Comparative Clinical and Health-Economic Literature Review on Newborn Polygenic Risk Scoring and Longitudinal Islet Autoantibody Screening for the Early Detection and Prevention of Type 1 Diabetes

Clinical Utility of Polygenic Risk Scores in Staging and Stratifying Type 1 Diabetes Susceptibility

The clinical identification of type 1 diabetes ($T1D$) has historically occurred at clinical onset, a reactive stage often marked by acute, life-threatening metabolic decompensation.[1] However, contemporary medical evidence defines $T1D$ as a chronic, progressive autoimmune disorder that can be detected and staged years before the clinical manifestation of symptoms.[1] Because more than 85% of individuals diagnosed with $T1D$ lack a family history of the disease, relying solely on family history-based screening is insufficient for broad population-level prevention.[5] To address this challenge, integrating polygenic genetic risk scores (GRS) at birth with subsequent longitudinal islet autoantibody (AAb) testing offers a prospective framework for early clinical diagnosis and staging.[2]

A GRS aggregates the risk contributions of multiple single nucleotide polymorphisms ($SNPs$) across the genome into a single continuous scale of genetic susceptibility.[2] While human leukocyte antigen (HLA) Class II genes—specifically the high-risk $DR3/DR4-DQ8$ and $DR4-DQ8/DR4-DQ8$ genotypes—remain the strongest single genetic predictors, they only partially capture the overall risk profile.[11] Incorporating non-HLA susceptibility loci associated with immunological pathways greatly improves the predictive performance of genetic screening.[11] These loci include genetic variations in genes such as *PTPN22* (rs2476601), *IFIH1* (rs1990760), *CTLA4* (rs3087243), *IL2* (rs2069763), and others.[12]

Two primary genetic risk models have been widely evaluated in clinical trials and cohort studies:

- **T1D GRS1**: A 30-variant weighted model developed to provide an inexpensive, integrated assessment of genetic susceptibility.[9] Standardized by dividing the total number of risk alleles, $GRS1$ has demonstrated strong clinical utility in adult and youth cohorts.[13] It aids in discriminating $T1D$ from type 2 diabetes ($T2D$) and monogenic diabetes (such as Maturity-Onset Diabetes of the Young, or $MODY$).[9] The assay is highly cost-effective, costing approximately $\$70$ in local clinical laboratories and less than $\$20$ when DNA extraction has already been completed.[9]
- **T1D GRS2**: An expanded model comprising 67 $SNPs$ that offers superior discriminative capacity.[13] $GRS2$ displays an elevated distribution in $T1D$ populations compared to non-diabetic controls, $T2D$, or pre-diabetic cohorts.[13] The score is highly predictive of extremely early-onset disease, achieving an area under the receiver operating characteristic curve (AUC) of 0.94 in identifying children diagnosed before age 2.[16]

Diagnostic Discrimination and Clinical Utility

The diagnostic value of a GRS extends beyond newborn screening to the clinical classification of diabetes in adults and youth. Due to rising obesity rates, distinguishing between $T1D$, $T2D$, and atypical diabetes at onset has become increasingly challenging.[14] When integrated into clinical care, a high GRS represents an independent, time-stable biomarker that aids in the differential diagnosis of diabetes.[14] For example, in adult-onset cohorts, a high GRS identifies patients with clinical $T2D$ who test positive for $GAD65$ autoantibodies ($GADA$) but are destined to rapidly progress to insulin therapy, reflecting latent autoimmune diabetes in adults ($LADA$).[9]

Furthermore, $GRS2$ assists in the targeted prioritization of patients for monogenic diabetes testing.[15] The absence of islet autoantibodies is a primary clinical indicator of monogenic diabetes.[15] However, because many true $T1D$ cases can also present as antibody-negative, genetic testing based on antibody status alone is not cost-effective.[15] Combining $T1D$ $GRS2$ with negative autoantibody status increases the diagnostic pick-up rate of genetic

testing for $MODY$ three-fold compared to utilizing antibody-negative status alone, thereby preventing misclassification and inappropriate clinical management.[15] This clinical utility is further highlighted in population datasets such as the UK Biobank, where $GRS1$ alone identified $T1D$ in 42% of adults aged $31–60$ years who carried high genetic risk but had been clinically classified otherwise.[14]

