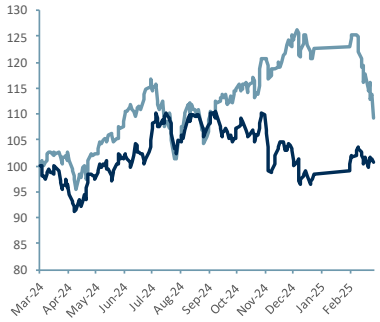
THEMATIC RESEARCH

Diabetes Treatment & Innovation



Price relative Nasdaq Comp (lighter line) vs. Nasdaq Biotech

Thursday, 13 March 2025

Thematic Sector
Biotechnology & Medical Research

Public Companies in Note	**% from 52 wk high**
NLS Pharmaceutics AG	91.3%
Sana Biotechnology, Inc.	75.6%
Tandem Diabetes	63.7%
Senseonics Holdings,	49.9%
CRISPR Therapeutics AG	48.0%
Hims & Hers Health, Inc.	44.5%
Teladoc Health, Inc.	42.3%
Dexcom, Inc.	42.0%
Novo Nordisk	40.9%
Tiziana Life Sciences Ltd	33.9%
Oramed	33.1%
The Kraft Heinz	20.5%
Kadimatsem Ltd	15.3%
Insulet Corporation	6.8%
Vertex Pharmaceuticals	6.5%
Eli Lilly	6.3%
Medtronic plc	2.7%
Abbott Laboratories	2.6%
Sanofi	2.5%

Healthcare Sector Research
NASDAQ Market Index

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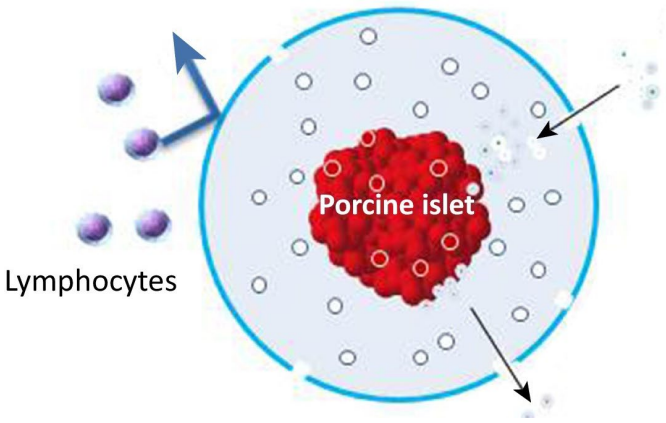
An Introduction to the Investment Opportunities

Diabetes mellitus, Type 1 (T1D) and Type 2 (T2D, 85-90% of cases), is a USD ~75bn global therapy market. Global economic costs of diabetes may exceed USD1 trn today and USD 450bn in the US, suggesting a pressing global health challenge. Diabetes is a chronic metabolic disorder characterized by high blood sugar levels. In 2024, consensus global estimates suggested there were ~800m adult diabetes sufferers. In 2021, according to the IDF there >530m sufferers globally. For 2027E we modestly forecast over 35m US T1D + T2D sufferers. According to the CDC in 2021 there were 29.4m US diagnosed diabetic sufferers. Undiagnosed diabetics could add 30-40% additional sufferers to hyper-developed economies, with better easier testing. Key diabetes growth drivers are aging demographics, sedentary lifestyles, and poor diets (read industrialized food products) and increasing obesity rates.

- Possibly 800m diabetes sufferers globally today and 1bn by 2034;
- ~30m US diabetes patients today;
- ~USD ~450bn direct and indirect healthcare costs today in the US;
- ~USD 75bn global therapy market today and 165bn by 2034E;
- An innovation wave for new therapies and curatives.



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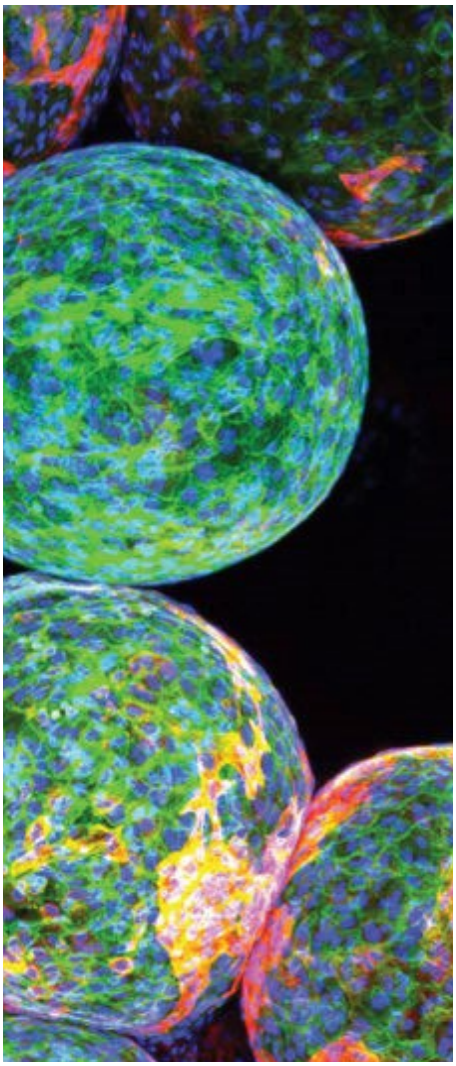
Microcapsules loaded with stem cell-derived insulin-producing cells retrieved after they had been transplanted into a mouse.
Daniel Anderson lab, Nature Medicine,
https://www.statnews.com/diabetes-cell-therapy/



The Global Diabetes Mellitus Landscape Differentiation - Type 1 vs. Type 2
Type 1 Diabetes (T1D) is an autoimmune condition requiring lifelong insulin therapy, T1D affects ~80m individuals globally. Despite being less prevalent than Type 2 diabetes, its management complexity presents significant market potential. Type 2 Diabetes (T2D), which comprises 85-90% of cases, may equate to 720m sufferers globally in 2024, is driven by insulin resistance and lifestyle factors leading to rising obesity rates. With its growing prevalence in low- and middle-income countries, T2D is a primary focus for innovation in terms of treatment, disease management and prevention.

US Diabetes Mellitus Landscape - Economic and Societal Burden - The economic costs of diabetes are direct and indirect. The direct expenses of medications, hospitalizations, outpatient visits, wound treatment and related medical supplies such as insulin pumps and the indirect costs of lost productivity. In the U.S. the American Diabetes Association (ADA) published a **direct cost estimate** of $306.6bn for 2022. Diabetes and its related conditions account for $1 in every $4 (25%) of the $1.24 trn spent on US healthcare (ADA, 2022). **Indirect economic costs** published in the Diabetes Care Journal in 2023, estimated by the ADA, total $106.3bn.

- $42.9bn - reduced workforce productivity.
- $22.0bn - diabetes-related absenteeism (missed workdays).
- $24.2bn - inability to work due to diabetes-related disability.
- $17.2bn Lost productivity due to premature mortality.
- $413bn – Total US economic burden estimate 2022 (direct+indirect costs).

As such, there is continuing demand and growing urgency for alternative solutions to 'insulin injections' that can or could alleviate the clinical and economic burdens of diabetes. Alternative solutions currently include GLP-1 receptor agonists (e.g. Ozempic, Wegovy, Mounjaro), SGLT2 inhibitors, beta cell regeneration and T1D immune therapies. Although early stage, the global cell and gene therapy market for diabetes are expected to surpass USD 5bn by 2030, driven by advancements in CRISPR for gene therapy and stem cell research.

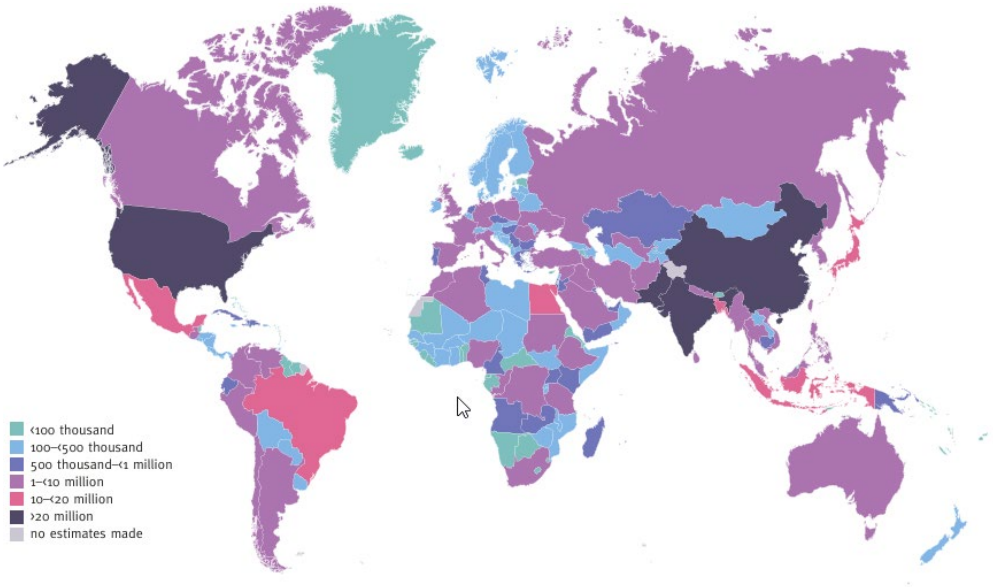
Investment Strategies

1. Growth-Oriented Approach - Focus on companies with strong pipelines in GLP-1 agonists, beta-cell therapies, and CGM devices. **2. Diversification** - Combine large caps e.g. Novo Nordisk with investigational pre-revenue stocks in cell therapy/digital health. **3. Thematic ETFs** - e.g. iShares Biotechnology ETF (IBB) or ARK Genomic Revolution ETF (ARKG) for diversified exposure to diabetes innovation.

Diabetes Biochemistry – An Introduction

Exhibit 1: **Diabetes by country - Adults (20-79) 2021 estimate**

The International Diabetes Federation (IDF) diabetes map here by country suggests that there were up to 10m diagnosed diabetes sufferers in the US in 2021. The US's CDC estimates that there were 29.4m sufferers in the US in 2021. Investors should note that we find in general that data estimate spreads for such a well defined and common condition are surprisingly wide and can vary in the range of 50%. Possible reasons include difference in definition, collection error and different statistical approaches. This map is best used to indicate relative prevalence/incidence rather than actual values.



