Costs of Public Health Screening of Children for Presymptomatic Type 1 Diabetes in Bavaria, Germany

Short running title: Costs of screening for type 1 diabetes

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Abstract

Objective: Evaluation of costs associated with public health screening for presymptomatic type 1 diabetes in 90,632 children as part of the Fr1da study in Bavaria and in forecasts for standard care.

Research Design and Methods: We report on resource utilization and direct costs for screening-related procedures in the Fr1da study coordination center and laboratory, and in participating pediatric practices and local diabetes clinics. Data was obtained from Fr1da study documents, an online survey among pediatricians, and interviews and records of Fr1da staff members. Data were analyzed with tree models that mimic procedures during the screening process. Cost estimates are presented as they were observed in the Fr1da study and as they can be expected in standard care for various scenarios.

Results: The costs per child screened in the Fr1da study were €28.17 (95% CI: 19.96; 39.63) and the costs per case diagnosed with presymptomatic type 1 diabetes were €9,117 (6,460; 12,827). Assuming a prevalence of presymptomatic type 1 diabetes of 0.31%, as in the Fr1da study, the estimated costs in standard care in Germany would be €21.73 (16.76; 28.19) per screened child and €7,035 (5,426; 9,124) per diagnosed child. Of the projected screening costs, €12.25 would be the costs in the medical practice, €9.34 for coordination and laboratory, and €0.14 for local diabetes clinics.

Conclusions: This study provides information for the planning and implementation of screening tests for presymptomatic type 1 diabetes in the general public and for the analysis of the cost-effectiveness of targeted prevention strategies.

Type 1 diabetes is a chronic autoimmune disease characterized by destruction of the insulin-producing pancreatic beta cells and requires lifelong treatment with insulin (1). The worldwide prevalence of type 1 diabetes in individuals <20 years of age was estimated to be 0.4% in 2019 (2, 3), and incidence rates are rising in many countries (1, 3). The clinical onset of type 1 diabetes is often associated with diabetic ketoacidosis (DKA), which is a severe acute complication that can be life-threatening and is mainly caused by a delayed diagnosis of type 1 diabetes. The frequency of DKA at the onset of the disease has increased in the last two decades and is over 20% in Germany and over 45% in the USA (4-6).

The health and economic consequences of type 1 diabetes and DKA are significant. People with type 1 diabetes have an increased risk for various micro- and macrovascular complications (1, 7), a lower life expectancy (8), and experience a significant decrease in health-related quality of life (9, 10). Presence of DKA at the time of clinical diagnosis is associated with worsened long-term blood glucose control and increases the risk of vascular complications and memory deficits (8, 11-13). Excess annual medical expenditure per person with type 1 diabetes are estimated to be $6,288 in the USA (14), and €3,745 in Germany (15). The annual excess health care costs associated with DKA in both countries have a similar dimension and are estimated to be $7,612 and €3,605 in the USA and Germany, respectively (16, 17).

Diagnosing type 1 diabetes at an early, presymptomatic stage may lower the incidence rate of DKA and could reduce morbidity in patients (18, 19). However, previous studies indicated that screening for presymptomatic type 1 diabetes is unlikely to be cost-effective if only the health and economic benefits associated with prevention of DKA at disease onset are considered, unless the screening costs are less than $1 (16, 20). Cost analyses must therefore also consider the long-term positive effects of screening for improved blood glucose control and reduced patient morbidity (20). In

addition, now that interventions that delay disease progression are becoming realistic in type 1 diabetes (21, 22), the cost-effectiveness of screening and early diagnosis required for any kind of targeted prevention strategy needs to be assessed from yet another perspective.

There have been few attempts to perform population-based screening for presymptomatic type 1 diabetes (23). Consequently, there are only limited estimates of the costs of such public health screening (16, 20). In 2015, we initiated the Fr1da study in Bavaria, Germany, which to date is the largest public health screening program for presymptomatic type 1 diabetes worldwide (24, 25). The study is conducted in collaboration with pediatric practices in the context of routine child care and included over 90,000 children at the time of our analysis.