Predicting Autoimmune Progression and Clinical Manifestation

The relationship between polygenic susceptibility and the physical rate of progression through the presymptomatic stages of $T1D$ reveals a critical clinical nuance. Data from the TrialNet Pathway to Prevention study, which followed $1,244$ first-degree relatives, demonstrated that a higher 30-variant GRS independently predicts a more rapid rate of clinical progression.[17] A 0.05 increase in the GRS was associated with a significantly elevated hazard ratio (HR) of 1.29 ($P = 0.011$) for progression to symptomatic clinical disease, even after adjusting for metabolic markers, age, and autoantibody profiles.[17] Additionally, a higher genetic score was strongly associated with a faster transition from single to multiple autoantibody positivity ($HR = 2.27$ for a $GRS > 0.295$, $P = 0.0002$).[17]

Conversely, another evaluation utilizing a 46-variant GRS on a different cohort of autoantibody-positive individuals found no significant association between the genetic score and the rate of progression from Stage 1 to Stage 2, or Stage 2 to Stage 3.[10] This suggests that while a polygenic score is a highly sensitive tool for predicting the *initiation* of islet autoimmunity (the development of multiple autoantibodies), the subsequent rate of clinical progression and beta-cell destruction may be governed more directly by individual metabolic factors, such as those captured by the Diabetes Prevention Trial–Type 1 (DPT-1) Risk Score (which integrates BMI, age, glucose, and C-peptide metrics).[17]

Immunological Staging and Global Screening Programs

The early detection paradigm divides the progression of $T1D$ into three distinct, biomarker-validated stages.[4] These stages provide clinicians with a structured pathway to intervene before the onset of symptomatic hyperglycemia and metabolic crisis [1]:

Stage	Immunological Marker	Metabolic Status	Clinical Presentation

Stage 1 [4]	Presence of ≥ 2 islet-specific autoantibodies	Normoglycemia	Asymptomatic
Stage 2 [10]	Persistence of ≥ 2 islet-specific autoantibodies	Dysglycemia	Asymptomatic
Stage 3 [1]	Autoimmune destruction of pancreatic beta-cells	Overt Hyperglycemia	Symptomatic clinical diabetes (often presenting as DKA)

The clinical significance of autoantibody staging is illustrated by the cumulative risk of progression.[3] While a single autoantibody represents a moderate 10-year progression risk of approximately 15%, the detection of two or more autoantibodies (targeting insulin [IAA], glutamic acid decarboxylase 65, insulinoma-associated antigen 2 [$IA-2A$], or zinc transporter 8) carries a lifetime risk of progression to symptomatic disease that approaches 100%.[3] The specific autoantibody profile also dictates risk, with $IA-2A$ and $ZnT8A$ carrying the highest predictive value for rapid clinical progression.[19]

Global Platforms and Clinical Screening Pilots

To translate these staging criteria into public health interventions, several large-scale screening initiatives have been established globally.[21] These programs utilize diverse strategies, spanning newborn genetic stratification followed by targeted autoantibody monitoring to universal, population-wide antibody screening.[4]

Program	Country / Region	Target Population	Screening Assay & Protocol	Positivity Rates & Core Clinical Outcomes
GPPAD (Global Platform for the Prevention of	Germany, Poland, Sweden, Belgium, UK	Infants <1 month old (general population and first-degree	47-SNP GRS on newborn capillary dried bloodspots	1.1% of infants identified with elevated

Autoimmune Diabetes) [11]		relatives)		genetic risk (expected risk $> 10\%$ for developing multiple AAbs by age 6).[21] Identified infants are offered participation in primary prevention trials.[11]
Fr1da [19]	Bavaria, Lower Saxony, Hamburg, Saxony (Germany)	Children aged 1.75–10.99 years	Capillary blood screening for GADA, IA2A, ZnT8A via ELISA, confirmed by RBA	Multiple AAb positive rate of 0.3%. Over 80% of positive screens are staged at Stage 1, preventing DKA and reducing clinical hospitalization at onset.[21]
ASK (Autoimmunity Screening for Kids) [21]	Colorado, USA	Children and adolescents aged 2–17 years	Capillary finger-stick or blood draw for islet AAbs and celiac transglutaminase AAbs	Screens for presymptomatic T1D and celiac disease; reduces DKA at diagnosis and validates pediatric feasibility.[21]
DIPP (Type 1	Finland	Newborns	Cord blood	~10% of infants

