Synthesize the current clinical and health-economic evidence regarding population-level genetic risk scoring combined with autoantibody screening for the early detection and prevention of type 1 diabetes. Explicitly address implementation barriers and cost-effectiveness.

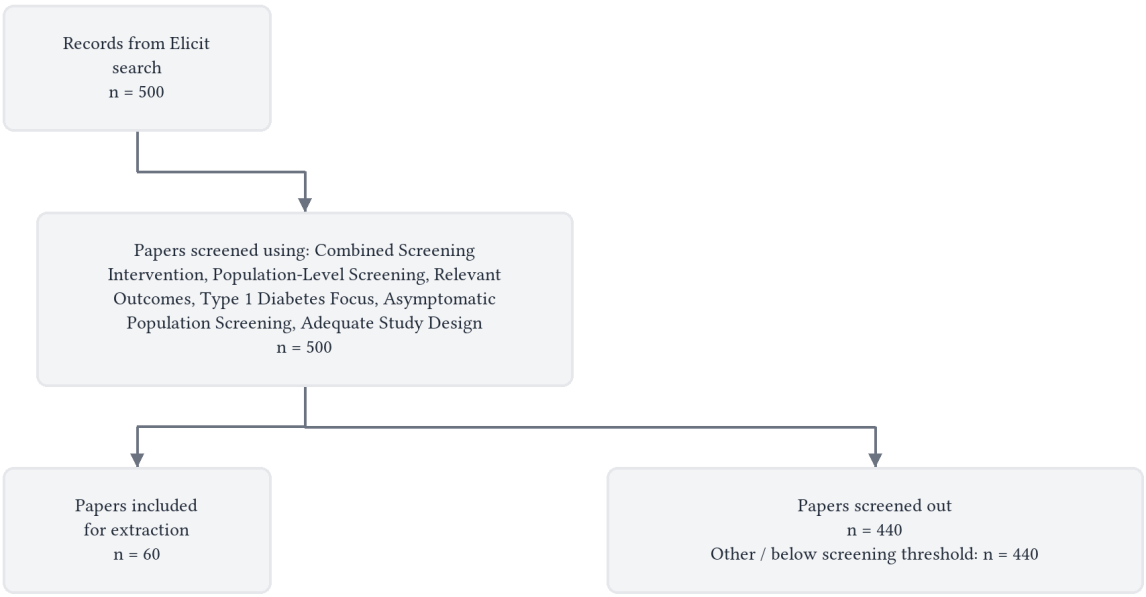
Population-level genetic risk scoring combined with autoantibody screening can accurately identify children who will develop type 1 diabetes (AUC ≥ 0.9), nearly eliminates diabetic ketoacidosis at diagnosis, and is cost-effective in high-income settings when paired with disease-modifying therapy such as teplizumab, but equitable implementation is constrained by poor genetic risk score performance in non-European ancestries, low uptake of blood-based autoantibody testing outside research infrastructure, and cost-effectiveness that remains highly sensitive to test pricing and therapeutic availability.

Abstract

Population-level genetic risk scoring combined with autoantibody screening for type 1 diabetes (T1D) is supported by a substantial evidence base spanning 60 sources across multiple countries and study designs. Two principal strategies have been evaluated: genetic pre-screening (using HLA typing or SNP-based polygenic risk scores with 30–67 variants) followed by sequential autoantibody testing in high-risk individuals, and population-wide autoantibody screening without genetic selection. Combined risk models integrating genetic risk scores, autoantibodies, and family history achieve strong predictive accuracy (AUC ≥ 0.9) for T1D over horizons up to 8 years in children aged 2 and older [1, 2]. Genetically targeted screening reduces per-child costs approximately threefold compared with pure immunological strategies ($217 vs. $619 over 10 years) [3], and newborn bloodspot genetic risk-stratified screening was identified as the most cost-effective approach in an Australian economic evaluation ($50,682 per QALY gained) [4]. The most consistent clinical benefit is a dramatic reduction in diabetic ketoacidosis at diagnosis, with rates as low as 3–5% in screened populations versus 15–80% in unscreened children [5, 6]. The approval of teplizumab, which delays clinical T1D onset by a median of 3 years [7], substantially strengthens the rationale for screening, particularly among individuals with higher genetic risk scores who show the greatest therapeutic benefit [8].

Key implementation barriers remain. Current genetic risk scores were developed and validated predominantly in European-ancestry populations, and real-world data confirm reduced performance in African ancestry newborns [9], limiting equitable deployment in diverse settings. While newborn screening acceptance exceeds 90% when integrated into existing infrastructure [10], consent for subsequent blood-based autoantibody testing drops sharply in community settings (as low as 7%) [11], identifying the transition from non-invasive genetic sampling to venipuncture as a critical bottleneck. Cost-effectiveness is highly sensitive to test costs, time horizon, and availability of disease-modifying therapy; breakeven in one US simulation required autoantibody test costs of $40 and GRS costs of $5 combined with a therapeutic delaying onset by at least 3 years [12]. In high-income countries with predominantly European-ancestry populations, newborn genetic risk-stratified screening followed by autoantibody surveillance represents the most cost-effective strategy when coupled with disease-modifying therapy, while population-wide autoantibody screening at well-child visits may be preferable where genetic testing infrastructure is limited or populations are ethnically diverse [13, 14].