Here, we present a detailed description of the costs associated with public health screening for presymptomatic type 1 diabetes in the Fr1da study research setting, including costs per child screened and costs per case diagnosed, and provide estimates of the corresponding costs that would be expected in standard care in Germany.

Research Design and Methods

Study participants

The Fr1da study offered screening for islet autoantibodies to children aged 1.75 to 5.99 years in Bavaria, Germany. Families of children who had multiple islet autoantibodies positive (i.e. presymptomatic type 1 diabetes) were invited to participate in a program of diabetes education, metabolic staging, assessment of psychological stress associated with diagnosis, and prospective follow-up for progression to clinical diabetes. Details on the Fr1da study protocol have been described previously (24, 25). The study was approved by the institutional review board at Technical University Munich. This analysis includes data from 90,632 children (median age 3.1

years; interquartile range [IQR] 2.1-4.2; 47% girls) who participated in the Fr1da study between February 2015 and May 2019 and of whom 280 (0.31%) were diagnosed with presymptomatic type 1 diabetes (25).

Procedures in the Fr1da study

Recruitment, consenting and blood sampling Study participants were recruited during medical check-ups in pediatric practices. Primary care pediatricians offered screening to families, obtained written informed consent from the parents or legal guardian, and took a capillary blood sample from the child. Once a week, the pediatricians sent the collected blood samples by courier to the Fr1da study coordination center and laboratory. The coordination center provided pediatricians with study materials (i.e. information and consent forms, lancets and blood collection tubes), and established a telephone hotline for additional information.

Blood sample processing, islet autoantibody measurements and results communication In the Fr1da study coordination center and laboratory, the samples were processed and prepared for analysis. Processing included centrifugation of capillary blood samples to obtain serum. Data associated with the samples were entered into the study database. If necessary, the study center contacted the pediatricians to complete missing information. Sera were tested for the presence of autoantibodies to GAD (GADA) and/or insulinoma-associated antigen-2 (IA-2A) and/or zinc transporter-8 (ZnT8A) using the 3-Screen Islet Cell Antibody ELISA (RSR Ltd., Cardiff, UK) (26, 27). If the ELISA result was positive, GADA, IA-2A, ZnT8A and insulin autoantibodies (IAA) were each tested separately in the remaining serum by radiobinding assay (RBA) (28-30). If two or more distinct islet autoantibodies were detected in the RBAs, a venous blood sample was requested for confirmation and retested separately for GADA, IA-2A, ZnT8A, and IAA with RBAs. The results of the autoantibody measurements were reviewed and discussed by a physician,

a scientist and a laboratory technician during weekly consultation meetings. Children were diagnosed with presymptomatic type 1 diabetes if two or more islet autoantibodies were positive in both the screening and confirmation samples. In these cases, the child's pediatrician was informed of the diagnosis and autoantibody status. The pediatrician then informed the family and arranged contact with the Fr1da study coordination center.

Staging and education Children with presymptomatic type 1 diabetes were invited to participate in metabolic staging and an educational program at a pediatric diabetes clinic close to the family's home. An oral glucose tolerance test (OGTT) was performed for staging, and glycated hemoglobin (HbA1c) was measured. Presymptomatic type 1 diabetes was classified as stage 1, 2 or 3 as previously advocated (31, 32).

Design of costing approach

We describe the direct medical costs that result from the Fr1da public health screening from a health care system perspective. For this purpose, we adopted a micro-costing approach, in which we evaluated the time and resources associated with screening using respective prices or reimbursement rates within the German health care system. Specifically, we examined the extra costs per child screened for presymptomatic type 1 diabetes. This included the cost of time for physicians, nurses, laboratory staff, and scientists, as well as the cost of materials used to inform families about the Fr1da study, obtain consent, draw capillary or venous blood, analyze samples, and report results. Furthermore, this included the cost of staging and educating children with presymptomatic type 1 diabetes at a local diabetes clinic.