Diabetes Prediction and Prevention) [11]		aged 0.25–15 years carrying high-risk HLA	HLA genotyping followed by longitudinal RBA (IAA, GADA, IA-2A, ZnT8A)	screened carry high-risk HLA. Of these, 2.2% develop ≥ 2 AAbs by age 2, rising to 5.0% by age 15.[21]
BABY-SCREEN [21]	Helsinki, Finland	Newborns to 3 years with high-risk HLA	HLA screening from cord blood, followed by longitudinal AAbs (islet and celiac) at ages 1, 2, and 3	Posibility of ≥ 2 AAbs is 1.8% by age 1 and 3.7% by age 2.[21]
PLEDGE [21]	North and South Dakota, Minnesota, USA	Children aged <6 years	Capillary blood spot for GRS; longitudinal AAbs at ages 2 and 5	Integrated health system clinics; leverages electronic health records (EHR) for family tracking and clinic communications.[21]
PRiMeD [21]	Virginia, USA	Children aged 2–16 years	Saliva GRS (82-SNP), followed by serum AAb testing in high-risk cohorts	1.3% (461 children) identified with high GRS (10-fold risk over expected); longitudinal AAb testing and CGM

				monitoring in progress.[21]
T1Detect (JDRF) [21]	United States (National)	General population and relatives aged $\geq$ year	Direct-to-consumer capillary blood spot via ADAP (GADA, IA-2A, IAA)	Non-relatives: 5.4% test positive for ≥ 2 AAbs. Relatives: 5.7% test positive for ≥ 2 AAbs.[21]

The clinical significance of primary prevention is further demonstrated by GPPAD's Primary Oral Insulin Trial (POInT).[11] In POInT, infants carrying a predicted genetic risk of $> 10\%$ (identified via GRS or family history coupled with HLA genotyping) receive daily oral insulin starting between 4.0 and 7.0 months of age and continuing until 36.0 months.[11] This approach aims to induce immune tolerance to preproinsulin—the primary initial target of T1D autoimmunity—before the first autoantibody appears, demonstrating how early GRS screening enables early therapeutic intervention.[11]

Health-Economic and Decision-Analytic Evaluations of Population Screening

The societal and economic impact of clinical $T1D$ is substantial, with an estimated cumulative annual economic burden in the United States exceeding $\$30$ billion.[18] On an individual level, the annual direct medical cost is approximately $\$5,960$ for pediatric patients and $\$20,320$ for adults, highlighting the potential value of effective prevention and staging.[18] Health-economic evaluations have modeled the cost-effectiveness of population-level screening, comparing unstratified general population antibody testing against GRS-stratified approaches.[4] These models utilize decision-tree and Markov simulation frameworks to project lifetime health outcomes, measured in Quality-Adjusted Life Years ($QALYs$) and incremental cost-effectiveness ratios ($ICERs$).[4]

Comparative Synthesis of National Economic Models

Economic analyses from the United Kingdom, Canada, and Australia highlight how differences

in screening design, testing costs, and clinical assumptions influence cost-effectiveness [4]:

Health-Economic Model	Modeled Strategies & Cohort	Key Cost and Clinical Inputs	QALY Projections (Discounted Lifetime)	Cost-Effectiveness Results & Justifiable Costs
United Kingdom (Pollard et al., 2025) [6]	Population-wide screening of all children at age 4 vs. No Screening in England and Wales.	• DKA baseline rate: 38% • Screening DKA reduction: 80% • DKA hospitalization cost: £3,278 • DKA utility decrement: -0.0091	• No T1D: 24.610 • T1D, no DKA: 20.001 • T1D, surviving DKA: 19.992 • T1D, dying DKA: 0.000	• **Base Case (DKA reduction only)**: Maximum justifiable program cost is **£3.17** per child screened (at £20,000/QALY) or **£3.31** (at £30,000/QALY). • **Long-term Benefit Case**: If screening yields a 0.5% ($5\ \mathrm{mmol/mol}$) lifetime HbA1c reduction, the justifiable cost rises to **£23.29 – £56.74**.[6]
Canada (Mital et al.) [8]	• General population screening once (age 4) or twice (ages 2	• Population incidence: $0.3\%–0.5\%$ • GRS	*Not reported as discounted lifetime values, measured primarily as*	• **Gen. Pop. (Age 4)**: Cost $404,534 more than family-history