Flow Diagram



Paper search

We performed a semantic search across over 138 million academic papers from the Elicit search engine, which includes all of Semantic Scholar and OpenAlex.

We ran this query: "Synthesize the current clinical and health-economic evidence regarding population-level genetic risk scoring combined with autoantibody screening for the early detection and prevention of type 1 diabetes. Explicitly address implementation barriers and cost-effectiveness."

The search returned 500 total results from Elicit.

We retrieved 500 papers most relevant to the query for screening.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Combined Screening Intervention**: Does the study evaluate both genetic risk scoring (polygenic risk scores, HLA typing, or other genetic markers) AND autoantibody screening (GAD, IA-2, ZnT8, IAA, or multiple autoantibodies) used together?
- **Population-Level Screening**: Does the study involve population-level or community-based screening programs targeting individuals at risk for type 1 diabetes (including general population, high-risk families, or specific age groups)?

- **Relevant Outcomes**: Does the study report on at least one of the following outcomes: early detection rates, prevention outcomes, implementation barriers, feasibility, acceptability, cost-effectiveness, or health economic outcomes?
- **Type 1 Diabetes Focus**: Does the study specifically investigate type 1 diabetes screening (rather than primarily focusing on type 2 diabetes, gestational diabetes, or other diabetes types)?
- **Asymptomatic Population Screening**: Does the study involve screening of asymptomatic populations for early detection/prevention (rather than diagnosis in symptomatic individuals or clinical confirmation of existing diabetes)?
- **Adequate Study Design**: Is the study design one of the following: randomized controlled trial, cohort study, cross-sectional study, case-control study, implementation study, economic evaluation, systematic review, or meta-analysis (i.e., NOT a case report, case series with <10 participants, or conference abstract without full publication)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

At abstract screening, the number of papers excluded for each primary reason was:

- **Other / below screening threshold**: n = 440

Data extraction

We asked a large language model to extract each data column below from each paper. We gave the model the extraction instructions shown below for each column.

- **Screening Approach**:

  Extract details about the population-level genetic risk scoring combined with autoantibody screening approach, including:

- Genetic testing method (HLA typing, SNP-based genetic risk scores, number of SNPs included)
- Autoantibody panel tested (which specific autoantibodies: insulin, GAD, IA-2, ZnT8)
- Screening algorithm (sequential vs. parallel testing, risk thresholds used)
- Age at screening (newborn, childhood, adolescent)
- Setting for screening delivery (newborn screening programs, well-child visits, specialized clinics)

- **Study Population**:

  Extract characteristics of the population screened for early detection and prevention of type 1 diabetes, including:

- Population type (general population vs. high-risk families)
- Geographic location and healthcare system context
- Sample size screened
- Age range of participants
- Family history of type 1 diabetes (percentage with first-degree relatives)
- Demographic characteristics relevant to implementation (ethnicity, socioeconomic status if reported)

- **Screening Performance**:

  Extract clinical effectiveness data for the combined genetic and autoantibody screening approach for type 1 diabetes detection/prevention, including:

- Prevalence of high genetic risk identified
- Autoantibody positivity rates in screened population
- Sensitivity and specificity for predicting type 1 diabetes development
- Positive and negative predictive values
- Time to diabetes progression in screen-positive individuals
- Proportion of future T1D cases identified through screening

- **Implementation Barriers**:

  Extract all barriers and challenges to implementing population-level genetic risk scoring combined with autoantibody screening for type 1 diabetes, including:

- Logistical challenges (sample collection, processing, result delivery)
- Healthcare system barriers (infrastructure requirements, training needs)
- Patient/family barriers (acceptance rates, psychological burden, follow-up compliance)
- Technical barriers (laboratory capacity, quality assurance, result interpretation)
- Regulatory or policy barriers
- Resource limitations or staffing challenges

- **Economic Data**:

  Extract all health-economic evidence related to population-level genetic and autoantibody screening for type 1 diabetes, including:

- Direct screening costs (per person screened, total program costs)
- Follow-up and monitoring costs for screen-positive individuals
- Cost-effectiveness ratios (cost per case detected, cost per quality-adjusted life year)
- Economic modeling assumptions and time horizons
- Cost comparisons with alternative screening strategies
- Budget impact assessments
- Cost-offset calculations (prevented DKA, complications avoided)

- **Clinical Outcomes**:

  Extract clinical outcomes and prevention effectiveness for individuals identified through population-level genetic and autoantibody screening for type 1 diabetes, including:

- Progression rates from screen-positive to clinical diabetes
- Prevention interventions offered to screen-positive individuals
- Effectiveness of prevention strategies in delaying diabetes onset
- Diabetic ketoacidosis rates at diagnosis in screened vs. unscreened populations
- Long-term clinical outcomes and complications
- Psychological impacts on screened families
- Participation rates in prevention trials among screen-positive individuals

- **Follow-up Protocol**:

  Extract details about monitoring and management of individuals identified as high-risk through population genetic and autoantibody screening for type 1 diabetes, including:

- Frequency and type of follow-up monitoring (glucose tolerance tests, HbA1c, repeat autoantibodies)
- Healthcare provider responsible for follow-up

- Criteria for intensified monitoring or intervention
- Patient education and counseling provided
- Integration with existing healthcare systems
- Duration of follow-up described
- Management protocols for different risk stages (stage 1, stage 2 T1D)