Sources: International Diabetes Federation, Diabetes Atlas 2021 www.diabetesatlas.org

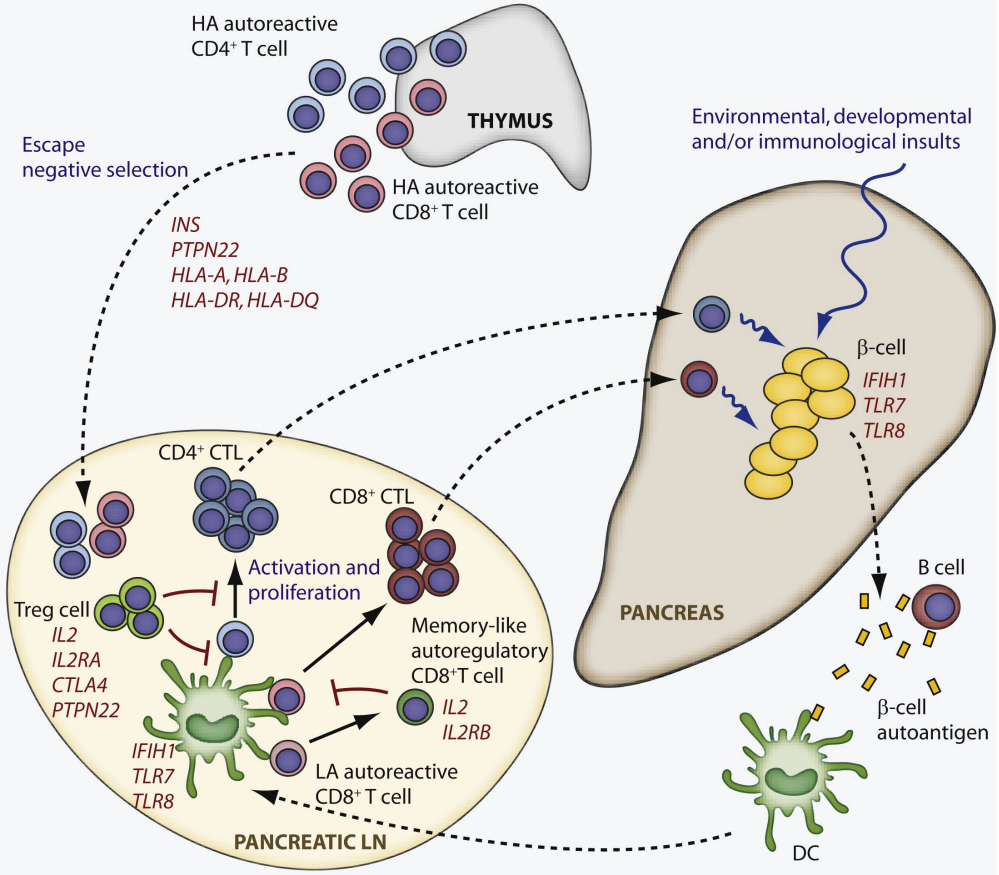
Diabetes mellitus, a disease of the pancreas and subsequently the liver, is a metabolic disorder characterized by chronic hyperglycemia (the level of blood glucose is consistently higher than normal) resulting from defective insulin secretion, insulin action, or both. Diabetes primarily manifests in two major forms - Type 1 diabetes (T1D) and Type 2 diabetes (T2D),

T1D and T2D have distinct pathophysiological mechanisms. Nevertheless, irrespective of the different etiologies, both T1D and T2D lead to complications that are the result of prolonged exposure to high glucose levels and affect multiple organ systems including eyes, kidneys, nerves and increased risk of cardiovascular disease.

T1D is associated with the destruction of insulin-producing beta cells by the immune system. T2D is associated with beta cell dysfunction leading to chronic insulin resistance.

Type 1 Diabetes (T1D) – The destruction of beta- cells. T1D is a multifactorial disease with an important genetic element and is generally thought of as an autoimmune disorder. In T1D, T-cell-mediated destruction of pancreatic β-cells leads to absolute (total) insulin deficiency. It is most commonly diagnosed in children and young adults, though it can develop at any age.

Exhibit 2: **T1D genes associated with T1D pathways**



Sources: The Long and Winding Road to Understanding and Conquering Type 1 Diabetes, Santamaria, Pere Immunity, Volume 32, Issue 4, 437 - 445

Pancreatic LN – pancreatic lymph nodes

HLA-DR & HLA-DQ (Human Leukocyte Antigen genes) genetic variants are most closely associated with T1D risk – they influence the immune systems ability to differentiate between self and non-self.

Treg cell – Regulatory T-Cell – help prevent autoimmune attack, when impaired attacks on insulin-producing beta cells man ensue.

LA autoreactive CD8+ T-cell – Latent Autoimmune (LA) – these cells are immune cells that in T1D mistakenly target and destroy insulin-producing beta cells.

HA autoreactive CD4+ & CD8+ T-cell – Human Antigen (HA) – immune cells that in T1D also mistakenly target and destroy insulin-producing beta cells. These cells ordinarily only destroy infected or dysfunctional cells.

CD8+CTL – Cytotoxic T- Lymphocyte (CTL) – ordinarily kill virus infected and cancerous cells. CD4+CTL help CD8+ cells fully differentiate into CD8+CTL cells.

DC – Dendritic Cell – in T1D, DCs present beta cell antigens to autoreactive T-cells triggering them to attack and destroy insulin-producing beta cells.

The T1D major susceptibility locus of genes maps to the HLA class II genes at 6p21, and accounts for 30%-50% of T1D risk. However, more than 40 non-HLA susceptibility gene markers have been identified. Non-MHC loci include insulin PTPN22, CTLA4, IL2RA and IF1H1.

Biochemical pathophysiology of T1D – The autoimmune destruction of pancreatic β-cells is initiated by both genetic abnormalities (e.g., HLA-DR3 and HLA-DR4 haplotypes) and environmental triggers (e.g., viral infections). CD4+ and CD8+ T-cells infiltrate the pancreas, leading to **apoptosis (destruction) of insulin-producing beta cells**.

The progressive **destruction of β-cells** results in absolute **insulin deficiency**, leading to unregulated hepatic (liver) glucose production, decreased glucose uptake by peripheral tissues, and excessive lipolysis (break down of fats through hydrolysis mediated by enzymes and water).

Ketogenesis and Diabetic Ketoacidosis (DKA) - the increase in lipolysis releases free fatty acids (FFAs), which are converted into ketone bodies (β-hydroxybutyrate and acetoacetate) in the liver.

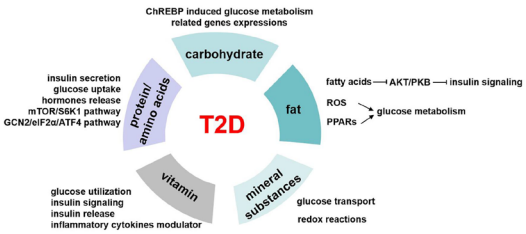
Excess ketones in turn lower blood pH, leading to diabetic ketoacidosis (DKA), a life-threatening condition characterized by metabolic acidosis, dehydration, and electrolyte imbalance, often characterized by accelerated heartbeat, confusion and fatigue and in turn alleviated by sodium bicarbonate, IV fluids and insulin.

T2D is associated with beta cell dysfunction leading to chronic insulin resistance due to defective insulin receptor signaling. T1D is associated with the destruction of insulin-producing beta cells by the immune system.

Type 2 Diabetes (T2D) - T2D is a metabolic disorder characterized by **insulin resistance and progressive β-cell dysfunction**. Unlike T1D, insulin is initially present, but diminished, leading to hyperglycemia. T2D is commonly associated with obesity, aging, and sedentary lifestyles. The biochemical pathophysiology of T2D is characterized by insulin resistance in peripheral tissues (muscle, liver, adipose) due to defective insulin receptor signaling.

Exhibit 3: **Insulin signaling - Fatty acids in T2D inhibit AKT/PKB**

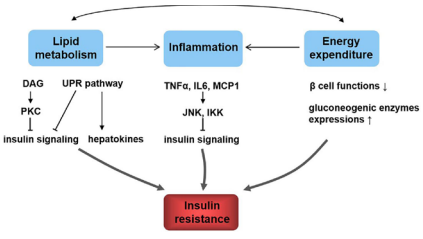
Insulin signaling - Fatty acids in T2D inhibit AKT/PKB which impairs insulin signaling



Sources: Front. Bioeng. Biotechnol., 15 Sep 20,Sec. Synthetic Biology Vol 8 2020 https://doi.org/10.3389/fbioe.2020.575442

In **adipose tissue**, excessive triglyceride accumulation increases secretion of inflammatory cytokines (TNF-α, IL-6) and adipokines (e.g., resistin, leptin, and reduced adiponectin), impairing insulin receptor function. In the **liver**, insulin resistance leads to increased gluconeogenesis, exacerbating hyperglycemia (raising blood glucose levels). **Pancreatic β-cell** dysfunction leading to chronic insulin resistance, which places stress on β-cells to produce more insulin (hyperinsulinemia). Over time, β-cells undergo lipotoxicity, glucotoxicity, and oxidative stress, leading to β-cell exhaustion and eventual insulin deficiency.

Exhibit 4: **Insulin resistance, lipid, energy, inflammation metabolism**



Sources: Front. Bioeng. Biotechnol., 15 Sep 20,Sec. Synthetic Biology Vol 8 2020 https://doi.org/10.3389/fbioe.2020.575442

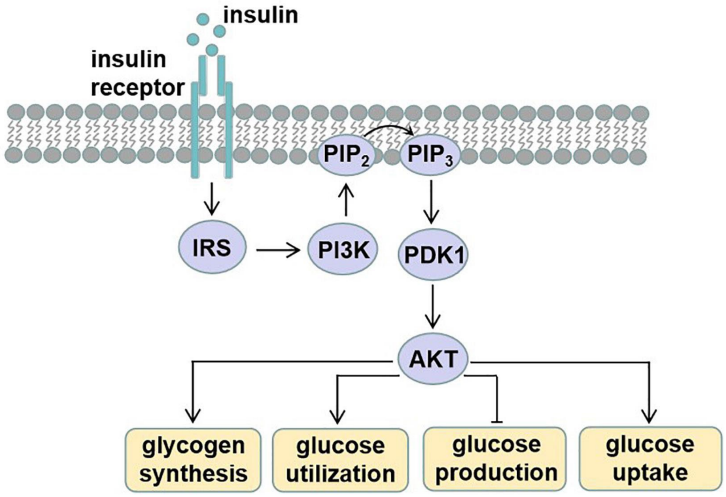
Role of Incretins - Incretin hormones such asGLP-1 (a glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide) enhance insulin secretion. In T2D, incretin effects are diminished which reduces postprandial (after eating) insulin release.

Exhibit 5: **Insulin mediation effect on glucose production**

Insulin mediates the production of glucose. In the liver insulin inhibits(stops or reduces) glucose production by suppressing hepatic glucogenesis (glucose production from non-carbohydrate sources) and glycogenolysis (breakdown of glycogen to glucose).

IRS – Insulin Receptor Substrate – protein that transmits signals from the insulin receptor.

PI3K – Phosphoinositide 3-Kinase – a key enzyme activated by IRS, and essential for the PI3K-Akt pathway and so the metabolic effects of insulin



Sources: Front. Bioeng. Biotechnol., 15 Sep 20,Sec. Synthetic Biology Vol 8 2020 https://doi.org/10.3389/fbioe.2020.575442

Activation of PI3K in Insulin Signaling - When insulin binds to its receptor, it triggers a signaling cascade that involves PI3K. Insulin binds to the Insulin Receptor (IR), a tyrosine kinase receptor. Once activated the Insulin Receptor phosphorylates insulin receptor substrate (IRS-1 and IRS-2). In turn IRS Recruits PI3K and activates it, leading to downstream signaling in which PI3K Converts PIP2 to PIP3.

Activated PI3K catalyzes the phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP_2) to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). In turn, PIP_3 as a secondary messenger, recruits Akt (Protein Kinase B, PKB) to the membrane and activates PDK1 (Phosphoinositide-dependent kinase-1), which in turn phosphorylates and activates Akt. **Akt is the major effector of insulin's metabolic actions**.

Downstream Effects of the PI3K-Akt Pathway - Once activated, Akt exerts multiple effects on glucose metabolism, lipid metabolism, and cell survival. **1. Akt stimulates** GLUT4 (glucose transporter 4) translocation to the plasma membrane in muscle and adipose tissue, which allows **glucose uptake from the bloodstream** into the cells, lowering blood glucose levels. **2.** In **glycogen synthesis** **Akt phosphorylates** and inactivates glycogen synthase kinase-3 (GSK-3), which removes inhibition from glycogen synthase, leading to increased glycogen storage in the liver and muscle.

