on the risk of the complications of diabetes is highly dependent upon the development and validation of methods for objectively assessing individual lifestyle behaviours.

### Milestone 1.5.02. Define environmental aetiological factors for diabetes progression and rate of complications

The pathophysiological processes underlying diabetes (such as impaired beta cell function) are known to develop both before and after disease recognition and are not generally impacted upon by existing therapy (see also Chapter 2. Islets). There is however heterogeneity among individuals in the rate of decline of these factors and also in the likelihood of development of complications given a specific level of hyperglycaemia. Analysis of carefully characterised patient cohorts may identify the environmental aetiological factors associated with progression.

### Milestone 1.5.03. Understand genetic aetiology of rate of diabetes disease progression and risk of complications

The technological advances in genetics research make it possible to identify genetic factors associated with the risk of complications of diabetes. However, such studies are dependent

upon the availability of large and carefully characterised patient cohorts (see *also* Goal 4.1).

**Milestone 1.5.04. Define role of ethnicity in determining risk of complications of diabetes**

There is ethnic diversity in the likelihood of specific complications of diabetes, but this is poorly defined and its biological basis is not understood. Studies of large patient cohorts may help identify the explanations for ethnic diversity (see *also* Goal 4.2).

**Milestone 1.5.05. Describe gene-environment interaction on markers of diabetes disease progression**

Once the separate genetic and environmental factors associated with complications are identified, it will become possible to study interactions. In the first instance, this would be undertaken in studies with intermediate outcomes linked to the underlying diabetes disease process.

**Milestone 1.5.06. Understand basis of gene-environment interaction on risk of complications of diabetes**

If large-scale patient cohort studies are established, then with the information obtained from studies of gene-environment interaction on markers of the underlying diabetes disease progression, it will be possible to study how such factors interact on the risk of the specific complications of diabetes.

**Milestone 1.5.07. Develop novel personalised diabetes treatment interventions**

The improved ability to sub-group individuals according to the risk of the complications of diabetes and increased understanding about the pathophysiology of those complications lays open the possibility of developing novel personalised interventions.

**Milestone 1.5.08. Develop and validate sensitive and specific biomarkers of progression of the underlying diabetes disease process**

A prerequisite to the study of the interaction of genetic and environmental factors on markers of diabetes disease progression is the development and validation of appropriate markers that are sensitive and specific. Such markers would also be required in order to sub-group individuals and more accurately predict risk of complications (see *also* Milestones 5.6.05, 6.4.04, Goals 5.2, 6.2).

**Milestone 1.5.09. Develop tools for diabetes stratification and prediction of complications**

Tools are required that sub-group people or individually predict risk of the complications of diabetes. Such tools need to be evaluated in the real-life settings in which they would be used. They form the starting point for the application of individualised treatments within novel personalised diabetes treatment strategies, whose effectiveness would need to be demonstrated (see *also* Milestones 4.11.02, 5.5.01, 5.6.01, Goals 4.6, 4.11, 5.2, 5.7, 6.2).

## Roadblocks Chapter 1

### **Roadblock 1. Ethical challenges of preventive trials in children**

The peak age of incidence of type 1 diabetes is in childhood, and since most of the complications of diabetes are duration-dependent, preventive strategies for type 1 diabetes have the greatest potential for health benefit in younger people. However, this is the very group in which prevention, particularly with invasive interventions, is most challenging from an ethical perspective (see *also* Goal 4.6).

### **Roadblock 2. Reluctance of policymakers to evaluate policy**

Many of the major interventions that will impact on diabetes incidence operate at the policy level. In order to develop sustainable understanding of what is (and what is not) effective at this level there needs to be a greater emphasis on 'evidence-based policy making', a development analogous to the change in approach in clinical practice. The production of information about policy effectiveness needs a change in culture among policy makers to embrace the notion of evaluation, including, where possible, the introduction of not only observational approaches but also more experimental designs.

### **Roadblock 3. Intellectual schism between disease prevention and health promotion strategies**

The discussion about the balance between population- and individual-level approaches to the prevention of diabetes is essentially an example of the contrast between a health promotion model and one more clinically focussed on disease prevention. It is imperative that there is a harmonisation of these two approaches, which can sometimes be erroneously presented as mutually exclusive alternatives. In reality, there needs to be the development of a balanced approach but to achieve this there is an important initial roadblock of narrowing the intellectual gulf between them.

### **Roadblock 4. Willingness of scientists to play individual small role in larger activity and the need for methods for determining output of European scientists giving credit for collaboration in larger activities**

Many contemporary issues in epidemiology and particularly genetic epidemiology are not resolvable by single cohort studies and require the combination of data from multiple studies. This requires scientists to work together in large consortia where their individual chance of prominence is lessened, but the resulting scientific discoveries are more likely to be valid. This requires a cultural change from the scientists but may also need to be encouraged by research funders and academic employers who have, in the past, judged scientific performance on authorship position that could become an outdated method for large collaborative projects.

### **Roadblock 5. Ethical issues about use of routine data for aetiological investigation**

Many classical aetiological studies are based around special cohort studies designed for that purpose. Individuals provide informed consent and the information collected both at baseline and at follow-up is standardised and often obtained specifically for the cohort study without clinical care. The increasing ability to collect data in more standardised ways in routine clinical practice, and the ever-increasing need for greater sample sizes, coupled with the spiralling costs of the construction and maintenance of special studies, creates an imperative to utilise data routinely collected in everyday clinical practice for aetiological investigations. This creates many operational issues, but foremost amongst them is the challenge of using routinely collected data for such studies where it is not possible to obtain specific consent (see *also* Goal 4.1).