- **Study Methodology**:

  Extract study design and methodological details relevant to evaluating population-level genetic and autoantibody screening for type 1 diabetes, including:

- Study design (RCT, cohort study, implementation study, economic evaluation)
- Study duration and follow-up period
- Primary and secondary endpoints related to screening effectiveness
- Sample size and power calculations
- Comparison groups or control conditions
- Data collection methods
- Statistical analysis approaches used for screening performance or economic evaluation

Results

Characteristics of Included Studies

The 60 included sources span over three decades of research (1993–2026) and encompass a wide range of study designs, populations, and geographic settings. The majority originate from high-income countries in Europe, North America, and Australia. Study designs include prospective birth cohorts, economic evaluations, implementation/pilot studies, systematic and scoping reviews, qualitative studies, simulation models, and clinical trial analyses. Populations range from general newborn cohorts to first-degree relatives of individuals with T1D.

Study	Full Text Retrieved?	Study Type	Population	Geographic Setting	Sample Size
Winnie Chen et al., 2025	No	Economic evaluation (Markov microsimulation) [4]	General population [4]	Australia [4]	100,000 (modeled) [4]
A. Kupila et al., 2001	Yes	Prospective cohort [10]	General population newborns [10]	Finland [10]	31,526 [10]
M. Trusheim et al., 2022	No	Cohort simulation model [12]	General population [12]	United States [12]	Simulated (20 US births) [12]
C. Winkler et al., 2019	Yes	Screening program / RCT [15]	General population and high-risk families [15]	Germany, UK, Poland, Belgium, Sweden [15]	50,669 [15]

Study	Full Text Retrieved?	Study Type	Population	Geographic Setting	Sample Size
C. Meehan et al., 2015	No	Economic evaluation (cost-benefit) [16]	High-risk families [16]	Not specified [16]	Not specified [16]
J. Hahl et al., 1998	Yes	Economic evaluation [3]	General population [3]	Finland [3]	11,721 [3]
Kristin A Guertin et al., 2024	Yes	Implementation/pilot study [11]	General population [11]	Virginia, USA [11]	3,818 [11]
Marco Rossetti et al., 2026	Yes	Prospective cohort [17]	High-risk families (FDR) [17]	Northern Italy [17]	1,247 [17]
M. Schenker et al., 1999	Yes	Prospective cohort [18]	High-risk families (offspring) [18]	Germany [18]	1,429 [18]
Heli Siljander et al., 2009	Yes	Prospective cohort [19]	General population [19]	Finland [19]	7,410 [19]
Gonçalo Leiria et al., 2026	No	Patient-level simulation model [20]	General population [20]	USA [20]	100,000 (modeled) [20]
V. Anand et al., 2019	No	Cohort study (harmonized) [21]	General population and FDR [21]	USA, Sweden, Finland [21]	22,312 [21]
P. Delivani et al., 2019	No	Pilot/implementation study [22]	General population [22]	Saxony, Germany [22]	8,107 [22]
Docent Aaro Miettinen, 2010	No	Cohort studies / RCT [23]	Both general and high-risk [23]	Finland [23]	Up to 7,410 [23]
L. Ferrat et al., 2019	No	Cohort study [2]	High-risk families [2]	International [2]	7,883 [2]
J. Hahl et al., 2012	No	Economic evaluation (simulation) [24]	High-risk / general [24]	Finland [24]	Not specified [24]
Erin L. Templeman et al., 2025	Yes	Cohort study (TEDDY/TrialNet) [7]	High-risk families [7]	USA, Sweden, Germany, Finland [7]	7,798 + 4,068 [7]
Lauric A. Ferrat et al., 2020	No	Cohort study [1]	High-risk families [1]	International [1]	7,798 [1]
Emily Wion et al., 2003	No	Implementation study [25]	General population [25]	Washington State, USA [25]	Not specified [25]
Andreas Weiss et al., 2022	Yes	Cohort study [26]	General population [26]	Bavaria, Germany [26]	154,462 [26]
N. Gaddis et al., 2026	No	Implementation study [9]	General population [9]	North Carolina, USA [9]	1,742 [9]

Study	Full Text Retrieved?	Study Type	Population	Geographic Setting	Sample Size
Iman Algadi et al., 2024	No	Prospective cohort (pilot) [27]	High-risk families (FDR) [27]	Saudi Arabia [27]	176 families [27]
E. Bonifacio et al., 2025	Yes	Review / analysis [28]	General population [28]	Europe (EDENT1FI) [28]	Not specified [28]
O. Kordonouri et al., 2023	No	Review [29]	High-risk families [29]	Finland, Germany, Sweden, USA [29]	Not specified [29]
R. Insel et al., 2015	Yes	Review / implementation [14]	General population [14]	Bavaria, Germany [14]	200,000 [14]
E. Bonifacio et al., 2018	Yes	Prospective cohort (TEDDY) [30]	High-risk (no FDR) [30]	USA and Europe [30]	4,543 [30]
S. Mital et al., 2026	No	Economic evaluation (decision tree-Markov) [13]	General vs. targeted [13]	Canada [13]	Not specified [13]
R. Besser et al., 2021	Yes	Review [6]	General population [6]	UK [6]	90,632 (Fr1da reference) [6]
L. Ferrat et al., 2025	Yes	Cohort study [31]	High-risk families (TrialNet) [31]	International [31]	3,967 [31]
R. Franceschi et al., 2026	No	Implementation study / review [32]	General and high-risk [32]	Italy [32]	Not specified [32]
Erin L. Templeman et al., 2025a	Yes	Cohort study (TEDDY/TrialNet) [33]	General + high-risk [33]	USA, Sweden, Germany, Finland [33]	7,798 + 4,068 [33]
A. Hommel et al., 2017	No	Pilot/implementation study [34]	General population + FDR [34]	Saxony, Germany [34]	4,178 [34]
K. Gillespie et al., 2014	Yes	Cohort study [35]	High-risk families (siblings) [35]	United Kingdom [35]	2,134 [35]
F. Gorus et al., 2003	No	Cohort study [36]	High-risk families (FDR) [36]	Belgium [36]	>6,000 relatives [36]
E. Sims et al., 2022	Yes	Review of cohort/implementation studies [37]	General and high-risk [37]	Germany, USA, Sweden, Finland [37]	Variable [37]