3. In **lipid metabolism** **Akt inhibits** hormone-sensitive lipase (HSL), reducing lipolysis and preventing excess free fatty acids from contributing to insulin resistance.
4. In the **suppression of hepatic glucose production** **Akt inhibits** gluconeogenesis by suppressing key gluconeogenic enzymes like PEPCK (phosphoenolpyruvate carboxykinase) and G6Pase (glucose-6-phosphatase). This helps prevent excessive glucose release by the liver. **5.** In **cell growth and survival** **Akt phosphorylates and inhibits** pro-apoptotic proteins (e.g., BAD, FOXO1), promoting cell survival. This is important for pancreatic β-cell survival, which is critical in preventing diabetes progression.

Free radicals destroy cells.

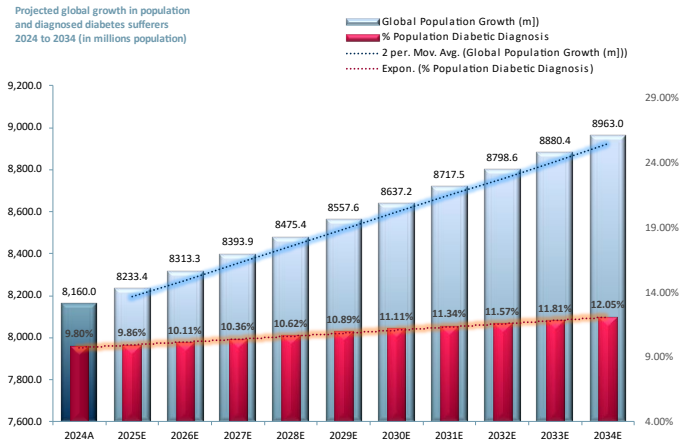
Molecular Mechanisms of Diabetes Complications - Both T1D and T2D lead to complications due to **chronic hyperglycemia** (high blood glucose levels), mediated by oxidative stress (too many free radicals produced vs. antioxidants), advanced glycation end-products (AGEs), which is the combining of fats or proteins with sugars in the bloodstream , and inflammatory pathways.

Microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy result from endothelial dysfunction (the lining of blood vessels are damaged and cease to function properly), excessive sorbitol pathway flux, and mitochondrial reactive oxygen species (ROS) production, which damages cells.

Macrovascular complications include atherosclerosis, hypertension, and cardiovascular disease, which develop due to chronic inflammation and lipid (fats) metabolism dysregulation. While T1D results from autoimmune β-cell destruction, leading to absolute insulin deficiency, T2D develops due to insulin resistance and β-cell dysfunction. The biochemical disruptions in both conditions lead to severe metabolic complications, emphasizing the need for glycemic control, lifestyle interventions, and therapeutic strategies targeting insulin production and action for T1D and T2D sufferers in order to mitigate the enormous direct (healthcare) and indirect (economic productivity) costs to an economy.

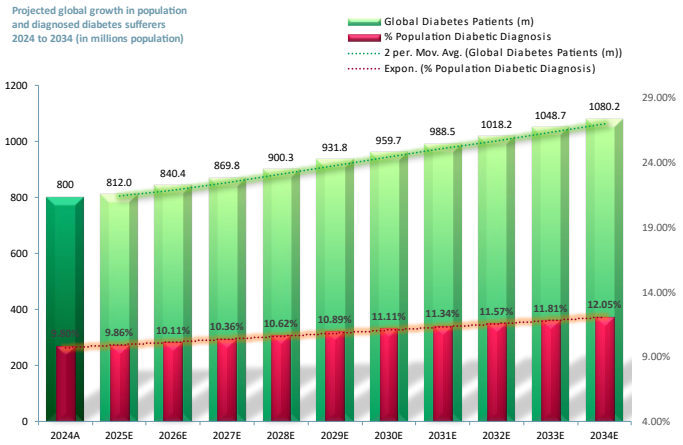
Diabetes Global Therapy Market Forecasts

Exhibit 6: **Diabetes vs. global pop growth**



Sources: ACF Estimates, ACF Graphics, CDC, BMC Population Health Metrics.

Exhibit 7: **Diabetic pop growth**



Sources: ACF Estimates, ACF Graphics, CDC, BMC Population Health Metrics.

Whilst we expect the overall proportion of the global population diagnosed as diabetic to rise as incomes rise and the environment deteriorates increasing the rate of gene malfunction via viruses and pollution, our growth assumption over our 10 year horizon is mediated by improved education, improved personal data tracking, more accessible personal research and data analysis via AI and the nascent presences of licensed curative therapies.

Market consenus numbers vary widely within the field of diabetics. We have therefore run our own forecasts informed by a number of sources for population growth, the US CDC and the BMC population health metrics. Our trend lines suggest a reasonably predictable rise in the global population and, whilst we have used a 3 phase growth model, a rising but relatively predictable rise in the proportion of the population with diabetes.

In the left hand exhibit above we project the global growth in population and the percentage (%) of the that population what we expect to be diagnosed as diabetic with either T1D or T2D (our models maintain the relationship of T1D between 10-15% of total diabetics). Whilst we expect the overall proportion of the global population diagnosed as diabetic to rise as incomes rise and the environment deteriorates increasing the rate of gene malfunction via viruses and pollution, our growth assumption over our 10 year horizon is mediated by improved education, improved personal data tracking, more accessible personal reasearch and data analysis via AI and the nascent presences of licensed curative therapies.

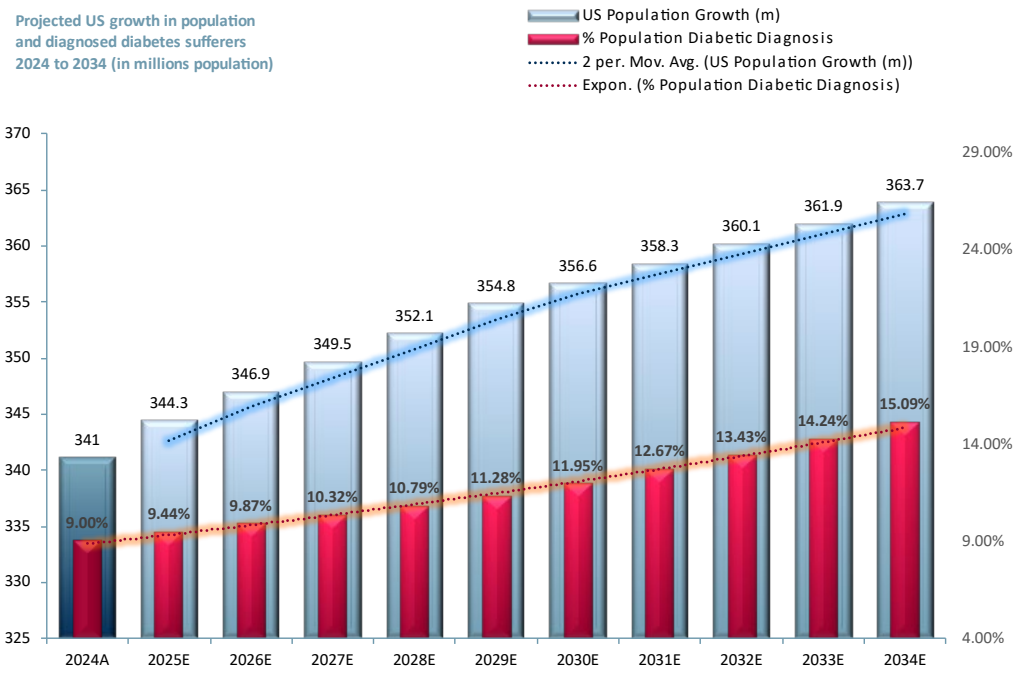
In the right hand exhibit above we show the modelling for our expectations for the actual number of diagnosed diabetics and overlay the percentage of the global population that our porjected patient numbers represent.

Diabetes US Therapy Market Forecasts

Projecting the number of individuals in the United States who will be on medication for diabetes over the next decade requires analyzing current prevalence data, demographic trends, and anticipated changes in disease incidence. Below is an overview of the current landscape, followed by projections segmented by age and sex. The exhibits below summarize these factors to provide a projection of the total US patient market evolution. **Current Diabetes Prevalence in the U.S.** - As of 2021, the Centers for Disease Control and Prevention (CDC) reported 29.4m US adults aged 18 years or older with diabetes. The CDC categorized these patients by age group and by sex:

- 18–44 years: 3.5m patients or 11.9%
- 45–64 years: 12.0m patients or 40.8%
- 65 years and older: 13.8m patients 46.9%
- Men: 16.1 million individuals or 54.8%.
- Women: 13.3 million individuals or 45.2%.

Exhibit 8: **Diabetic US pop % cf. US pop (m) growth**



Sources: ACF Estimates, ACF Graphics, CDC, BMC Population Health Metrics.

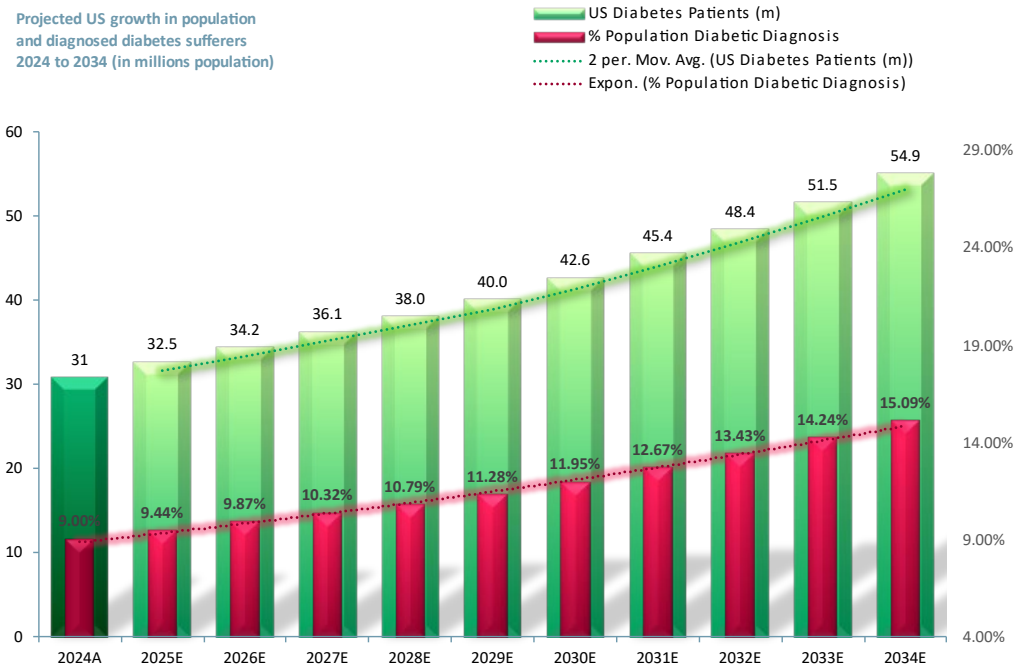
Projected Diabetes Prevalence by 2035 - A study published in Population Health Metrics projected the prevalence of diagnosed diabetes among U.S. adults through 2060, considering factors such as incidence rates, mortality, and demographic shifts.