In our analysis, we subdivided the costs per child screened in the Fr1da study into three categories; a) costs of sample acquisition, b) costs of sample analysis and result communication, and c) costs of staging and education. Within the first two categories, we distinguished between costs for

participating pediatricians and for the Fr1da study coordination center and laboratory. Costs for metabolic staging and education of children diagnosed with presymptomatic type 1 diabetes were incurred only by local diabetes clinics.

To determine these costs, we described the patient-flow and associated resource utilizations within the three categories of the screening process in respective tree models. Main data sources were the Fr1da study documents detailing the sequence of tests and communication for each of the 90,632 participating children, an online survey returned by 134 of the 682 participating primary care pediatricians, and documentation of timesheets and interviews with Fr1da study coordination center and laboratory staff.

Assessment of costs and probability of screening procedures

Costs were estimated by identifying all events during the screening process that were associated with any resource utilization (e.g. time or material). For each identified event, we assessed the amount of resources consumed and multiplied this amount with the unit-costs of the respective resource.

The amount of resources was assessed in different ways. Regarding time spent by pediatricians, we used survey data (Supplementary Material) that contained information on who (i.e. nurse or pediatrician) performed a specific procedure (e.g. blood collection) at the practice, and how much time it took. In the analysis, we used 75% of the time estimated by doctors to take into account an overestimation, as previously reported (33, 34). Furthermore, the data was whiskered excluding the upper and lower 5% of response values. Regarding time spent by staff at the Fr1da study coordination center and laboratory, we conducted interviews and reviewed timesheets to estimate the time needed for logistics (e.g. hotline or data management), sample processing, antibody

measurements and evaluation of test results. An overview of the estimated resource units utilized per child screened is provided in Supplementary Table S1.

The cost of medical staff time utilized was estimated using federal income statistics for nurses', laboratory workers', and scientists' time costs (35, 36) and data from a representative survey on the economic situation of ambulatory physicians (ZiPP), including income statistics for pediatricians (37). The material costs were drawn from the cost plan of the Fr1da study. Costs for staging and education were drawn from the uniform valuation standard (EBM) of the National Association of Statutory Health Insurance Physicians (KBV) (38). Details on the estimated costs per unit are provided in Supplementary Table S2.

The cost per procedure was multiplied with the respective probability of occurrence. The main data source for the probability assessment were Fr1da study documents, which tracked the sequence of tests and communication (e.g. sample requests) regarding every sample.

Assessment of uncertainty We used empirical distributions on key cost and probability parameters to estimate the uncertainty around our cost estimates. In order to estimate respective 95% confidence intervals, we drew 1000 random values of the respective distributions. Likewise, we conducted 1000 simulations of the different models, simultaneously drawing random values from all underlying cost and probability distributions.

Scenarios for islet autoantibody screening in routine care

Further to the analysis of costs as observed in the Fr1da study, we adapted the analysis model to mimic screening for presymptomatic type 1 diabetes in standard care in Germany. For the projected standard care scenario, we considered only 50% of the costs associated with obtaining informed consent in the Fr1da study and assumed that negative screening results would be

communicated to families only if a second blood sample was requested to confirm the initial screening results. Furthermore, we assumed that all children diagnosed with presymptomatic type 1 diabetes would receive metabolic staging and diabetes education as part of standard care.

In addition, several other scenarios were analyzed. First, we repeated the analysis under standard care conditions, but included higher (€4.96 per minute) or lower (€1.24 per minute) pediatrician time costs, as these costs vary across countries. Second, we analyzed the standard care scenario with higher (€3.60 per test) or lower (€1.40 per test) costs for the 3-Screen ELISA; a range based on the expected market price of the test kit when purchased outside of a research setting where special discounts are granted.

Results

Cost of screening for presymptomatic type 1 diabetes as observed in the Fr1da study

The costs associated with screening in the Fr1da study were estimated for a) sample acquisition, b) sample analysis and result communication, and c) staging and education, and are summarized in Figure 1 (cost of each measure) and Table 1 (total cost per child), with the calculation of costs explained in Supplementary Table S3.