Study	Full Text Retrieved?	Study Type	Population	Geographic Setting	Sample Size
W. Hagopian et al., 2011	Yes	Prospective observational cohort [38]	General population + FDR [38]	USA, Finland, Germany, Sweden [38]	421,047 [38]
J. Felton et al., 2023	Yes	Systematic review [39]	High-risk families [39]	Primarily European [39]	Median 510 per study [39]
O. Boiko et al., 2026	No	Mixed-methods (protocol) [40]	General population [40]	Eight European countries [40]	Not specified [40]
In This Issue of Diabetes Care, 2017	No	Cohort study summary [41]	High-risk families [41]	Belgium [41]	~7,000 relatives [41]
Florian M. Karl et al., 2022	Yes	Economic evaluation [42]	General population [42]	Bavaria, Germany [42]	90,632 [42]
J. Sherr et al., 2008	No	Review [43]	High-risk families [43]	Not specified [43]	Not specified [43]
B. Webb-Robertson et al., 2020	Yes	Nested case-control [44]	High-risk families (TEDDY) [44]	USA, Germany, Sweden, Finland [44]	314 [44]
Kruthika Narayan et al., 2025	Yes	Review [5]	General and high-risk [5]	Australia, NZ, Finland, Germany, USA [5]	Not specified [5]
Chantal Mathieu & P. Martens, 2022	Yes	Scoping review [45]	General and high-risk [45]	Europe [45]	Not specified [45]
Kimber M. Simmons & A. Michels, 2015	Yes	Review [46]	General and high-risk [46]	United States [46]	Not specified [46]
C. Lévy-Marchal, 1993	No	Review [47]	High-risk families [47]	Multi-country [47]	Not specified [47]
T. Danne et al., 2025	No	Review / consensus [48]	High-risk families [48]	Germany [48]	Not specified [48]
M. Redondo et al., 2018	Yes	Observational cohort [49]	High-risk families (TrialNet) [49]	USA (international) [49]	1,244 [49]
P. Achenbach et al., 2005	No	Review [50]	High-risk families [50]	Not specified [50]	Not specified [50]
L. Quinn et al., 2024	Yes	Qualitative study [51]	General population [51]	England [51]	38 parents [51]
B. Webb-Robertson et al., 2022	No	Prospective birth cohort [52]	General and high-risk [52]	Finland, Germany, Sweden, USA [52]	702 [52]

Study	Full Text Retrieved?	Study Type	Population	Geographic Setting	Sample Size
O. Kordonouri et al., 2021	No	Review [53]	General population [53]	Not specified [53]	Not specified [53]
Kate Citron-Zafrin et al., 2025	No	Review [54]	High-risk families [54]	Not specified [54]	Not specified [54]
L. Quinn et al., 2022	Yes	Qualitative study (protocol) [55]	General population [55]	UK (West Midlands) [55]	Up to 30 families [55]
M. Redondo et al., 2024	No	RCT analysis [8]	High-risk (autoantibody-positive) [8]	Not specified [8]	848 total [8]
M. A. Martínez-Brocca et al., 2025	No	Consensus document [56]	High-risk families (FDR) [56]	Spain [56]	Not specified [56]
Taylor M. Triolo et al., 2025	No	Cohort study [57]	High-risk (autoantibody-positive) [57]	Not specified [57]	4,324 [57]
Heidi Cope et al., 2025	No	Implementation study [58]	General population [58]	North Carolina, USA [58]	Not specified [58]
A. Steck et al., 2025	No	Cohort study [59]	High-risk (TrialNet) [59]	Not specified [59]	Up to 4,314 [59]
A. M. Luckett et al., 2025	No	Observational study [60]	T1D patients (retrospective) [60]	Not specified [60]	6,773 [60]

The included sources represent a substantial evidence base, with the largest screening programs enrolling over 400,000 infants (TEDDY) [38] and over 150,000 children (Fr1da) [26]. Most primary studies were conducted in populations of predominantly European ancestry [31, 39], which is an important limitation for generalizability. Geographic representation spans Finland, Germany, the UK, the USA, Australia, Canada, Belgium, Sweden, Poland, Italy, Saudi Arabia, and Spain, although most large-scale data originate from Northern Europe and North America.