Key Projections - The prevalence of diagnosed diabetes is expected to rise significantly in the US (and in other developed and hyper developed economies) due to factors

including aging demographics and increasing obesity rates. The highest prevalence of diabetes is expected to be among adults aged 65 and older. In terms of sex distribution both men and women are forecast to suffer from increases in diabetes prevalence, with men maintaining a slightly higher prevalence rate.

Medication Usage Among Diabetic Patients – Whilst projections for the number of individuals on diabetes medication by age and sex in 2035 are not readily available, data does suggest that the majority of individuals diagnosed with diabetes are likely to be prescribed medication as part of their management plan. Older adults are more likely to be on multiple medications due to longer disease duration and the presence of comorbidities. Medication adherence and prescription patterns can vary between men and women, influenced by factors such as healthcare access and comorbidity and attitudes to healthcare in which men tend to under diagnose and are less likely to adhere to medication compared to women.

Exhibit 9: **Diabetes US patients projection (m)**



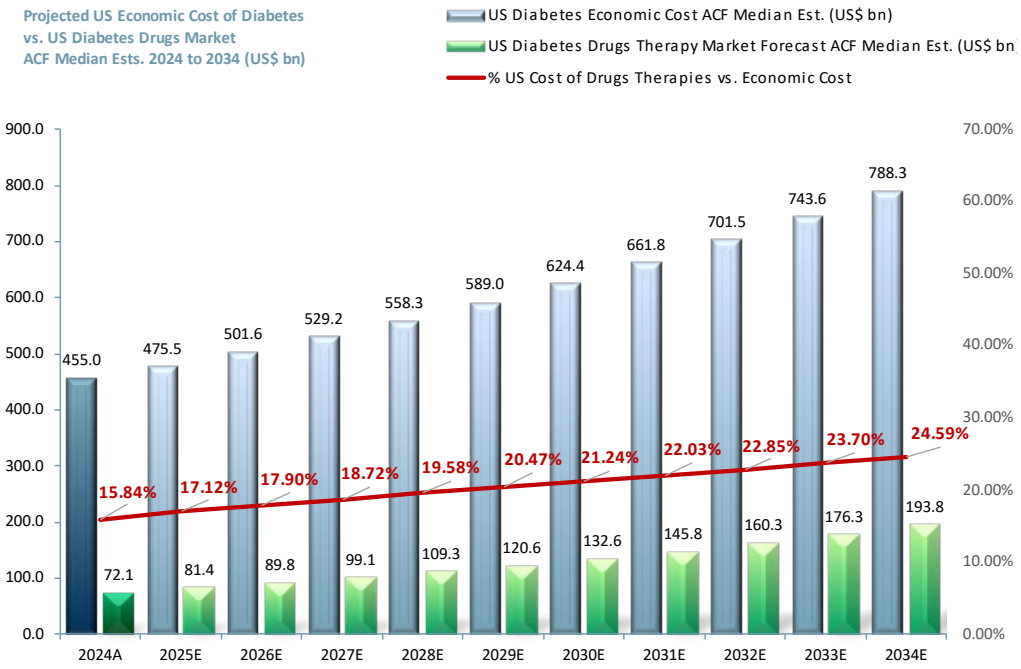
Sources: ACF Estimates, ACF Graphics, CDC, BMC Population Health Metrics.

Investment Implications – Market consensus and supporting data, point to a substantial increase in the economic burden of diabetes in the United States over the next decade, with significant implications for healthcare systems and policy planning. In turn, this suggests growing demand and increasing FDA support for companies with innovative therapies under development. We infer that bring-to-market time scales for new innovative therapies will contract driven by policy and AI research techniques, leading to enhanced NPVs. In our view these trends, drivers and economic implications, favor gene and stem therapies.

In 2022, the total economic cost of diabetes in the U.S. was estimated at $412.9bn, which was accounted for as $306.6bn in direct medical costs and $106.3bn in indirect costs such as lost productivity. Our forecasts below attempt to capture the drug therapy element of treatment costs, which we assess accounts for 42% of direct medical costs in 2024 at a highly conservative USD 72bn vs. an implied USD 128.7bn based on US government data. Therefore even our base cast estimates are at the low side of the estimated per patient annual cost range for the drug element of diabetes healthcare. We have taken this approach because market consensus data has spreads sometimes exceeding 50%, which suggests a market in significant flux driven by innovations yet to gain marketing licenses, and surprisingly wide spreads on patient costs from government data.

Projection Axioms – diabetes prevalence will increase due to an ageing population and increasing obesity rates. Healthcare costs are more likely to rise than to contract driven by general inflation, specific healthcare cost inflation and increased value generation. Market consensus ranges assume a base CAGR of 5% and low CAGR of 3% to reach a forecast for 2034 of between USD 606bn and USD 779bn. Our more conservative range for the US low and base case total economic costs is USD 577bn to USD 788bn 2034E.

Exhibit 10: **Diabetes US economic cost base case 2024A to 34E**



The exhibit shows our forecast for the economic cost of diabetes in the US rising to USD 788bn in 2034E; the value of the US diabetes drugs therapy market rising to >USD 193bn in 2034E and a line that indicates the proportion of our drugs therapy market value expressed as a % vs. the economic cost. In our forecast drugs therapies rise to 24.59% 2034E up from 15.84% 2024A. The drugs therapy market value rises faster due to innovation, greater value generation and earlier diagnosis. The economic cost rises less fast because of an assumption that better drugs lead to lower economic indirect costs.

Sources: ACF Estimates, ACF Graphics.

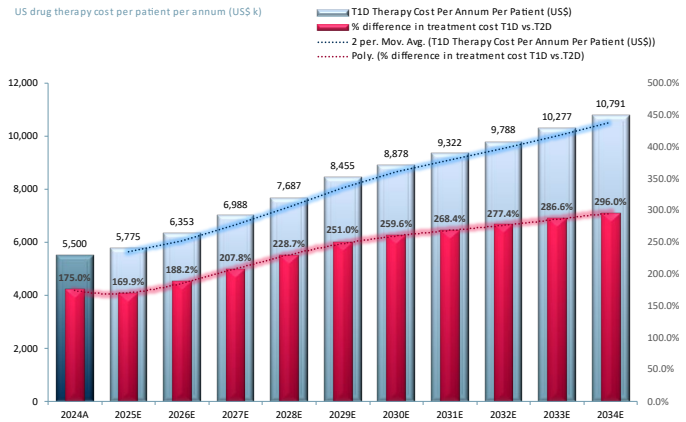
Annual Per-Patient Treatment Costs - In 2022, the average annual healthcare expenditure for a person with diabetes was USD 19,736, compared to USD 7,714 for individuals without diabetes.

In the exhibits below we show our estimates for the development of the US diabetes market per patient per annum (p.a.) and for the total US diabetes drugs market, followed by a breakout of our estimates for T1D vs. T2D future US market value. Note that consensus estimates have very significant spreads, which we infer is as a result of hitting a therapy point of radical expected disruption. Our market projections are underpinned by a conservative view of drug costs and the diagnosed diabetic US population.

Type 1 Diabetes (T1D) Per Patient Costs - T1D patients require insulin therapy, (cost estimates USD 4.8k and USD 6.0k p.a., depending on insulin type and dosage). Additional supplies including continuous glucose monitors (CGMs), test strips, and syringes, raise this cost by ~USD 3.0k to ~USD 5.0k p.a.. Our total estimated cost assumption for T1D treatment is between ~USD 7.8k to ~USD 11.0k p.a.

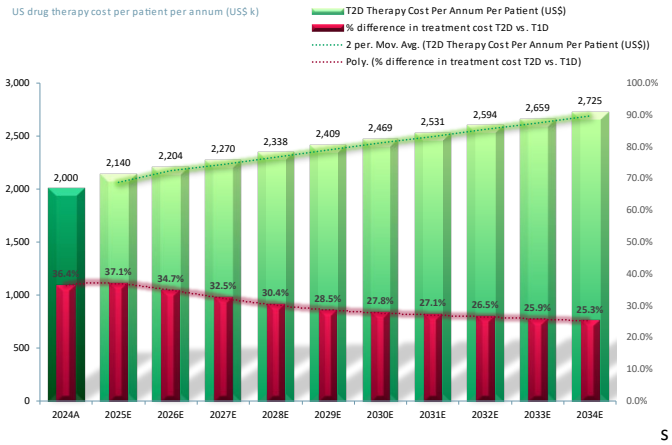
Type 2 Diabetes (T2D) Per Patient Costs – Medication costs vary based on treatment plans, ranging from USD 0.5k p.a. for metformin to USD 9.0k for newer medications including GLP-1 receptor agonists. For patients requiring insulin or monitoring devices, we add approximately USD 1.0k to USD 3.0k p.a.. Our total T2D estimated range per patient p.a. is USD 1.5k to USD 12.0k. Our base case starts at USD 2.0k per patient p.a. Note: Estimates are subject to change based on factors such as healthcare policy reforms, pharmaceutical pricing and advances in diabetes management technologies.

Exhibit 11: **T1D US cost per patient p.a.**



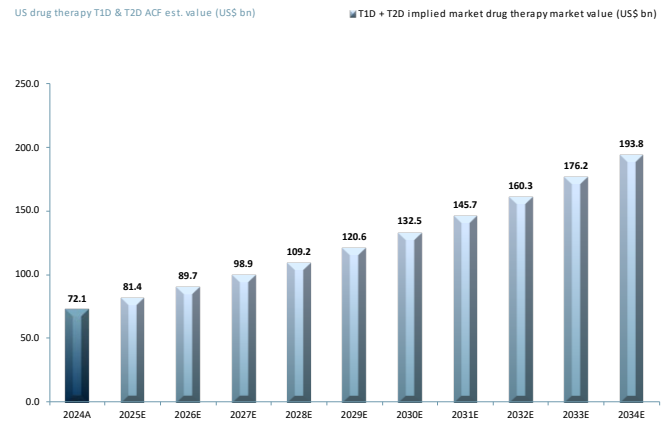
Sources: ACF Estimates, ACF Graphics

Exhibit 12: **T2D US cost per patient p.a.**



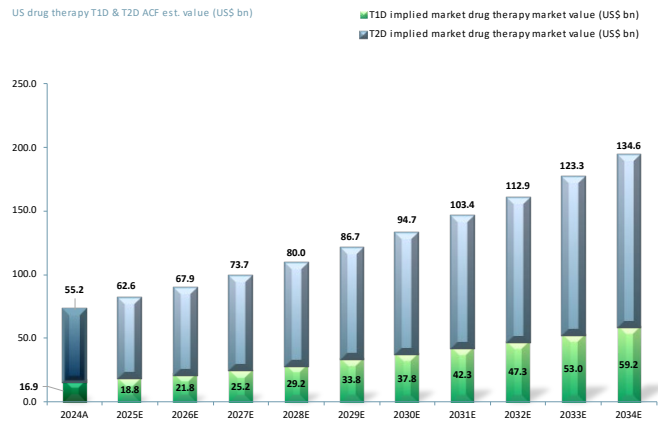
Sources: ACF Estimates, ACF Graphics, Precedence Research, Wikipedia, UN.

