International Diabetes Federation
Europe

IDF EUROPE

Position Paper on Unmet Medical Needs for People Living with Diabetes

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idfeurope@idf-europe.org
www.idf-europe.org

INTRODUCTION

In November 2020, the **European Commission** released its **Pharmaceutical Strategy for Europe**[1] with four main objectives, one of which is to ensure access to affordable medicines and address unmet medical needs (UMN). One of the flagship initiatives foreseen in the Pharmaceutical Strategy was a revision of the basic pharmaceutical legislation, with a view to making this framework future-proof and innovation friendly.

IDF Europe supports the revision of the EU pharmaceutical framework, which represents a unique opportunity for people living with diabetes (PwD) to gain improved access to medicines, and to promote the need for their engagement at all stages of medicine development – from the definition of research needs through to engagement during the health technology assessment and reimbursement decision processes.

On April 26, 2023, the European Commission adopted a proposal for a new Directive and a new Regulation, revising and replacing the existing general pharmaceutical legislation[2] (GPL). The proposed Directive provides, inter alia, a **definition of what constitutes "Unmet Medical Needs"**. This definition is critical to ensure that PwD can benefit from the revision of the legislation, as the proposal also introduces the concept of variable incentives to reward innovation.

WHAT ARE THE UNMET MEDICAL NEEDS IN DIABETES PREVENTION AND CARE?

Diabetes management has one main objective – lowering the risk of acute and chronic diabetes-related complications, while maintaining the highest possible quality of life. This is achieved through controlling glycaemic levels and managing co-morbidities as well as through preventative approaches aiming to prevent organ and tissue damage. More information on diabetes, its various types, its impact on individuals, health systems and society, and diabetes-related complications can be found in Annex 1.

Despite significant advances over recent years in tools, medicines and technologies to support an improvement in diabetes management, **one in two PwD do not meet their blood glucose targets and/or develop diabetes-related complications**[3, 4, 5] **and there also remain many UMN with regard to prevention.**

To optimally manage their condition, PwD require access to:

- **Medicines** to help manage glycaemia and prevent the development of, and/or treat, diabetes-related complications such as cardiovascular diseases, diabetic retinopathy, nephropathy, neuropathy, etc.
- **Technologies** to support the administration of insulin and for glucose monitoring.
- **Self-management education** and overall health literacy.
- **Integrated, person-centred care**, incorporating not only the management of glycaemia but associated risk factors, comorbidities and diabetes-related complications.
- **Personalised care**, taking into consideration the social determinants of health and needs/preferences of PwD.

As well as ensuring that PwD across Europe have uninterrupted, affordable access to all of the above, at the right time, **more effective medicines, tools and technologies are also required. In the context of the revision of the pharmaceutical legislation, this position paper specifically examines the unmet medical needs relating to medicines**.

REVIEW OF CURRENT UMN FOR DIABETES

There are **numerous UMN regarding treatment and prevention for children and adults living with Type 1 and Type 2 diabetes, as well as other types of diabetes**. These urgently require an acceleration of scientific research and innovations.

Prevention

In Type 1 Diabetes (T1D), a major breakthrough occurred in 2022 with the approval of an immunomodulatory drug to delay the onset of stage 3 T1D in some high-risk individuals. However, more research is needed to broaden the range of preventive agents and address the side effects of the existing treatment. Additionally, identifying individuals at risk of developing T1D remains a challenge, with autoantibody testing being the primary method currently used.

In Type 2 Diabetes (T2D), lifestyle modifications can be effective but are difficult to achieve and sustain. Recent studies have shown that pharmacological interventions, along with lifestyle changes, can substantially improve the prevention or delay the onset of T2D in some high-risk groups. However, **further exploration is needed to optimise these approaches and identify other prevention strategies**.

Cure

The development of a cure is a critical UMN for both T1D and T2D. For T1D, a cure would restore the body's ability to produce insulin naturally. In T2D, a cure would address insulin resistance and the progressive decline in insulin-producing cells (β-cell) function and mass. Extensive research is necessary to achieve these goals.