Screening Approaches and Performance

Genetic Screening Methods

Two principal genetic screening strategies have been evaluated: traditional HLA typing and SNP-based polygenic genetic risk scores (GRS). Early programs in the 1990s and 2000s relied on HLA-DQB1 allele typing to identify at-risk newborns, as in the Finnish DIPP study [10] and the German BABYDIAB study [18]. The TEDDY study used a two-stage HLA genotyping approach across six international sites, screening 421,000 infants [38]. More recent initiatives have transitioned toward SNP-based GRS incorporating 30 to 67 T1D-associated variants. The GPPAD-02 study used a 46-SNP score [15], while TrialNet analyses have used a 30-SNP GRS [49] and subsequently the 67-SNP GRS2 [8, 31]. The Early Check program in North Carolina implemented whole-genome sequencing to derive a 67-variant GRS2 in a real-world newborn screening setting [9].

The Freder1k pilot study demonstrated the feasibility of integrating a simplified 3-SNP HLA approach into routine newborn screening [34], while the Virginia PrIMeD project used a custom genotyping panel with saliva-based DNA collection in children aged 2–16 years [11]. These approaches reflect the evolving balance between comprehensiveness and practical scalability.

Autoantibody Panels

Most programs test combinations of insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), islet antigen-2 antibodies (IA-2A), and zinc transporter 8 antibodies (ZnT8A) [5, 11, 26, 37, 45]. Earlier studies used islet cell antibodies (ICA) as a primary screen [3, 19], while more recent work has shifted to the four biochemically defined autoantibodies. The Fr1da study employed a 3-screen ELISA for initial screening followed by radiobinding confirmation assays [26]. One Italian cohort included a comprehensive five-marker panel (GAD65, IA-2, ZnT8, IAA, ICA) [17].

Sequential Versus Parallel Screening

The dominant paradigm across studies is sequential screening: genetic risk stratification first, followed by autoantibody testing in those identified as high risk [3, 5, 9, 10, 15, 22, 34]. This approach substantially reduces the number of individuals requiring autoantibody testing. An alternative strategy—population-wide autoantibody screening without prior genetic selection—has been implemented in the Fr1da study, testing children at well-child visits between ages 1.75 and 10 years [14, 26]. Bonifacio et al. (2025) proposed that repeated islet autoantibody screening at ages 2, 6, and 10 years remains the most effective standalone approach, potentially achieving up to 80% sensitivity [28], though genetic pre-screening may be practical in certain contexts.

Prevalence of High Genetic Risk

The proportion of individuals identified as having elevated genetic risk varies substantially depending on the score and threshold used:

Study / Program	Genetic Method	Prevalence of High Risk	Population
DIPP (Kupila et al., 2001)	HLA-DQB1 typing [10]	14.8% [10]	Finnish newborns [10]
DIPP (Hahl et al., 1998)	HLA-DQB1 typing [3]	13.0% [3]	Finnish newborns [3]
GPPAD-02 (Winkler et al., 2019)	46-SNP GRS [15]	1.1% [15]	European newborns [15]
Freder1k pilot (Delivani et al., 2019)	SNP-based GRS [22]	2.5% [22]	Saxony newborns [22]
Freder1k (Hommel et al., 2017)	3-SNP HLA score [34]	2.6% [34]	Saxony newborns [34]
TEDDY (Hagopian et al., 2011)	HLA class II typing [38]	4.8% [38]	International newborns [38]
PrIMeD (Guertin et al., 2024)	Custom SNP panel [11]	14.2% [11]	Virginia children (2–16 yrs) [11]
Early Check (Gaddis et al., 2026)	67-SNP GRS2 via WGS [9]	3.9% (higher concern) [9]	NC newborns [9]
BABYDIAB (Schenker et al., 1999)	HLA typing [18]	7.1% (DR3/4) + 5.0% (DR4/4) [18]	Offspring of T1D parents [18]

The higher-resolution polygenic risk scores (GPPAD, Freder1k) yield a smaller high-risk fraction (1–3%) than traditional HLA typing alone (5–15%), but they identify a subgroup at substantially greater absolute risk. In the TEDDY cohort, a merged genetic score above the upper quartile (>14.4) identified children with an 11.0% risk of developing multiple islet autoantibodies by age 6, compared with 4.1% in lower-scoring children [30]. The GRS2 demonstrated high discriminative ability, with an AUC of 0.92 in one analysis [5] and 0.94 specifically for very early onset T1D (diagnosed before age 2) [60].

Predictive Performance of Combined Screening

Combined genetic and autoantibody screening yields predictive accuracy that rivals or exceeds that achievable in high-risk family cohorts alone. In the Finnish DIPP study, combined HLA-based and autoantibody screening produced cumulative disease risks in general population children comparable to those observed in autoantibody-positive siblings of T1D patients (83% vs. 86% for combined GADA and IA-2A positivity) [23]. Siljander et al. (2009) reported that the combination of persistent ICA and IAA positivity achieved a positive predictive value of 91.7% and specificity of 100% [19]. Sensitivity for four-antibody positivity was 54.4% with a negative predictive value of 98.3% [19].

The combined risk score developed by Ferrat et al. (2020), integrating GRS, family history, and islet autoantibodies, achieved an AUC of 0.9 or greater for predicting T1D at ages 2 years and older over horizons up to 8 years [1]. The same group demonstrated that by age 2, combined scores were highly predictive of T1D in the next 5 years (AUC >0.91, 95% CI 0.88–0.95) [2]. A model integrating infant metabolite, genetic, and autoimmunity signatures in the TEDDY cohort achieved an AUC of 0.84 for predicting T1D by age 6 [52].