Exhibit 13: **Diabetes US drug value**



Sources: ACF Graphics, ACF Estimates

Exhibit 14: **Diabetes US T1+T2 drug value**



Sources: ACF Graphics, ACF Estimates

Large Cap Investment Themes

1. Novo Nordisk (NVO:NYSE): Insulin/ GLP-1 agonists (weight management) leader.
2. Eli Lilly (LLY:NYSE): GLP-1 agonists (weight management drugs) dominant.
3. Sanofi (SNY:NYSE): Insulin production leader/ novel therapies
4. Vertex Pharmaceuticals VRTX:NASDAQ): Pioneering gene-editing approaches.
5. Dexcom (DXCM:NASDAQ): Devices leader/Continuous Glucose Monitoring (CGM).
6. Abbott (ABT:NYSE): Devices leader/CGM.
7. Medtronic (MDT:NYSE): Devices /Automated Insulin Delivery (AID)

1. Pharmaceutical Innovations: Beyond Insulin - The diabetes treatment landscape is shifting beyond traditional insulin therapies, injections for T1D and metformin for T2D, toward novel therapeutics that target underlying pathologies and enhance patient adherence. Leading new therapy areas include GLP-1 agonists, SGLT2 inhibitors, gene editing and beta-cell regeneration/transplantation therapies and immunotherapies.

- **GLP-1 Receptor Agonists and SGLT2 Inhibitors** - Eli Lilly's (LLY:NYSE) Tirzepatide (marketed as Mounjaro and Zepbound), a dual GLP-1/GIP agonist, and Novo Nordisk's (NVO:NYSE) Semaglutide (marketed as Rybelsus, Wegovy and Ozempic) have demonstrated blood sugar control and weight loss benefits, addressing two interconnected health challenges in a huge growing marketing.

Note that the there is a significant difference between medical need (T2D) and cosmetic usage for weight management.

Market Outlook for GLP-1 receptor agonists - The GLP-1 receptor agonist market value 2024 was ~$50bn. In 2025 it is expected to rise to ~$70b and is expected to grow at a CAGR of between 12.7% and 17.5% between 2024 and 2029. Regenerative therapies and immunotherapy for T1D, though in their nascent stages, hold immense long-term potential as they address root causes rather than symptoms.

- **Stem Cell Therapies (Beta-Cell Regeneration)** - Stem-cell-derived beta-cell replacements for T1D patients, a potential cure, as under development by Vertex, VRTX:NasdaqGS) through its ViaCyte and Semma Therapeutics acquisitions for USD 350m and 950m cash respectively.

Market Outlook for Gene and Cell Therapy - Although early stage, the global cell and gene therapy market for diabetes is expected to surpass USD 50bn by 2034, driven by advancements in CRISPR based gene editing and stem cell research.

As of June 2023, the FDA has approved private company CellTrans, Inc.'s donislecel (Lantidra) for the treatment of T1D. Lantidra is an allogeneic (donor-derived) pancreatic islet cell therapy. Lantidra is indicated for adults with T1D who experience severe hypoglycemia and are unable to achieve target glycated hemoglobin levels even with diabetes management and education.

In clinical studies, Lantidra demonstrated that some patients were able to achieve insulin independence for varying durations post-treatment. However the Lantidra therapy **requires lifelong immunosuppressive medication** to prevent rejection of the transplanted islet cells.

• **Immunotherapy in T1D** - Teplizumab (marketed as Tzied by Sanofi (SAN.PA) was recently FDA-approved. Teplizumab has been approved for the delay of the onset of stage 3 T1D in individuals with stage 2 T1D. Teplizumab modulates the immune response to preserve existing beta-cell function, rather than regenerating new beta cells.

2. Other Technological Advancements in Diabetes Management - Diabetes management technologies have transformed patient care, offering enhanced accuracy and convenience. Key Innovations include CGM, AID and digital health platforms:

• **Continuous Glucose Monitoring (CGM)** - Dexcom's (DXCM:NASDAQ) G7 and Abbott's (ABT:NYSE) FreeStyle Libre 3 allow real-time glucose monitoring, improving glycemic control and reducing complications.

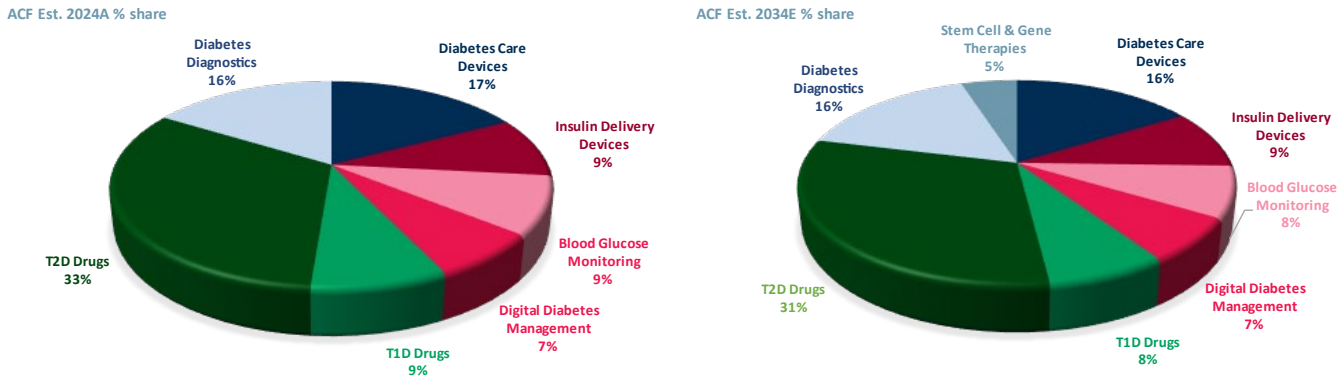
• **Automated Insulin Delivery (AID) Systems** – Include AI and closed-loop insulin pumps that mimic pancreatic function, as introduced by Insulet Corporation (PODD:NASDAQ) and Medtronic (MDT:NYSE). Tandem Diabetes' Control-IQ leverages AI to optimize insulin dosing.

• **Digital Therapeutics/Health Platforms** - Integrate CGM data with behavioral coaching to drive better outcomes, a model gaining traction in value-based healthcare such as that offered by Livongo, a startup acquired by Teladoc Health (TDOC:NYSE).

Market Outlook for Technological Advancements in Diabetes Management/Devices - The global diabetes devices market, led by CGMs and insulin pumps, is projected to reach USD 35bn by 2030E. Integration with digital health ecosystems presents an additional layer of growth. However, investors should note that the global GLP-1 receptor agonist market for T2D and obesity/weight management is forecast by some market participants to exceed USD 125bn by 2034E.

Investment Risks and Challenges – 1. Clinical Risks - Failures in late-stage trials can impact valuations significantly. **2. Regulatory Risks** - Stringent FDA approval processes may delay product launches. **3. Market Competition** - The competitive landscape for GLP-1 agonists and CGMs, in particular, could erode margins, for example Hims & Hers Health (HIMS:NYSE) GLP-1 offering. **4. Cost and Access** - High treatment costs of innovative therapies could limit adoption in low-income populations, despite rising prevalence and the huge indirect economic gains.

Exhibit 15: **Diabetes global market segments 2024A and 34E**



Sources: ACF Estimates, ACF Graphics, American Diabetes Association, IMARC Group, Healio

Our estimates on market segmentation for the global diabetes market are based upon our assumptions with respect to market development, particularly for drugs demand. Investors should note that market consensus estimates come with very wide spreads indicating a view that the market is undergoing significant technological innovation, in particular via gene and stem cell therapies.

We also assume that the undiagnosed market will reduce as a total proportion of the diabetes market through better testing, education, personal health monitoring and AI research tools.

The likely rise in therapy costs as a result of greater value propositions from gene and stem cell therapies (including curatives) will a) not have fully penetrated the market and will mean in the next 10 years that insulin therapies will have a significant market share outside developed and hyper developed economies due to both innovation in this segment and our rising costs of drug therapies assumption.

Micro/Small Cap Investment Themes

Outside of the pharmaceutical and medical device large and mega cap giants, the reshaping of the diabetes therapy in terms of stem cell and gene editing potential curatives landscape is driven by innovative nano, micro and small cap biotechs. These firms often focus on breakthrough approaches to tackle the underlying metabolic faults causing diabetes. Nano, micro and small caps come with inherent investment risks not apparent in large and mega cap stocks.

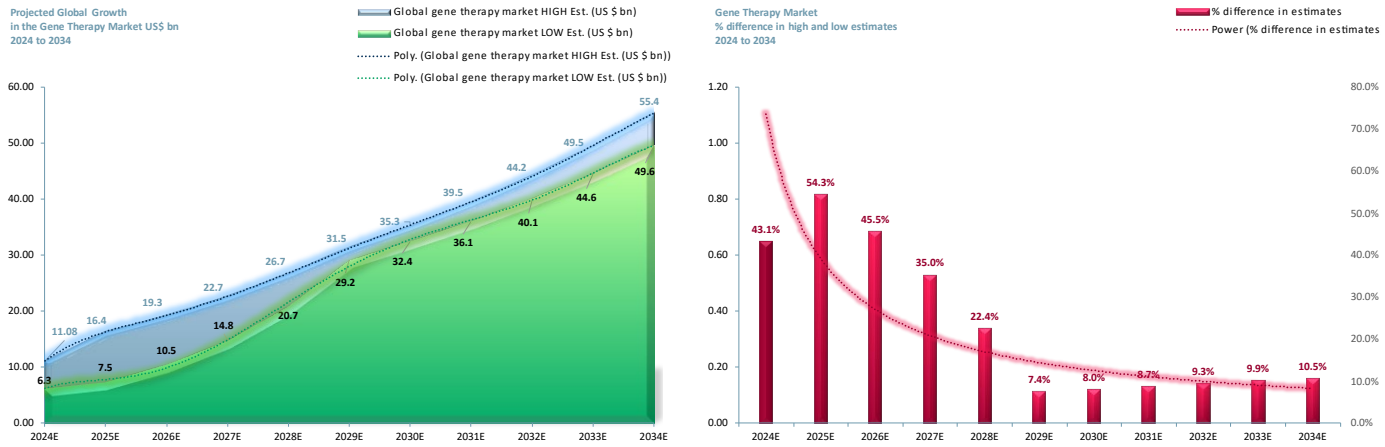
CRISPR Therapeutics (CRSP) is engaged in research aimed at correcting insulin production at the genetic level, primarily focusing on Type 1 Diabetes (T1D). In Sep 2018, CRSP partnered with ViaCyte (regenerative medicine) to develop gene-edited allogeneic stem cell therapies for diabetes. In early 2024, ViaCyte, now part of Vertex Pharmaceuticals (VRTX) opted out of the collaboration. CRSP assumed full rights to the program and is continuing development independently. CRISPR Therapeutics has started its P1 clinical trial for CTX211, an allogeneic gene edited immune evasive stem cell for the treatment of T1D. As of 11 Feb 2025 the CTX211 trial was ongoing.

However, nano, micro and small caps offer very significant upside for investors willing to navigate these higher risk-reward scenarios. In general, nano to small caps are researching and innovating the cutting-edge technologies of gene editing, stem cell therapy applications, and novel molecular pathways. They tend to be pre-revenue. However, if these therapies secure marketing approval from the U.S. Food and Drug Administration (FDA) and or the European Medicines Agency (EMA), they could transform diabetes care and provide compelling investment returns.

Key Emerging Themes in Nano to Small-Cap Diabetes Biotech - Disease prevention via gene editing, beta-cell regeneration, removal of the need for immunosuppression, novel delivery mechanisms for insulin and other therapies.

1. Gene Therapy (CRISPR technology) – Gene-editing therapies aimed at correcting insulin production at the genetic level are under research by companies such as CRISPR Therapeutics (CRSP:NasdaqGM).