Management/Treatment

While advances in insulin therapies for T1D, such as insulin analogues, have improved diabetes management, many people living with T1D struggle to reach their glycaemic target goals and develop acute or chronic diabetes-related complications. **Exploring alternative insulin administration routes, such as the intestinal or oral route, need to be further evaluated and expanded**, as they could enhance diabetes management. **ISLET transplantation and stem cell therapy**, which could restore the body’s ability to produce insulin **are also promising new approaches. Meanwhile, more research needs to be done on agents offering cardio-renal protection for people living with T1D**, which are often still only prescribed off label.

In T2D, new classes of therapeutic agents have shown promise in simultaneously managing blood glucose levels as well as protecting various organs from diabetes-related complications. Interestingly, these treatments were initially developed for their ability to lower blood glucose rather than for organ protection.

However, further investigation is required to determine optimal usage and identify specific populations that would benefit the most from these treatments, as they differ depending on the specificities of diabetes-related complications.

Maturity Onset Diabetes in the Youth (MODY), the main form of monogenic diabetes, often gets misdiagnosed as T1D or T2D and hence, wrongly treated. Treatment has not been very well studied and therapeutic options for MODY are not well-established, and **more research is needed in this field**.

	PREVENTION	CURE	MANAGEMENT/ TREATMENT
TYPE 1 DIABETES (T1D)	Broadening the spectrum of agents for the prevention and/or delay of T1D onset	Developing a cure to restore insulin production	Advancing insulin therapies
	Addressing side effects of preventive agents		Exploring alternative insulin administration routes
	Improving screening to identify people at risk of developing T1D		Researching the use of currently off-label medications for agents preventing complications
TYPE 2 DIABETES (T2D)	Optimising pharmacological interventions	Developing a cure to address insulin resistance and insulin production decline	Optimising the use of new classes of therapeutic agents for blood glucose control and the prevention of complications
	Identifying other prevention strategies		
MONOGENIC DIABETES	Improving diagnosis		
	Identifying and establishing therapeutic options		
	Expanding research in the field		

Table 1: Unmet Medical Needs for People Living with Diabetes

A more detailed overview of the UMN in T1D, T2D and monogenic diabetes can be found in Annex 2.

IDF EUROPE'S PROPOSED DEFINITION OF UNMET MEDICAL NEEDS

Article 83 of the proposed Directive specifies that:

A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

Numerous UMN in diabetes persist, encompassing not only treatment and disease prevention but also the quality of life and health outcomes that current medications offer.

In light of this, and based on the proposed Commission's definition, **IDF Europe considers the proposed definition to be inadequate and suggests that an adequate definition might be as follows**:

A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a progressive, high-impact, life threatening or severely debilitating disease and the following conditions are met:

a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high burden;

b) the use of the medicinal product results in:
- *a meaningful reduction in disease morbidity or;*
- *an improvement in the course of the disease and/or a reduction in mortality for the relevant patient population or;*
- *an improvement in the diagnosis, prevention or delaying of the onset of the disease and/or its complications or;*
- *improvements in overall quality of life and/or health outcomes.*

We call on the co-legislators to adapt the definition of UMN in the Directive as suggested above, to allow for an appropriate consideration of the numerous UMN still existing in diabetes.

In addition, we call on the EU institutions to define the notion of UMN (and the set of criteria therein) in a process of collaborative deliberation that has the perspectives of citizens at its heart, and to ensure that patient organisations are included as partners – and recognised as such in the Directive – in this process.

ABOUT IDF EUROPE

IDF Europe is the European chapter of the International Diabetes Federation (IDF). We are an umbrella organisation representing 73 national diabetes organisations in 46 countries across Europe. We are a diverse and inclusive multicultural network of national diabetes associations, representing both PwD and healthcare professionals. More information can be found on our website.

ANNEX 1: BACKGROUND ON DIABETES

What is diabetes?

Diabetes is a group of chronic metabolic disorders characterised by elevated levels of blood glucose. Diabetes is a highly complex condition, whose onset involves different mechanisms, facilitated by risk factors. The World Health Organization recognizes more than 10 forms of the disease[6].