Progression from autoantibody positivity to clinical diabetes follows a well-characterized trajectory. In a harmonized analysis of four birth cohorts (n = 22,312), T1D developed in 26% of single-autoantibody-positive, 62% of double-autoantibody-positive, and 84% of triple-or-more-autoantibody-positive subjects within 15 years of seroconversion [21]. The T1D GRS2 independently predicted transitions through each preclinical stage, with hazard ratios of 1.11 (single autoantibody to stage 1), 1.05 (stage 1 to stage 2), and 1.13 (stage 2 to stage 3) [59].

The proportion of future T1D cases identifiable through screening depends on the strategy. The Finnish DIPP identified approximately 75% of children who developed diabetes at an early age using HLA genotyping [10]. Genetic scores in TEDDY identified nearly 50% of children who developed multiple autoantibodies or diabetes [30]. The GRS2 above the 90th population percentile captured 77% of future T1D cases [5]. Population-wide autoantibody screening at ages 2 and 6 could achieve 72% sensitivity [28].

Health-Economic Evidence

Direct Screening Costs

The cost per child screened varies by strategy, setting, and era of assessment:

Study	Strategy	Cost per Child Screened	Cost per Case Detected	Currency / Year	Country
Hahl et al., 1998	Genetic-targeted (10-yr)	$217 (PV) [3]	Not reported [3]	USD	Finland
Hahl et al., 1998	Pure immunological (10-yr)	$619 (PV) [3]	Not reported [3]	USD	Finland

Study	Strategy	Cost per Child Screened	Cost per Case Detected	Currency / Year	Country
Karl et al., 2022 (Fr1da)	Autoantibody screening (study)	EUR 28.17 [42]	EUR 9,117 [42]	EUR	Germany
Karl et al., 2022 (Fr1da)	Autoantibody screening (standard care)	EUR 21.73 [42]	EUR 7,035 [42]	EUR	Germany
Insel et al., 2015	Autoantibody at well-child visits	EUR 20 [14]	Not reported [14]	EUR	Germany
Bonifacio et al., 2018	GRS from bloodspot	<US$8 [30]	Not reported [30]	USD	International
Bonifacio et al., 2025	Islet autoantibody single-age	<EUR 10 [28]	Not reported [28]	EUR	Europe
Ferrat et al., 2025	GRS2	US$20 [31]	Not reported [31]	USD	USA
Rossetti et al., 2026	Full autoantibody panel	EUR 50–80 [17]	Not reported [17]	EUR	Italy
Weiss et al., 2022	Fr1da public health screening	EUR 21.73 [26]	EUR 33,400 (stage 2/3) [26]	EUR	Germany

The cost of the genetic component alone has declined substantially; GRS from dried blood spots can now be performed for less than US$8 [30], and the GRS2 is estimated at approximately US$20 [31]. Autoantibody testing costs range from under EUR 10 for a single assay [28] to EUR 50–80 for comprehensive panels [17]. The genetically targeted prediction strategy is markedly cost-saving compared with the pure immunological strategy: 10-year costs per child were $217 versus $619 (present value, 5% discount rate) in the Finnish analysis, primarily because fewer subjects require retesting [3].

Cost-Effectiveness Ratios

Study	Strategy Compared	ICER or Cost per Case	Threshold Context
Chen et al., 2025	Newborn bloodspot GRS + autoantibody (Strategy 1) vs. no screening	$50,682/QALY [4]	Australia (most cost-effective) [4]
Chen et al., 2025	Infant saliva GRS + autoantibody (Strategy 2) vs. no screening	$85,440/QALY [4]	Australia [4]
Chen et al., 2025	Population-wide autoantibody at two ages (Strategy 3) vs. no screening	$133,285/QALY [4]	Australia [4]

Study	Strategy Compared	ICER or Cost per Case	Threshold Context
Chen et al., 2025	Strategy 1 — per screen-detected T1D	$480,798/case [4]	Australia [4]
Chen et al., 2025	Strategy 1 — per DKA episode avoided	$12,183 [4]	Australia [4]
Trusheim et al., 2022	GRS + annual autoantibody + glucose	$225,000/case intercepted [12]	USA [12]
Mital et al., 2026	General population screening at age 4 vs. family history at ages 2 & 6	$11,383/case detected [13]	Canada [13]
Mital et al., 2026	General population screening at ages 2 & 6 vs. age 4	$25,923/case detected [13]	Canada [13]
Leiria et al., 2026	Multi-objective optimized strategies	Meet commonly cited thresholds [20]	USA [20]

The Australian analysis by Chen et al. (2025) identified newborn bloodspot genetic risk-stratified screening as the most cost-effective approach, with an ICER of $50,682 per QALY gained, sensitive to changes in time horizon, discount rates, and screening test costs [4]. The Canadian analysis found that general population screening at age 4 detected 35 more cases per 10,000 children than family history-based screening, at an incremental cost of $11,383 per case detected, which is comparable to other pediatric screening initiatives [13]. Notably, screening targeted solely at infants with high genetic risk involved higher costs and detected fewer cases than general population screening in the Canadian model [13].