Exhibit 16: **Gene therapy global market high & low estimates ($bn)**

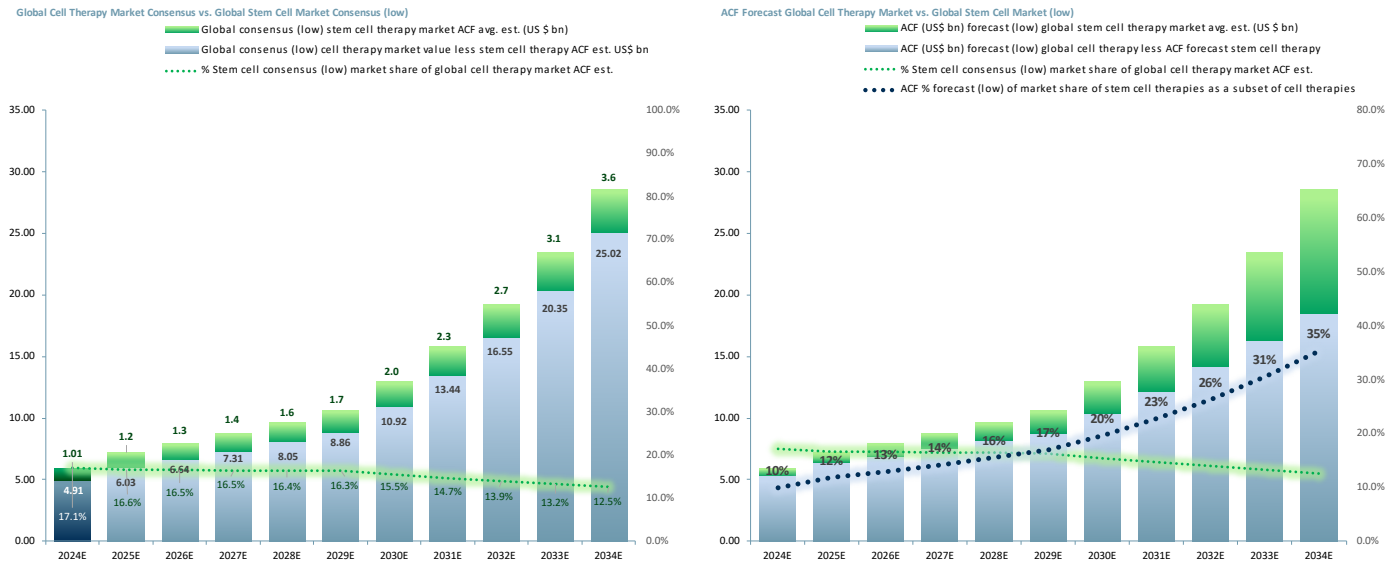


Sources: ACF Estimates, ACF Graphics.

Vertex's (VRTX) Zimislecel VX-880 (islet cell engraftment, P1/2 trials - 12 patients- promising data w/ 3 patients at 1^0 and 2^0 endpoints (no hypoglycemic events + insulin independence), initiated P3 as per VRTX 12 Jan 25. VRTX's VX-264 - encapsulated T1D therapy aimed at no immunosuppression P1/2 initiated.

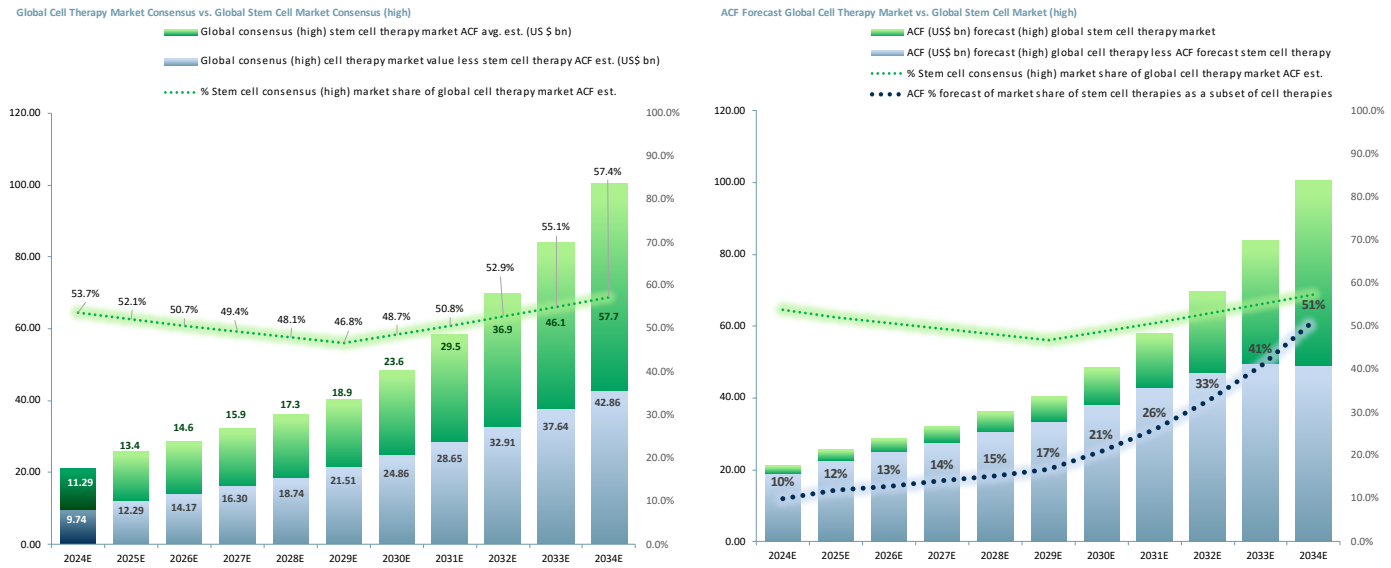
2. Stem Cell Based Therapies – Regeneration of insulin-producing beta cells, which may reverse T1D such as those under development by Provention Bio and Kadimatstem (KDST.TA) and Vertex (VRTX), are advancing curative therapies (VRTX could be argued to have achieved this with VX-880) for T1D using stem-cell-derived beta cells. **Outlook:** If licensed, these therapies could eliminate insulin injections entirely in developed and hyper develop economies, where they can be afforded.

Exhibit 17: Stem cell subset market consensus vs. ACF forecasts (low)



Sources: ACF Estimates, ACF Graphics.

Exhibit 18: Stem cell subset market consensus vs. ACF forecasts (high)



Sources: ACF Estimates, ACF Graphics.

Our estimates suggest that the stem cell therapy market will account for between 35% and 51% of the global cell therapy market by value within 10 years. Consensus numbers range from 12.5% to 57.4% stem cell share of the global cell therapy market.

Microencapsulation devices Involve coating individual (or small clusters of) cells with semi-permeable membranes, allowing nutrient and oxygen exchange while protecting cells from immune attack.

Macroencapsulation devices encapsulate larger cell masses (cf. single or small cell clusters in micro) within a single barrier type device that protects the cells from immune system attack.

According to competitors, Sigilon Therapeutics (acquired by Eli Lilly) is developing an implantable microencapsulation device via its Afibromer™ technology for T1D, similar in approach to KDST.TA. The Sigilion-Eli Lilly approach aims to create a "living therapeutic" that can restore insulin production in T1D without the need for life long immunosuppressive therapy.

3. Encapsulation Technologies (Micro/Macro) - Avoiding Immune Response – Encapsulation (micro and macro) are implantable 'devices' that protect insulin-producing cells from immune system attack. Examples using microencapsulation for immune protection in T1D cell transplantation include Sigilon Therapeutics (acquired by Eli Lilly for USD 34.6m cash, a 300% premium, closed 14 Aug 2023); Procyon Technologies (private, encapsulation technology) in collaboration with Novo Nordisk (NVO, stem cell technology); and Kadimastem (KDST.TA) merging with NLSP:NASDAQ. Macronecapsulation for beta cells approaches are under development by ViaCyte (acquired by VRTX). **Outlook:** Encapsulation platforms could cure T1D without the need for life-long immunosuppression and so reduce the frequency of intervention, improving patient quality of life.

4. Oral and Non-Invasive Insulin Delivery - Example: Oramed Pharmaceuticals (ORMP:NASDAQ) is developing oral insulin, addressing adherence challenges for both T1D and T2D patients. **Outlook:** The global insulin delivery market, currently dominated by injectables, could see significant disruption if oral or non-invasive solutions gain traction.

5. Digital Therapeutics Integration - Programs providing coaching, dietary adjustments, and telemedicine to reverse T2D, supported by evidence-based clinical outcomes such as that offered by Virta Health (2021 Series E funding valued Virta at USD 2bn). Glooko (private, estimated post-money valuation Oct 2024, USD 500m to 1bn) integrates real-time monitoring with AI-driven health coaching to optimize glycemic control. Glooko has also been acquiring companies. **Outlook:** Extremely attractive to insurers and national healthcare providers via cost savings (time and cash) savings.

6. Lifestyle Interventions and Prevention (a sub-set of digital therapeutics) - Preventive strategies targeting T2D are a critical component of healthcare policy and investment focus. Key Innovations include weight management interventions and digital therapeutics. The success of GLP-1-based drugs in weight loss has spurred interest in interventions that target obesity—a primary risk factor for T2D.

Investment direction - Gene and Cell (Stem Cells) Therapy, are they the future of diabetes care? - Emerging technologies in gene editing and cell therapy hold the promise of curing diabetes rather than managing it. Key innovations include, CRISPR and encapsulated stem cell therapies (KDST.TA+NLSP) and metabolic pathway management.

Outlook: As healthcare systems shift toward value-based models, digital solutions offer a scalable way to reduce complications and improve outcomes for T2D patients.

Micro/Small Cap Exit Premium Case Studies

An alternative way to assess the nano, micro and small cap companies is as PII acquisition/exit targets, so a capital return based upon an acquisition premium delivered by a large, mega cap or private acquirer.

PEC-Direct and PEC-Encap are two stem cell-derived islet therapy approaches developed by ViaCyte (now part of Vertex Pharmaceuticals) for the treatment of T1D. These therapies aim to replace lost pancreatic β-cells using pluripotent stem cell-derived insulin-producing cells.

PEC-Direct is an implantable cell therapy that delivers stem cell-derived pancreatic progenitor cells in a semi-permeable encapsulation device. These cells mature into functional β-cells capable of producing and releasing insulin in response to blood glucose levels.

PEC-Encap uses the same stem cell-derived pancreatic progenitor cells, but they are housed in a fully encapsulated device that is designed to block immune cell entry. This means patients do not need immunosuppressive drugs.

- **ViaCyte** (Acquired by Vertex, VRTX:NASDAQ, in a USD 320m cash deal, the premium is undisclosed, ViaCyte was private, but we infer it might have been around 2.2x) - **Focus:** Stem-cell-derived therapies for Type 1 Diabetes (T1D). **Pipeline:** PEC-Direct and PEC-Encap, therapies designed to implant stem-cell-derived pancreatic precursor cells. PEC-Direct's treatment target cohort is high-risk T1D patients requiring intensive insulin therapy. PEC-Direct would typically require immunosuppression. Viacyte is also working on hypoimmune stem cells with CRISPR Therapeutics, these cells are less likely to require immunosuppression. **Investment Opportunity/Route:** Acquired by VRTX, ViaCyte's collaboration with CRISPR Therapeutics (CRSP:NasdaqGM, MCAP USD ~3.4bn, revenue generating, EBIT -ve) to integrate gene editing into ViaCyte's therapy pipeline could lead to transformative potential and create a leading offering in curative diabetes treatments.