Type 2 diabetes is the most common form, which develops due to a combination of unmodifiable, genetic, physiological, environmental and modifiable, behavioural risk factors. In Type 2 diabetes, the body may not produce enough insulin and/or not be able to use the insulin it produces effectively. As a result, glucose cannot get into the cells, causing glucose levels in the blood to rise, potentially creating life-altering complications. Blood glucose levels in people living with T2D can be managed in a variety of ways, with some oral medications sometimes associated with lifestyle programmes, and for some people, through administering insulin.

Type 1 diabetes is an auto-immune disease, whereby the body destroys insulin-producing cells (β-cells) in the pancreas. Living without insulin is impossible, so a person living with Type 1 will receive insulin through injections (generally, in Europe, through insulin pens) or via an insulin pump.

Gestational diabetes (GDM) is a form of diabetes which develops during pregnancy. It is managed through a mix of diet, exercise, and as required, appropriate medication (insulin or oral medication). Once the mother has given birth, diabetes disappears, but the mother and baby are at a higher risk of developing T2D later in life.

Many **other, much rarer, forms of diabetes** exist, of which the most frequent is monogenic diabetes.

What is the impact of diabetes?

Diabetes is a major health burden on individuals, health systems and society. Across Europe, more than **61 million people** live with diabetes (32 million in the EU), forecast to increase by 2030 to 67 million and 33 million, respectively; direct **European expenditure** on diabetes stood at **€147.9 billion** (€104bn in the EU) in 2021; and it is the **root cause of several other non-communicable diseases (NCDs).**

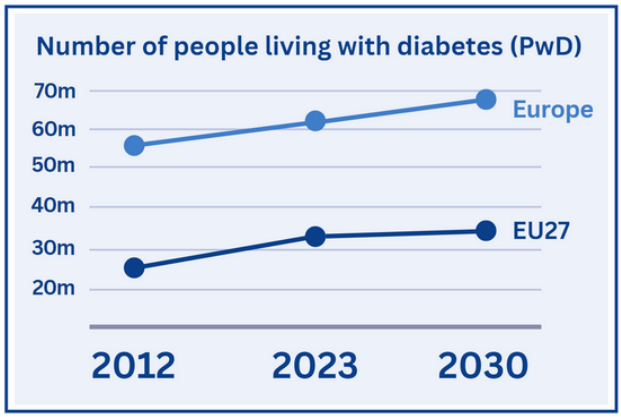


Figure 1: Diabetes Prevalence [7]