The US simulation by Trusheim et al. (2022) estimated short-term incremental costs reaching $1.1 billion at current test costs, with breakeven achievable only if IAB test costs fell to $40 and GRS costs to $5, combined with a therapeutic that delays T1D onset by 3 years [12]. Hahl et al. (2012) estimated that a 2-to-3-year delay in disease onset could make a practice-oriented prevention model cost-saving in Finland, with annual per-person costs of EUR 797 compared to much higher diabetes treatment costs [24].

Cost Offsets

Several studies projected meaningful cost offsets from DKA prevention and delayed diagnosis. Avoiding DKA at diagnosis could save approximately $33,000 per event, and delaying diagnosis by 5 years could save approximately $88,000 per individual over a lifetime, against an average lifetime T1D cost of approximately $500,000 [5]. In Germany, screening 200 children was estimated to save approximately EUR 680,000 through DKA and hospitalization prevention [14]. The annual average medical cost for a child with T1D is approximately $9,000, and a single DKA hospitalization can exceed $20,000 [46].

Clinical Outcomes

DKA Prevention

One of the strongest and most consistent findings across studies is the reduction in DKA at diagnosis among screened populations. The Fr1da study and similar programs report DKA rates as low as 3.2–5% in screened children, compared

with 15–80% in unscreened general populations [5]. Besser et al. (2021) reported a 90% reduction in DKA rates in screened populations [6]. Insel et al. (2015) documented rates of 16.1% versus 39.5–54% in children under 2 years, and 13.1% versus 16.9–36.4% in children under 5 years, when comparing screened to unscreened populations [14]. Screened children also showed lower hospitalization rates (<10% vs. >40%) and lower HbA1c at diagnosis [14].

Disease-Modifying Therapies

The therapeutic landscape has shifted substantially with the approval of teplizumab, an anti-CD3 monoclonal antibody that delays progression from stage 2 to clinical (stage 3) T1D by a median of approximately 3 years [6, 7, 33, 55]. The effect appears to be modulated by genetic risk: in the TN10 trial, teplizumab reduced T1D risk significantly in participants with GRS2 ≥13 (HR 0.263, 95% CI 0.123–0.562) but not in those with GRS2 <13 (HR 0.898) [8]. Other prevention trials tested oral insulin, nasal insulin, abatacept, and nicotinamide [10, 15, 19, 45, 47, 53]. The Finnish nasal insulin trial and the DPT-1 oral insulin trial did not demonstrate overall efficacy, though a subgroup with high insulin autoantibody levels showed a delay of approximately 5 years with oral insulin [19, 46]. The GPPAD network has launched the POInT trial testing oral insulin for primary prevention of beta-cell autoimmunity [22, 53].

Psychological Impact

Screening programs consistently report that psychological distress, while present initially, is transient and manageable. In the Freder1k pilot, none of 31 assessed families demonstrated signs of excessive burden [34]. The DIPP study noted only transient anxiety among families [10]. Parents in the UK qualitative study expressed uncertainty about screening benefits versus potential anxiety, and described preferences for less invasive testing, structured healthcare support, and peer support [51]. Higher anxiety levels were observed in non-white ethnicities and those with lower educational attainment [5]. The EDENT1FI program is prospectively studying psychosocial impact across eight European countries with longitudinal assessments [40].

Implementation Barriers

Technical and Logistical Challenges

A major technical barrier is the limited performance of current genetic risk scores in non-European ancestry populations. GRS2 scores were lower in African ancestry newborns in the Early Check program, highlighting the need for ancestry-specific thresholds or models [9]. The systematic review by Felton et al. (2023) found that populations studied were almost exclusively of European ancestry [39], and the TEDDY-derived genetic scores were originally developed from case-control studies of mainly European-descent populations [30]. Only 43% of studies included in the Felton et al. review reported autoantibody assay standardization efforts [39], raising quality assurance concerns for multi-site implementation.

Sample collection logistics vary by approach. The saliva-based collection used in Virginia PrIMeD was feasible but consent for subsequent blood-based autoantibody testing was limited to 7.0% of eligible high-risk children, largely due to the SARS-CoV-2 pandemic and the invasiveness of venipuncture [11]. Dried blood spot collection is more readily integrated into existing newborn screening infrastructure [25, 30], while whole-genome sequencing from dried blood spots has been demonstrated as feasible but not yet at scale in the US [9].

Healthcare System and Resource Barriers

Infrastructure requirements include laboratory capacity for both genotyping and autoantibody measurement, trained personnel for counseling and result delivery, and coordination systems for longitudinal follow-up [15, 42]. The Fr1da

study documented costs of EUR 12.25 per child in the medical practice and EUR 9.34 for coordination and laboratory [42]. Screening programs require integration with existing pediatric care visits; Besser et al. (2021) recommended aligning with NHS well-child visits [6], and Franceschi et al. (2026) described primary care physicians performing capillary blood sampling [32].

Cost remains a fundamental barrier. Trusheim et al. (2022) estimated short-term net incremental costs reaching $1.1 billion at current test costs in the US [12]. Mital et al. (2026) noted that while general population screening detects more at-risk children, it also incurs higher costs than targeted approaches [13]. The absence of disease-modifying interventions was historically the primary argument against screening [45], though the approval of teplizumab has partially addressed this [54].