- **Provention Bio** (Acquired by Sanofi (SNY:NasdaqGS, SNY.PA, MCAP USD ~127bn, revenue generating, in 2023 for USD 2.9bn, a 273% premium, closed 27 Apr 23). 30 days prior to Sanofi's acquisition Provention's MCAP was USD 600m (EV ~600m), representing an implied 4.8x take out multiple to MCAP or EV. Provention's revenues for the financial year end prior to Sanofi's acquisition were USD 2.2m, a take-out multiple of 1,318x to revs. Provention Bio **Focus:** Immunotherapy to delay or prevent T1D onset. **Pipeline:** FDA-approved Teplizumab (Tzield) is the first therapy shown to delay the onset of T1D in at-risk individuals. **Investment Opportunity:** Whilst now part of Sanofi, Provention Bio's early success illustrates the significant market impact small-cap players can have with targeted solutions.

- **Sigilon Therapeutics** (formerly STGX), acquired by Eli Lilly, LLY:NASDAQ, MCAP USD ~680bn. LLY paid USD 34.6m cash for STGX, a 300% premium, and included a potential contingent value rights package attributable to shareholders in Sigilon, equating to USD ~310m, closed 14 Aug 22). **Focus:** Encapsulation technologies for insulin delivery. **Pipeline:** Sigilon's SIG-002 uses encapsulated cell therapies to produce insulin autonomously in response to glucose levels without triggering an immune response. **Investment Opportunity:** Acquired by Eli Lilly, Sigilon's encapsulation technology could address critical unmet needs in insulin delivery for T1D patients. Eli Lilly might be deemed a significant future beneficiary of Sigilon's therapy, if it is approved for marketing. At the time of the acquisition Sigilon was revenue generating USD ~10.5m per annum; 30 days prior to the Eli Lilly offer STGX's MCAP was USD ~10m and EV ~ 20m, representing a possible exit multiple for stockholders of 30x MCAP or 15x EV if the CVR is crystallized at a point in the future.

Micro/Small Cap Current Opportunities

Nano to Small-Cap Biotech: High Risk, High Reward

• **Senseonics Holdings** (SENS:Nasdaq, MCAP USD ~520m, revenue generating, EBIT -ve). **Focus:** Continuous glucose monitoring (CGM). **Product:** Senseonics' Eversense CGM system offers long-term glucose monitoring through an implanted sensor lasting up to six months. **Investment Opportunity:** With recent FDA approval of Eversense E3 for extended use, Senseonics occupies a unique niche in the CGM market, appealing to patients who prefer fewer sensor replacements.

• **Oramed Pharmaceuticals** (ORMP:NasdaqCM, MCAP USD ~93m, TTM pre-revenue). **Focus:** Oral insulin delivery. **Pipeline:** Oramed is developing an oral insulin capsule (ORMD-0801) designed to improve adherence and reduce the burden of injections for T2D patients. **Investment Opportunity:** The success of ORMD-0801 could create a paradigm shift, providing T2D patients with a more convenient therapeutic option for insulin delivery.

• **Tiziana Life Sciences** (TLSA:NasdaqCM, formerly AiM, MCAP USD ~78m, pre-revenue) **Focus:** Anti-inflammatory approaches to T1D. **Pipeline:** Tiziana is investigating TZLS-501, a monoclonal antibody that could mitigate autoimmune-driven beta-cell destruction in T1D. **Investment Opportunity:** If successful, this therapy could complement beta-cell regeneration strategies, creating a comprehensive approach to managing T1D.

• **Sana Biotechnology** (SANA:NadaqGS, MCAP USD ~600m, pre-revenue). **Focus:** Cell-based therapies for T1D. **Pipeline:** Sana is advancing SC451, a hypoimmune-modified stem cell-derived pancreatic islet cell therapy designed to restore insulin production in T1D patients without the need for immunosuppression. This approach is supported by initial clinical data demonstrating survival and function of transplanted cells without immunosuppression. **Investment Opportunity:** SANA's innovative approach addresses a significant unmet need in T1D treatment and positions SANA as a leader in the evolving diabetes cell therapy landscape.

KDSP and iTolerance collaboration - iTOL-102 - an investigational biologic under development in which KDST provides the allogeneic (single donor that is not the patient) stem cell-derived human-like insulin secreting pancreatic islets (IsletRx) and iTolerance is provides its iTOL-100, an immunomodulatory technology, derived from Streptavidin-FasL fusion protein combined with a biotin-PEG microgel from algae.

• **KDST+NLSP Merger** (Ticker TBD, MCAP TBD, pre-revenue). **Focus:** Multi-targeted cell and pharmaceutical therapy for T1D and insulin-dependent T2D. **Pipeline:** KDST+NLSP merger will integrate KDST's IsletRx, an allogeneic pancreatic islet cell therapy, along with its proprietary microencapsulation technology to restore insulin production **without the need for lifelong immunosuppression**. NLSP's DOXA platform introduces a Dual Orexin Agonist-based therapy, targeting glucose metabolism, neuroinflammation, and circadian rhythm disruptions, addressing metabolic and neurological complications of diabetes. **Investment Opportunity:** Merged KDST+NLSP's unique combination of cell therapy with neuro-metabolic modulation would differentiate it from many 'standard' beta-cell replacement therapies. By leveraging encapsulation technology to protect transplanted cells and pharmacological interventions to enhance metabolic balance, KDST+NLSP offers a holistic diabetes treatment approach that could rival GLP-1 receptor agonist therapies. If successful, this multi-pathway approach would expand treatment options for T1D insulin-dependent and T2D diabetes patients.

Micro/Small Cap Spec Opps – NLSP + KDST cf. SANA

Exhibit 19: KDST+NLSP merged - Competitive advantage analysis

Advantage	Description
Comprehensive Treatment Modality	Combines IsletRx's cell-based insulin and glucagon delivery with the DOXA platform's metabolic regulation, providing a dual-faceted therapy targeting both glycemic control and metabolic dysregulation.
Enhanced Cell Survival and Function	Micro-encapsulation technology shields transplanted cells from immune rejection while promoting cell viability. Validated via Defymed's MailPan® device, showing successful islet cell integration and sustained functionality.
Reduction of Systemic Complications	DOXA's orexin modulation may mitigate diabetes-related neuropathies and cognitive impairments by improving sleep quality and reducing neuroinflammation, enhancing overall patient quality of life.
Elimination of Chronic Immunosuppression	Encapsulation technology enables allogeneic cell transplantation without lifelong immunosuppression, reducing risks of infection. Collaboration with iTolerance aims to develop immunomodulatory strategies to further eliminate the need for immunosuppression.

Sources: ACF Equity Research

The expected merger of Kadimastem Ltd (KDST.TA). and NLS Pharmaceutics Ltd.,(NLSP:NasdaqCM) approved by shareholders and subject to SEC approval positions the potential new company as able to offer a multifaceted approach to diabetes therapy by integrating advanced cell therapy with innovative pharmacological interventions.

Kadimastem's IsletRx and Encapsulation Technology - IsletRx is an allogeneic cell therapy comprising functional human pancreatic islet cells capable of secreting insulin and glucagon in response to blood glucose levels.

A critical component of IsletRx is its proprietary micro-encapsulation technology, which serves to protect the transplanted islet cells from the host's immune system. KDST's encapsulation technology obviates the need for potentially harmful immunosuppressive drugs, thereby enhancing patient safety and improving the longevity of the therapeutic effect. Preclinical studies have demonstrated that IsletRx can normalize blood glucose levels in diabetic animal models over extended periods, with treated subjects maintaining health throughout the study duration.

NLS Pharmaceutics' DOXA Platform - The Dual Orexin Agonist (DOXA) platform developed by NLS Pharmaceutics focuses on modulating the orexin system, which plays a pivotal role in regulating sleep-wake cycles and energy homeostasis (glucose). Orexin receptor antagonists appear to improve sleep quality **and glucose metabolism**. Studies in dual orexin receptor antagonists (DORAs) in diabetic mouse models show ameliorated sleep disturbance and enhanced glucose tolerance.

Exhibit 20: **Diabetes therapies compared - SANA and KDST+NLSP**

Aspect	Sana Biotechnology	KDST+NLSP Merged
Therapeutic Approach	Development of hypoimmune (HIP)-modified allogeneic **pancreatic islet cells** designed to evade immune detection, enabling transplantation without immunosuppression.	Combination of Kadimastem's IsletRx allogeneic **pancreatic islet cell therapy** with NLSP's Dual Orexin Agonist (DOXA) platform, aiming to address both metabolic and neurological aspects of diabetes.
Immune Evasion Strategy	Utilizes genetic modifications to create HIP-modified cells that evade both innate and adaptive immune responses, **eliminating the need for immunosuppressive therapy**.	Employs proprietary **micro-encapsulation** technology to protect transplanted islet cells from the host's immune system, reducing or **potentially eliminating the need for immunosuppression**.
Clinical Development Status	Reported positive initial results from an investigator-sponsored, first-in-human study of HIP-modified primary islet cells (UP421) transplanted without immunosuppression, demonstrating cell survival and function.	Preparing for Phase 2a clinical studies in the U.S. for IsletRx, focusing on the combined therapeutic potential with the **DOXA** platform to enhance both **glycemic control** and **address neurological complications** .
Competitive Advantages	- Immune Evasion: Genetic modifications allow for **transplantation without immunosuppression,** reducing associated risks. - Scalability: **Potential for large-scale production** of standardized cell therapies. However, requires advanced manufacturing for gene-editing due to CRISPR deployment.	- Comprehensive Treatment: Addresses both glycemic control and neurological complications through a multi-targeted approach. - **Encapsulation Technology: Protects transplanted cells, potentially reducing the need for immunosuppression**. - DOXA Platform: Targets neuroinflammation and circadian rhythm disruptions, offering benefits beyond traditional glucose-lowering therapies. **Potentially more scalable** with neuromodulation and islet encapsulation

Sources: ACF Equity Research

The merger of KDST and NLSP leading to the integration of Kadimastem's IsletRx and NLS Pharmaceutics' DOXA platform positions the new entity at the forefront of innovative diabetes therapies. The synergistic effects of advanced cell therapy, protective encapsulation technologies, and metabolic modulation, if successful, could offer a comprehensive solution for diabetes management, potentially setting new standards in patient care and therapeutic efficacy.

Market Differentiation - SANA's hypoimmune platform positions it for leadership in curative therapies, while KDST + NLSP's combined approach may dominate the space for patients with complications.

Investors should carefully evaluate clinical and regulatory milestones, scalability, and competitive positioning when assessing these opportunities. Both approaches have the potential to transform the diabetes market, delivering outsized returns if successful while advancing the broader field of diabetes care.

Micro/Small Cap Investment Risks and Mitigation

Risks:

1. Clinical Trial Failures: Early-stage companies face significant risks in clinical trials, where a single failure can undermine valuations in a 0:1 sum game investment scenario.

2. Regulatory Uncertainty: FDA and EMA approvals are stringent, and without fast track approval, delays or rejections can limit commercialization opportunities.

3. Funding Challenges: Nano, micros and small-cap firms often rely on equity raises, diluting shareholder value during early-stage development, these dilution events often feel very painful to retail investors on whom nano, micro and small caps often depend. In turn these dilution events can create a crisis situation that may progress to the courts leading to irretrievably damaged management credibility. Nano, micro and small caps are disproportionately reliant on their executive management teams compared to mid, large and mega caps.