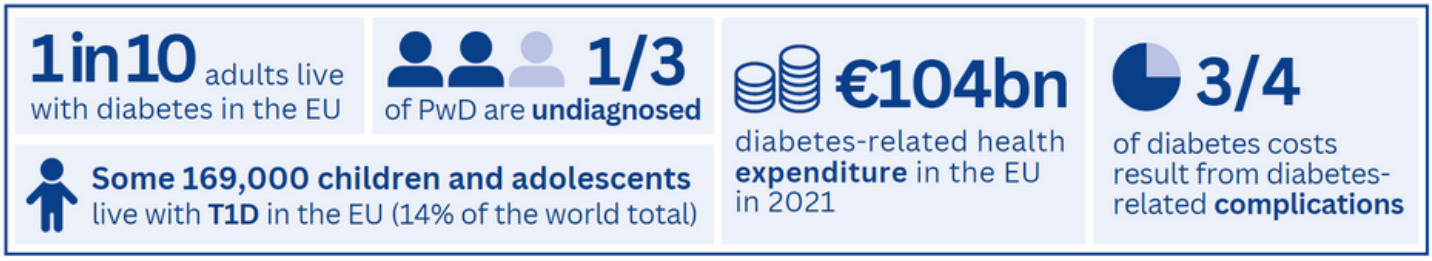
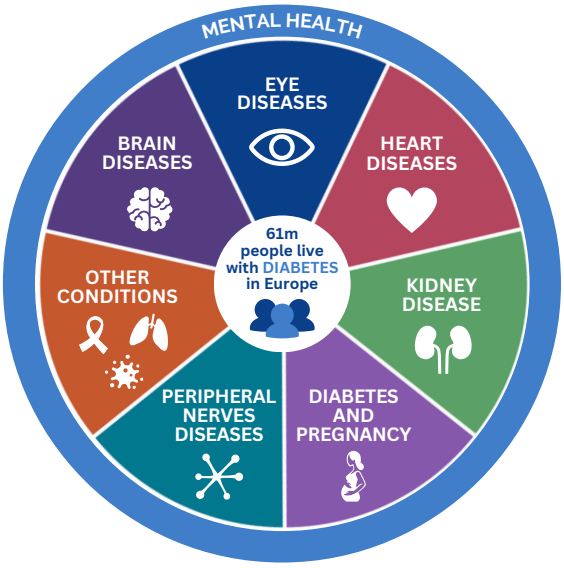
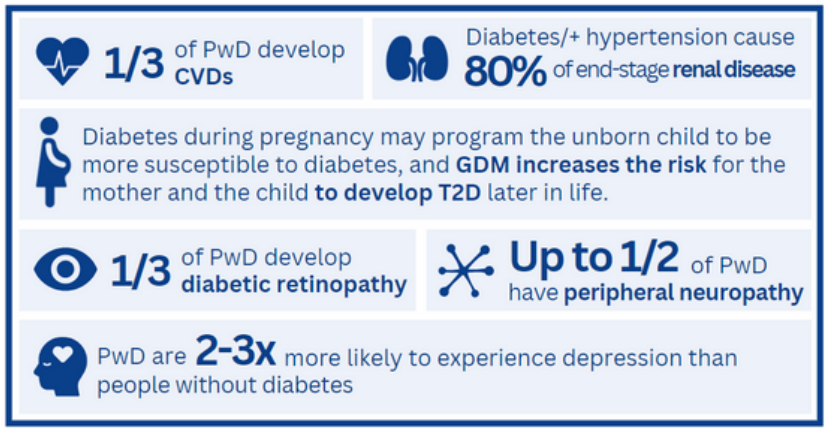


Figure 2: Diabetes Prevalence; Undiagnosed Diabetes; and Diabetes-related Expenditure

Despite significant advances in treatment options, **diabetes management remains hard, relentless and all-consuming**. PwD and/or their relatives/carers need to take care of their diabetes seven days a week, 24 hours a day, to prevent the development of life-altering diabetes-related complications. Despite strenuous management, **many PwD do not meet their health outcome targets and many develop diabetes-related complications** such as cardiovascular diseases (CVD), diabetes retinopathy and chronic kidney disease. **Less visible and front-of-mind, but no less damaging, are mental health-related complications.** Besides the mental stress of those potential long-term complications, the everyday routine of treating a life-long condition for a minimum of 20-30 and potentially, up to 80+ years, can become overwhelming.





A detailed description of all diabetes-related complications can be found here.

Figure 3: Diabetes-related Complications: CVD [8]*, Kidney Disease* [9]*, GDM* [10]*, Diabetic Neuropathy* [11]*, Diabetic Retinopathy* [12]*, Mental Health* [13]

ANNEX 2: UNMET MEDICAL NEEDS IN DIABETES

Unmet needs in T1D

Prevention of T1D: preventative pharmacological interventions

2022 represented a major turning point for all people living with T1D, since for the first time, after 50 years of unsuccessful attempts, an immunomodulatory drug, was approved in the USA[14] for people with a high risk of T1D, to delay the onset of the disease. The medicine has been approved to delay the onset of stage 3 T1D in people aged eight years of age and older with stage 2 T1D. It has not been demonstrated to prevent the development of the disease though, only to delay its onset, while its cost-effectiveness also needs to be further established, as does its accessibility for broader use.

Stage 1	Stage 2	Stage 3
2+ autoantibodies	2+ autoantibodies	Clinical symptoms of T1D
Normoglycaemic	Dysglycaemia (from loss of functional β-cell mass)	

Table 2: T1D Development Stages [15]

There is therefore a **need for further research to broaden the spectrum of agents** enabling a significant pharmacological prevention/delay, and address the side effects of the currently approved medication, which may include lymphopenia (low white blood cells), skin and subcutaneous tissue disorders.