Patient and Family Factors

Participation rates are generally high when screening is offered within newborn programs—94.4% acceptance in the Finnish DIPP [10], 65.5% in the Freder1k pilot [22], and 80% follow-up adherence in Freder1k [34]. However, follow-up for autoantibody testing may be challenging: in the PrIMeD study, only 7.0% of high-risk children consented to blood-based autoantibody screening [11]. Bonifacio et al. (2025) emphasized that low recall rates, socioeconomic biases, and limited applicability across diverse ancestries remain significant hurdles, and that the ultimate success of screening depends less on specific strategies and more on maximizing public engagement [28]. Quinn et al. (2024) found that parents expressed uncertainty about benefits versus anxiety, and described preferences for peer support and psychological counseling [51].

Monitoring and Follow-Up of Screen-Positive Individuals

Follow-up protocols vary across programs but generally involve serial autoantibody testing at defined intervals. The DIPP study used 3-month intervals until age 2, then semiannual visits [10]. TEDDY monitored participants every 3 months until age 4, with frequency adjusted by autoantibody status thereafter [7, 33]. The Fr1da program used 2–6-month interval assessments with OGTT and HbA1c for children with multiple autoantibodies [26]. Insel et al. (2015) recommended 6-monthly visits for stage 1 (normoglycemia) and 2–3-monthly visits for stage 2 (dysglycemia) [14], with HbA1c increase of 10% or absolute value ≥5.9% triggering intensified monitoring [14].

Healthcare providers responsible for follow-up range from primary care pediatricians in population programs [32, 46] to specialist pediatric diabetes clinics for staged monitoring [5, 26]. Narayan et al. (2025) described monitoring modalities including OGTTs, fingerprick glucose tests, and continuous glucose monitoring (CGM), with frequency determined by age and autoantibody status [5]. Multiple studies highlight the importance of integrating psychological support and education into follow-up, including information about progressive dysglycemia, DKA signs, and emerging immunotherapies [5, 14, 51].

Synthesis

The apparent tension in this literature—between studies concluding that population screening is feasible and cost-effective, and those raising substantial concerns about cost and scalability—can be reconciled by examining several key distinctions.

First, the cost-effectiveness of screening is highly sensitive to the availability and effectiveness of disease-modifying therapy. The Australian model yielded an ICER of $50,682/QALY for the most favorable strategy [4], which is within conventional willingness-to-pay thresholds in high-income countries. In contrast, the US simulation projected breakeven only with substantially reduced test costs and a therapeutic delaying onset by at least 3 years [12].

The approval of teplizumab, which delays clinical T1D by a median of 3 years [7], fundamentally alters these calculations and shifts the cost-effectiveness calculus in favor of screening, particularly for individuals with higher genetic risk scores (GRS2 ≥13) who show the greatest treatment benefit [8].

Second, the choice between genetic pre-screening followed by autoantibody testing versus population-wide autoantibody screening alone reflects a trade-off between per-case cost and population reach. The genetically targeted strategy reduces per-child costs by approximately threefold compared with pure immunological screening (10-year present-value costs of $217 vs. $619 per child in Finland) [3], because 85–99% of the population is excluded from costly autoantibody surveillance. However, this comes at the expense of sensitivity: HLA-based genetic screening identifies 60–80% of future T1D cases [3], while the higher-resolution GRS captures approximately 50% with a >10% risk threshold [30]. The Canadian analysis paradoxically found that targeting only genetically high-risk infants detected fewer cases at higher cost than general population screening [13], suggesting that the test characteristics and prevalence dynamics of the general population may favor broader approaches in some settings.

Third, the challenge of ethnic and ancestral diversity fundamentally limits the current evidence base. GRS2 was developed and validated predominantly in European-descent populations [30, 39], and early real-world data from the Early Check program confirmed lower GRS2 scores in African ancestry newborns [9]. Until ancestry-specific or multi-ancestry risk scores are validated, population screening programs in diverse settings will produce systematically biased risk stratification, disproportionately underserving non-European populations.

Fourth, the practical difference between research-based screening adherence and real-world uptake is substantial. While newborn screening acceptance exceeds 90% when embedded in existing infrastructure [10], consent for subsequent blood-based autoantibody testing falls dramatically in community settings (7% in the PrIMeD study) [11]. The transition from capillary or saliva-based genetic testing to venipuncture-based autoantibody testing represents a critical drop-off point that must be addressed through less invasive autoantibody assays, point-of-care testing, or capillary blood sampling approaches [14, 46].

In specific contexts, the evidence supports the following conclusions: (1) in high-income countries with predominantly European-ancestry populations, newborn genetic risk-stratified screening followed by autoantibody surveillance is the most cost-effective strategy, particularly when coupled with teplizumab or equivalent disease-modifying therapy [3, 4]; (2) population-wide autoantibody screening at well-child visits (ages 2–6) without genetic pre-selection may detect more cases in settings where genetic testing infrastructure is limited or where diverse populations reduce GRS utility [13, 14]; (3) for first-degree relatives, autoantibody-based screening remains highly effective given the elevated baseline risk, and GRS further improves risk stratification for clinical trial enrollment and therapeutic selection [8, 49]; and (4) the greatest immediate public health benefit of any screening strategy is the near-elimination of DKA at diagnosis, which alone produces meaningful clinical and economic benefits independent of disease-modifying therapy [5, 6, 14].

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