	and 6) vs. Newborn GRS-stratified screening vs. No Screening.	calculated at birth (41-SNP) • Evaluates attrition rates ($25\%, 50\%, 75\%$) at the second AAb test.	*cost per case detected*.	screening but detected 35 more cases (per 10,000), $ICER =$ per case detected. • **Gen. Pop. (Ages 2 and 6)**: $ICER =$ per case detected. • **GRS-Stratified Strategy**: Incurred higher costs and detected fewer cases due to high genetic assay costs and longitudinal attrition.[26]
Australia (JDRF Model) [4]	• **Strategy 1**: Newborn GRS (heelprick), targeted AAbs at ages 1, 2, and 6. • **Strategy 2**: Infant saliva GRS, targeted AAbs at 1, 2, and 6.	• Baseline cohort: 100,000 children tracked from birth to age 30. • Cost inputs derived from local trial-based estimates.	*Reported as comparative incremental lifetime QALY gains across strategies*.	• **Strategy 1 (Optimal)**: $ICER =$ per QALY gained. Cost per screen-detected T1D: $480,798; cost per DKA avoided: $12,183.

	• **Strategy 3**: Population AAb at 2 and 6.			• **Strategy 2**: $ICER =$ per QALY gained. • **Strategy 3**: $ICER =$ per QALY gained.[4]

Key Drivers of Economic Viability

The economic viability of population-wide screening depends on several critical clinical and administrative factors:

Diabetic Ketoacidosis (DKA) Reduction and Hospitalization Costs

DKA is a severe, acute complication of undiagnosed $T1D$.[1] In England and Wales, 38% of pediatric patients present with DKA at clinical onset.[6] Pediatric DKA treatment requires hospitalization, incurring an immediate direct medical cost of £3,278 and introducing a clinical quality-of-life utility decrement of -0.0091.[6] Screening programs have been shown to reduce DKA incidence at diagnosis by up to 80%.[6] However, economic models indicate that if DKA prevention is the *only* clinical benefit of a screening program, the maximum justifiable expenditure per child is highly constrained, requiring all testing, registry, and follow-up costs to be covered under £3.17 to £3.31 per child.[6]

Long-Term Glycemic Control (HbA1c) and Beta-Cell Preservation

To justify higher up-front screening expenditures, early diagnosis must lead to sustained improvements in long-term glycemic control.[6] Preventing clinical DKA is associated with the preservation of residual beta-cell function (measured via C-peptide preservation), which translates to a more stable clinical course and lower lifetime glycated hemoglobin ($HbA1c$) levels.[6] In the UK model, if a screening program achieves a persistent 0.5% ($5\ \mathrm{mmol/mol}$) reduction in $HbA1c$, the reduction in future microvascular and macrovascular complications increases the maximum justifiable cost per child screened to a range of **£23.29 to £56.74** (depending on whether the benefit is maintained for 20 years, 30 years, 40 years, or a lifetime).[6] In the US ASK model, achieving standard cost-effectiveness thresholds of $\$50,000$ to $\$150,000$ per QALY gained requires a minimum 20% reduction in DKA

combined with a 0.1% ($1.1\ \text{mmol/mol}$) lifetime improvement in $HbA1c$.[23]

Longitudinal Attrition Rates

The economic viability of multi-stage screening protocols is highly sensitive to patient compliance over time.[4] In the Canadian model, which evaluated screening at ages 2 and 6, the base-case cost-effectiveness was modeled with perfect retention.[26] However, if the attrition rate (loss to follow-up) at the second autoantibody test reaches 25%, 50%, or 75%, the cost per case detected increases dramatically.[26] Specifically, with 50% attrition, the cost to detect a single presymptomatic case rises from $26,321 to $299,768, illustrating how patient attrition can undermine the economic justification for multi-stage screening.[26]