Mitigation Strategies:

1. Diversification: Invest in a basket of nano, micro and small-cap biotech firms to spread risk across multiple candidates and technologies.

2. Avoid companies with nil research coverage: Whilst investment research coverage does not guarantee outperformance, a lack of research coverage guarantees underperformance and undervaluation and often failure in the longer term.

3. Focus on Catalysts: Identify companies with upcoming regulatory milestones or clinical trial readouts to align investments with near-term value drivers.

4. Monitor Partnerships: Look for firms with strong collaborations with larger biotech or pharmaceutical companies, as these partnerships reduce development and distribution risk and provide a natural exit strategy from PII trials results onwards.

Investment Conclusions:

Transformative Potential in a High-Growth Sector - As evidenced by take-out premiums sited in this thematic investment research, the nano, micro and small-cap biotech space offers significant opportunities for investors to engage in a sub-segment undergoing technological innovation. Whilst risk is inherently higher in nano to small cap biotech when compared to mid, large and mega cap players, the crystalized valuation effect of breakthrough therapies that secure FDA or EMA approval and disrupt traditional treatment paradigms can provide super-normal returns.

By strategically investing in the healthcare/biotech diabetes sector, investors can position themselves to capitalize in a healthcare sub-sector enjoying a wave of advancements in therapy, in a sadly large, global, growing and high value market.

Peer Groups

Exhibit 21: Peer group metrics large cap diabetes therapies

TTM Metrics / Company Name	Market	Tkr	MCAP US$(m)	Rev / Per Head	FCF / Per Head	RoA	RoE	RoIC	β 5yr	EV / FCF	P/ book
Eli Lilly	**XNYS**	**LLY**	**780,145**	**958,355**	**10,868**	**15.86%**	**77.11%**	**52.55%**	**0.01**	**1586.8x**	**52.2x**
Novo Nordisk	XNYS	NVO	335,059	3,805,968	917,984	28.47%	84.96%	39.07%	0.17	6.0x	2.4x
Sanofi	XNAS	SNY	144,363	675,352	48,270	8.33%	7.45%	5.97%	0.46	37.9x	0.9x
Vertex Pharma	XNAS	VRTX	126,321	1,804,230	-129,557	-2.60%	-3.28%	2.79%	0.42	N/M	7.7x
Average				2,095,183	278,899	11.40%	29.71%	15.94%	0.35	21.97	3.7x
Median				1,804,230	48,270	8.33%	7.45%	5.97%	0.42	21.97	2.4x

Sources: ACF Equity Research; Refinitiv.

Exhibit 22: Peer group metrics large cap diabetes devices

TTM Metrics / Company Name	Market	Tkr	MCAP US$(m)	Rev / Per Head	FCF / Per Head	RoA	RoE	RoIC	β 5yr	EV / FCF	P/ book
Abbott Labs	**XNYS**	**ABT**	**226,502**	**367,982**	**55,711**	**25.94%**	**32.37%**	**19.30%**	**0.69**	**36.8x**	**4.8x**
Medtronic	XNYS	MDT	117,070	349,463	57,547	11.52%	8.69%	6.15%	0.82	26.1x	2.4x
DexCom	XNAS	DXCM	27,518	351,680	61,233	9.06%	26.30%	10.20%	0.03	46.7x	13.3x
Average				350,571	59,390	10.29%	17.50%	8.18%	0.43		7.9x
Median				350,571	59,390	10.29%	17.50%	8.18%	0.43		7.9x

Sources: ACF Equity Research; Refinitiv.

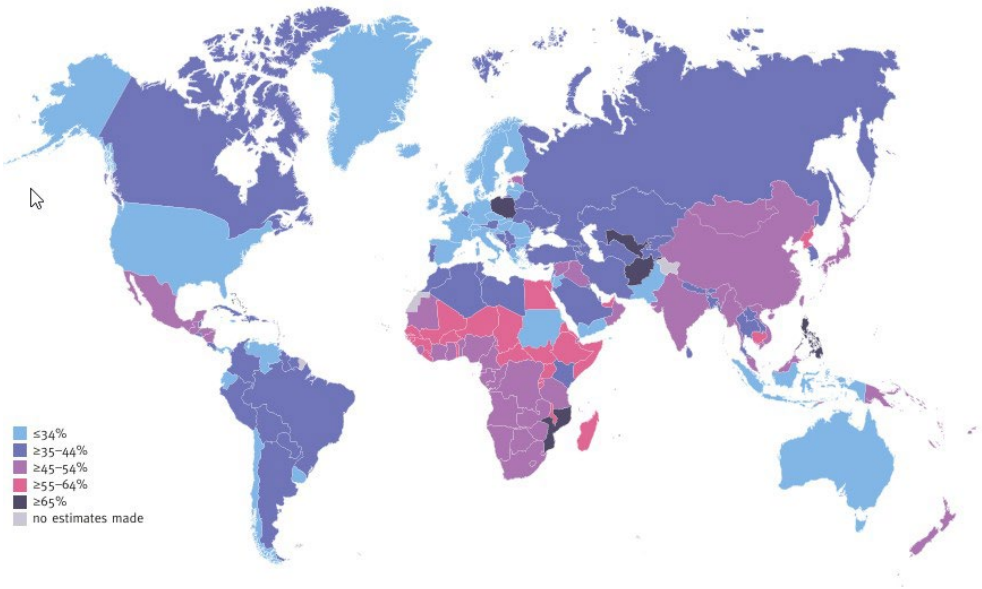
Exhibit 23: Peer group metrics micro/small cap gene & cell therapies

TTM Metrics / Company Name	Market	Tkr	MCAP US$(m)	Rev / Per Head	FCF / Per Head	RoA	RoE	RoIC	β 5yr	EV / FCF	P/ book
Kadimastem	**XTAE**	**KDST**	**21**	**0**	**-16**	**-0.18%**	**0.16%**	**1.01%**	**0.01**	**N/M**	**N/M**
NLS Pharmaceutics	XNAS	NLSP	4	0	-510,963	-170.96%	22.54%	42.77%	-0.31	N/M	N/M
Sana Biotechnology	XNAS	SANA	617	0	-838,387	-85.05%	-94.47%	-58.81%	1.64	N/M	2.2x
Tiziana Life Sciences	XNAS	TLSA	162	0	-1,003,778	-145.20%	-140.92%	-319.08%	0.04	N/M	N/M
CRISPR Therapeutics	XNAS	CRSP	3,705	941,476	-368,130	-16.34%	-18.46%	-21.70%	1.76	N/M	1.8x
Average				235,369	N/M	N/M	N/M	N/M	0.78		2.0x
Median				N/M	N/M	N/M	N/M	N/M	0.84		2.0x

Sources: ACF Equity Research; Refinitiv.

Diabetes - The Undiagnosed Market

Exhibit 24: **Diabetes undiagnosed in Adults (20-79) 2021 estimates**



Sources: International Diabetes Federation, Diabetes Atlas 2021 www.diabetesatlas.org

The map above estimates the proportion of total diabetes sufferers that are undiagnosed and ranges from <34% to >65%. This is a significant undiagnosed market.

The undiagnosed diabetes market is estimated by using a combination of epidemiological modeling, large scale screening studies, and demographic trends. (e.g., NHANES in the U.S., UK Biobank, and IDF). Measuring blood glucose levels and HbA1c in randomly selected populations also assists in revealing the prevalence of undiagnosed diabetes. The US's CDC uses predictive modeling based on known risk factors (obesity, family history, age, ethnicity), screening data extrapolated to the general population and trends in healthcare access (how many people are unlikely to get tested).

Other healthcare data is also used - researchers analyze hospital records, insurance claims, and outpatient visits to identify patients with frequent high blood sugar levels but no formal diabetes diagnosis. Machine learning models also predict cases and biomarkers and genetic screening in high-risk populations access genetic markers and early stage metabolic dysfunction prior to disease progression.

Impact on the Diabetes Therapy Market – more diagnoses earlier expands the diabetes market in several ways high demand for therapies and lifestyle intervention programs, for longer periods of time. It also increases the attractiveness of the overall market for innovators. By improving early detection, patients and the healthcare industry benefit—reducing complications while driving market growth for diabetes-related therapies and technologies.

Companies Referenced In Report

Exhibit 25: Companies mentioned in report

Companies Mentioned in this report	Tkr	Exchange	EV ($bn)	Listing Currency	52 wk hi	52 wk lo	Previous Close	% from 52 wk High
Novo Nordisk	NVO	NYSE	2,335.3	DKK	148.2	73.8	78.1	47.3%
Eli Lilly	LLY	NYSE	809.6	USD	972.5	711.4	824.1	15.3%
Abbott Laboratories	ABT	NYSE	233.4	USD	141.2	99.7	132.7	6.1%
Sanofi	SNY	NASDAQ	143.5	EUR	60.1	45.2	58.7	2.3%
Medtronic plc	MDT	NYSE	142.7	USD	96.3	76.0	93.3	3.1%
Vertex Pharmaceuticals Incorporated	VRTX	NASDAQ	124.4	USD	519.9	377.9	488.3	6.1%
The Kraft Heinz Company	KHC	NASDAQ	54.1	USD	39.0	27.3	31.1	20.2%
Dexcom, Inc.	DXCM	NASDAQ	29.6	USD	142.0	62.3	70.3	50.5%
Insulet Corporation	PODD	NASDAQ	16.6	USD	289.5	160.2	245.4	15.2%
Hims & Hers Health, Inc.	HIMS	NYSE	7.0	USD	73.0	11.2	34.7	52.4%
CRISPR Therapeutics AG	CRSP	NASDAQ	3.7	USD	76.9	36.5	42.4	44.9%
Teladoc Health, Inc.	TDOC	NYSE	1.8	USD	15.7	6.8	9.0	42.6%
Tandem Diabetes	TNDM	NASDAQ	1.7	USD	53.7	17.6	17.9	66.7%
Sana Biotechnology, Inc.	SANA	NASDAQ	0.621	USD	10.5	1.5	2.8	73.8%
Senseonics Holdings, Inc.	SENS	AMEX	0.386	USD	1.4	0.3	0.6	57.1%
Tiziana Life Sciences Ltd	TLSA	NASDAQ	0.157	USD	1.9	0.4	1.4	28.3%
Oramed Pharmaceuticals Inc.	ORMP	NASDAQ	0.058	USD	3.1	2.0	2.6	16.6%
Kadimatsem Ltd	KDST.TA	TLV	0.082	ILS	2,277.0	430.0	1,819.0	20.1%
NLS Pharmaceutics AG	NLSP	NASDAQ	0.005	USD	18.4	1.5	1.6	91.1%
CellTrans, Inc.	Private	Private	Private	Private	Private	Private	Private	Private
Virta Health	Private	Private	Private	Private	Private	Private	Private	Private
Havea Group	Private	Private	Private	Private	Private	Private	Private	Private
Glooko (post money valuation US$ 500m-1bn)	Private	Private	Private	Private	Private	Private	Private	Private
Procyon Technologies	Private	Private	Private	Private	Private	Private	Private	Private
Provention Bio, Inc. (Acquired by Sanofi, $2.9bn)	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired
ViaCyte (Acquired by Vertex, $350m cash)	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired
Livongo (Acquired by Teladoc Health)	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired
Semma Therapeutics (acquired by Vertex, $950m cash)	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired
Sigilon Therapeutics (acquired by Eli Lilly, $34.6m cash)	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired	Acquired

Sources: ACF Equity Research

Notes [Intentionally Blank]

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Managing Director
Head of Research
ACF Equity Research Ltd

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