Alongside this, a key challenge to the prevention of type 1 diabetes is the **identification of the people who may be at risk of developing the disease**. For the time being, the only way of determining if somebody might be at risk is to test for autoantibodies. The only well-established risk factor is having a family history of type 1 diabetes, where the probability of developing diabetes ranges from 1 in 100 for children of women with Type 1 who gave birth after they were 25 to 1 in 4 for children whose both parents live with T1D[16].

Development of a cure for PwD

Perhaps the most critical unmet medical need for those people living with T1D is the **development of a cure**, which would help restore the body's ability to produce insulin naturally.

New molecules for more effective treatment of T1D and the prevention of diabetes-related complications

Advances in insulin therapies during the last two decades, including the development of insulin analogues as a result of basic research on the molecular level, have enabled a major step forward in improving diabetes management, decreasing glucose variability and reducing the risk of hypoglycaemia (low blood glucose levels).

Despite these advances, these therapeutic approaches have not yet enabled a complete achievement of therapeutic goals in the majority of PwD and the prevention/effective treatment of diabetes-related complications. As mentioned above, **up to half the PwD do not reach glycaemic target goals or develop diabetes-related complications**.

One of the reasons behind the failure to meet glycaemic targets/the development of diabetes-related complications is the **mode of administration of insulin through subcutaneous tissues**, rather than through the physiologic route (in the portal vein system, going first through the liver before reaching the systemic circulation). Efforts to administer insulin through the intestinal route or intraperitoneally have been explored in the past, but have not been very successful so far. These efforts need to be further evaluated and expanded, alongside potentially other ways of administering insulin (e.g., orally), because they will certainly help in better controlling diabetes.

Newer agents offering organ protection have also recently been developed, notably for use in people living with T2D, and are often prescribed off-label but **more research needs to be conducted on their use including potential side effects in people living with T1D**.

Unmet needs in T2D

Prevention of T2D: preventative pharmacological interventions

Lifestyle modification can help prevent T2D but has proven to be difficult to achieve and sustain. It was recently demonstrated that the administration of metformin or glucagon-like peptide 1 receptor agonists (GLP-1 RA), together with lifestyle modification, can substantially improve the prevention/delay of the onset of T2D in certain high-risk groups. Still, there are urgent unmet needs to explore the opportunities for the use of these or other approaches in T2D prevention.

Development of a cure for PwD

As with T1D, a critical unmet medical need for those people living with T2D is the **development of a cure**, which would address insulin resistance and the progressive decline in β-cell function and mass.

New molecules in the simultaneous treatment of T2D, its comorbidities and prevention of its complications

The research on the agents that might have a potential effect not only on blood glucose lowering but also on protecting other organs from diabetes-related complications has recently resulted in the **discovery and administration of new classes of therapeutic agents**.

Interestingly, these treatments were initially developed for their ability to lower blood glucose rather than for organ protection, which may or may not have taken place if a different research framework was in place.

However, there is still **a substantial need to investigate the optimal requirements for the use of these agents** in the reduction of obesity and protection from cardiovascular and renal complications, in order to define their optimal use and address the specificities of diabetes-related complications. It is especially important to investigate which populations might most benefit from their protective role against CVD, heart failure and nephropathy. Established CVD and nephropathy were defined very differently in the various studies conducted and the “high-risk” groups were also very heterogeneous in their risk factors’ composition. A better delineation of the people who really benefit from these medicines is needed.

Unmet needs in other types of diabetes

Treatment of monogenic diabetes

Maturity Onset Diabetes in the Youth (MODY) affects around 3-5% of PwD and is often misdiagnosed as T1D or T2D, and hence wrongly treated. But even after its correct diagnosis, its treatment has not been very well studied and, depending on the type of MODY (there are currently 14 different types recognised), therapeutic options are not well established. More research is needed in this field since the newer classes of medicines have shown promise in some studies[17].

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Our mission, in Europe, is to be the voice of people living with diabetes and engage with them and all stakeholders in creating a person-centred diabetes ecosystem within an informed and health promoting environment.

idfeurope@idf-europe.org

www.idf-europe.org

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