The Teplizumab Paradigm: Clinical Progress and the Cost-Effectiveness Conundrum

The clinical and economic landscapes of $T1D$ screening have been fundamentally altered by the development and FDA approval of teplizumab on November 17, 2022.[19] Teplizumab is a humanized monoclonal antibody that binds to the CD3 chain of the T-cell receptor complex on T lymphocytes.[18] In patients with early-stage $T1D$, infiltration of autoreactive CD8+ T cells leads to progressive pancreatic beta-cell destruction.[20] By binding to CD3, teplizumab delivers a partial agonistic signal that increases the proportion of regulatory T cells and promotes the exhaustion of autoreactive CD8+ T cells in the peripheral blood.[18] This dampens the autoimmune response, preserving functional beta-cell mass and delaying progression from Stage 2 to clinical Stage 3 disease.[18]

Teplizumab is indicated for adult and pediatric patients aged ≥ 8 years with confirmed Stage 2 $T1D$ (defined as carrying ≥ 2 positive islet autoantibodies and dysglycemia on an Oral Glucose Tolerance Test or alternative glycemic assessment).[18] The therapy is administered via a daily 30-minute intravenous infusion over a 14-day course.[20] Dosing scales progressively to minimize adverse reactions:

$$\text{Day 1: } 65\ \mu\text{g/m}^2 \quad \text{Day 2: } 125\ \mu\text{g/m}^2 \quad \text{Day 3: } 250\ \mu\text{g/m}^2 \quad \text{Day 4: } 500\ \mu\text{g/m}^2 \quad \text{Days 5–14: } 1,030\ \mu\text{g/m}^2$$

To mitigate common acute side effects—such as cytokine release syndrome (CRS), transient leukopenia, or viral reactivation—baseline complete blood counts and liver enzymes must be obtained, and patients should be premedicated with NSAIDs, antihistamines, or antiemetics during the first five days of dosing.[20]

Clinical Efficacy and Long-Term Delay of Stage 3 Onset

The landmark TN-10 phase 2 randomized, double-blind, placebo-controlled trial demonstrated the efficacy of a single 14-day course of teplizumab in delaying clinical onset.[18] The trial randomized 76 non-diabetic, high-risk first-degree relatives aged ≥ 8 years carrying ≥ 2 autoantibodies and dysglycemia to either teplizumab or placebo.[18]

- **Primary Trial Findings**: Over a median follow-up of 51 months, only 43% of the teplizumab group progressed to Stage 3 clinical T1D, compared to 72% of the placebo group.[20] The median time to clinical diagnosis was 48.4 months in the teplizumab arm versus 24.4 months in the placebo arm ($HR = 0.41$, 95% CI: $0.22–0.78$, $P = 0.006$).[20] The clinical benefit was most pronounced in the first year, during which only 7% of the teplizumab-treated cohort progressed, compared to 44% of the placebo cohort.[20]
- **Extension Trial Findings**: Long-term follow-up (median 76.9 months) showed a median time to diagnosis of 59.6 months with teplizumab versus 27.1 months with placebo, representing a median delay of approximately 32.5 months.[20] Furthermore, 50% of the teplizumab-treated cohort remained entirely diabetes-free at the end of the follow-up period, compared to 22% of the placebo group.[20]

The Health-Economic Paradox and Regulatory Hesitancy

While the clinical efficacy of teplizumab is clear, its cost introduces a significant health-economic challenge.[18] Teplizumab is priced at approximately $\$13,850$ per vial, equating to an average cost of $\$194,000$ for a single 14-day treatment course.[18] This up-front cost is substantially higher than the annual direct management cost of clinical diabetes ($\$5,960$ for pediatric patients and $\$20,320$ for adults).[18] While immunotherapy preserves C-peptide and reduces long-term complications, the immediate cost-effectiveness of this "screen-and-treat" pathway remains an area of ongoing debate.[28]
This economic challenge is reflected in the draft guidance issued in August 2025 by the UK National Institute for Health and Care Excellence ($NICE$).[29] $NICE$ declined to recommend routine NHS funding for teplizumab, citing substantial uncertainties within the economic model, including [29]:

- The precise definition and size of the clinical population eligible for teplizumab in real-world practice.[29]

- Uncertainties regarding the long-term healthcare costs of managing Stage 3 $T1D$ over a lifetime.[29]
- Inconsistent data regarding the precise impact of delaying clinical $T1D$ on a child's long-term quality of life.[29]

Importantly, $NICE$ highlighted the "Screen-and-Treat" paradox.[29] Because $T1D$ Stage 2 is entirely asymptomatic, eligible patients can only be identified through systematic autoantibody testing.[29] In its regulatory submission, the manufacturer excluded screening costs, arguing they were outside the evaluation's remit.[29] However, the Evidence Review Group (EAG) concluded that because no national screening programs exist, the costs of establishing a screening registry and follow-up framework must be considered alongside the drug's price to determine its true societal value.[29]

Systemic Barriers to Implementation and Clinical Care Integration

Translating integrated polygenic risk scoring and longitudinal autoantibody testing into routine clinical practice requires overcoming several substantial barriers.[2]

Ancestral Bias and Genetic Inequity

A primary limitation of existing $T1D\ \ GRS$ models is their historical development in cohorts of predominantly European-Caucasian ancestry.[2] Because the frequency of risk-associated alleles varies across ancestral populations, genetic risk scores lose predictive accuracy when applied to non-European cohorts.[2]

- **Predictive Drop**: A European-derived genetic risk score ($T1D_{EUR}\ \ GRS$) exhibits an AUC of only 0.798 when tested on independent cohorts of African ancestry.[10] Conversely, an ancestry-specific African genetic risk score ($T1D_{AFR}\ \ GRS$), optimized with weighted allele frequencies from African populations, achieves an AUC of 0.871 on the same cohort ($P < 2.2 \times 10^{-16}$).[10]
- **The Principle of Justice**: Applying a European-biased GRS to a diverse population can lead to clinical misclassification.[2] Minoritized infants may be miscategorized as low-risk and excluded from monitoring, while others may receive unnecessary clinical follow-up.[2] This discrepancy violates the ethical principle of justice by distributing the benefits of early screening unequally across racial and ethnic groups.[2]

Diagnostic Variability and Laboratory Logistical Hurdles

Implementing a national screening program is further complicated by diagnostic variability and laboratory logistical challenges:

- **AAb-Negative Clinical Presentations**: Approximately $6\% \text{ to } 7\%$ of children with clinically confirmed $T1D$ present with no detectable islet autoantibodies at onset, a rate that is higher in younger cohorts.[19] Early screening may yield false-negative results due to the temporal dynamics of autoimmunity, as some children seroconvert later.[19]
- **Assay Platform Discordance**: Autoantibody detection is highly dependent on the assay platform, with differences in sensitivity and epitope recognition between Radioligand Binding Assays (RBA), Enzyme-Linked Immunosorbent Assays ($ELISA$), Luciferase Immunoprecipitation Systems ($LIPS$), and Antibody Detection by Agglutination PCR ($ADAP$).[19]
- **Out-of-Pocket Expenses and Coding**: While screening kits may be free in research contexts (such as the ASK program or TrialNet), commercial clinical assays (e.g., Quest Health at $\$149$ plus fees) can impose out-of-pocket expenses on families.[2] Current billing relies on CPT codes 86341 and 86337, which do not differentiate the number of autoantibodies tested within a single claim, complicating clinical reimbursement.[24]
- **Provider Gaps**: Primary care providers often report insufficient knowledge regarding the interpretation of GRS and the clinical staging of presymptomatic $T1D$.[2] There are currently few established national pathways to guide primary care clinicians in transitioning an asymptomatic child from a positive screen to specialized endocrine monitoring.[29]

Psychological Impact and Family Distress

Screening healthy children for a chronic disease can also have a significant psychological impact on families.[31] Parents navigating newborn genetic and longitudinal antibody testing experience notable psychological distress [33]:

- **Anxiety Dynamics**: State Anxiety Inventory (SAI) data from the prospective TEDDY cohort showed that parents experience highly elevated anxiety upon learning their infant carries a high genetic risk.[34] While this anxiety declines to normal levels following repeated negative autoantibody ($AAb-$) tests, it rises sharply and persists if a child develops positive autoantibodies ($AAb+$).[34] Families faced with ≥ 2 positive autoantibodies experience high levels of state anxiety for extended periods.[34]
- **Gender and Age Disparities**: Mothers report higher levels of clinical anxiety and

depression than fathers.[35] In childhood management cohorts, 55% of mothers met clinical thresholds for anxiety disorders, compared to 22% of fathers; maternal depression was 26%, compared to 19% for fathers.[35] Furthermore, parents of younger children (aged $8–12$ years) experience significantly higher diabetes-specific distress than parents of adolescents (aged $13–18$ years), as the daily burden of care is more intensive.[36]

- **Clinical Integration Gaps**: While the American Diabetes Association (ADA) recommends routine, standardized screening for psychosocial concerns as an integral part of clinical diabetes care, these recommendations have not yet been widely adopted in comprehensive primary care or endocrine centers.[37]

Synthesis of Policy Recommendations

Implementing a national childhood screening program for $T1D$ requires a structured approach that addresses clinical, health-economic, and ethical considerations. Based on the synthesized evidence, several policy recommendations are proposed:

1. Integration with Existing Newborn Screening Panels

To optimize cost-effectiveness, newborn genetic risk scoring should be integrated into existing state or national dried bloodspot programs, rather than being established as a standalone service.[2] Routine newborn screening for rare diseases (which affect approximately 1 in 600 infants) typically costs between $\$125$ and $\$150$ per child.[5] In contrast, the combined prevalence of early $T1D$ and celiac disease is approximately 1 in 30, and these conditions can be screened for under $\$50$ per child, representing a favorable cost-to-benefit ratio.[5] This newborn genetic score can then be used to risk-stratify the population, limiting subsequent, more expensive longitudinal autoantibody testing to the high-risk cohort (e.g., those in the top population centiles).[4]

2. Multi-Ethnic GRS Validation and Standardized Assays

Public health agencies and research consortia should prioritize the development and validation of multi-ethnic polygenic risk scores.[2] Funding should support large-scale genome-wide association studies ($GWAS$) in diverse populations to ensure that GRS algorithms perform with high sensitivity and specificity across all ancestral backgrounds, thereby promoting equity in healthcare delivery.[2] Additionally, clinical laboratory standards must be established to harmonize autoantibody testing platforms (such as $ELISA$ and $ADAP$)

and minimize diagnostic discordance.[19]

3. Unified "Screen-and-Treat" Economic Modeling

Health technology assessment agencies and regulators should evaluate the cost-effectiveness of disease-modifying therapies (such as teplizumab) in conjunction with the screening registries required to identify eligible patients.[29] Drug manufacturers and public health systems should negotiate value-based pricing agreements and managed entry schemes.[29] These agreements should tie reimbursement to long-term clinical outcomes—such as the delay of Stage 3 onset and sustained reduction in $HbA1c$ —to offset the high upfront cost of therapy.[6]

4. EHR-Integrated Clinical Pathways and Provider Education

Healthcare systems should design and implement standardized clinical pathways within electronic health records (EHR).[2] When a child is identified as carrying high genetic risk, the EHR should automatically trigger clinical alerts at key milestones (e.g., ages 1, 2, and 6) to prompt primary care providers to order capillary autoantibody screens.[4] Furthermore, standardized clinician educational modules must be developed to guide primary care providers on antibody interpretation, the clinical staging of asymptomatic patients, and the appropriate referral of Stage 2 patients to specialized pediatric endocrine centers for intervention and monitoring.[2]

5. Standardized Family Psychosocial Support Networks

To address the psychological distress associated with positive genetic and autoantibody screening, public health programs must integrate standardized psychosocial counseling into the screening workflow.[31] When families receive high GRS or positive autoantibody results, they should be automatically connected with clinical health psychologists or trained counselors.[34] Standardized educational resources should be provided to reduce parental anxiety, clarify the distinction between presymptomatic stages and clinical onset, and offer clear pathways for clinical trial participation or therapeutic delay.[11]

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