Costs for sample acquisition A total of 90,632 children were recruited to participate in screening for presymptomatic type 1 diabetes (Fig. 1A). Per child, the pediatric practice incurred an average of €12.77 for obtaining informed consent, €3.40 for the collection of a capillary blood sample and €0.72 for packaging the sample. The average time required for sample acquisition in the pediatric practice was 14 minutes, including information and consent (5.14 min), capillary blood collection (4.00 min) and packaging of samples (4.90 min). These activities were performed by physicians in 100%, 23% and 6% of cases, respectively, and by nurses in the remaining proportions. The costs

of the Fr1da study coordination center per child for sample acquisition were on average €0.18 material costs for lancets and tubes, €0.23 shipping costs per sample, and €2.57 logistics and infrastructure costs.

From 535 children, the blood sample sent to the laboratory was not sufficient for screening, so the coordination center contacted the pediatrician and requested a new sample (€0.80 postage per child). A second screening sample was obtained from 108 of the 535 children resulting in costs for time and materials for capillary blood collection and for packaging and shipping the samples (Fig. 1A).

The average total cost of sample acquisition per child enrolled in the Fr1da study was €19.96 (95% CI: 12.16; 30.97), of which €16.96 (9.25; 28.05) was for the pediatric practice and €2.99 (2.25; 3.68) for the coordination center and laboratory (Table 1).

Costs for sample analysis and result communication For each of the 90,205 blood samples received with sufficient volume for screening (Fig. 1B), the average laboratory costs were €2.70 for sample processing (including €0.18 material costs and €0.07 for queries to the pediatric practice) and €2.98 for the ELISA test (including €1.20 material costs). In addition, the average costs for RBA testing of GADA, IA-2A, and ZnT8A in 3763 samples were €8.13 (including €5.50 material costs) and of IAA in 2336 samples were €9.51 (including €6.50 material costs). For the review and interpretation of RBA results by a medical specialist, a scientist and a laboratory staff member, an average cost of €3.65 (for 1 minute) per sample was estimated. Following data review, the pediatricians of 310 children were contacted by the coordinating center because two or more islet autoantibodies were detected positive in the screening sample, and an additional venous blood sample was requested for confirmation in each case (€0.80 postage per child). Nineteen children developed clinical type 1 diabetes before the confirmatory sample was collected. A venous blood

sample was obtained from 278 children. Pediatricians incurred average costs of €12.75 per venous blood draw. As previously described for capillary blood, other costs were associated with sample collection materials, sample packaging and shipping, sample processing and RBA testing, and assessment of results. Of the 278 venous blood samples, 261 were confirmed as multiple islet autoantibody-positive in RBAs, and the children were diagnosed with presymptomatic type 1 diabetes. The child's pediatrician received a letter with the findings and diagnosis (€0.80 postage per child), while negative screening results were communicated by automated e-mail (€0.00). The average cost of the pediatrician to communicate the diagnosis to the family was estimated at €27.16 (time costs only). In addition, pediatricians discussed a negative screening result in the confirmatory sample with families in 18% of cases, which was associated with a time cost of €9.59 per case (€1.73 per negative result).

The average total cost of sample analysis and result communication per child enrolled in the Fr1da study was €8.10 (95% CI: 6.33; 11.03), of which €1.74 (0.35; 4.66) was for the pediatric practice and €6.36 (5.47; 7.20) for the coordination center and laboratory (Table 1).

Costs for staging and education A total of 220 children diagnosed with presymptomatic type 1 diabetes received metabolic staging and education at local diabetes clinics (Fig. 1C). The costs for an OGTT and HbA1c measurement were €14.17 and €4.00, respectively (38). The cost per child and family educated was estimated at €33.00. The average total cost of staging and education per child enrolled in the Fr1da study was €0.11 (95% CI: 0.10; 0.13) (Table 1).

Composite cost of screening for presymptomatic type 1 diabetes The average total cost of screening for presymptomatic type 1 diabetes per child enrolled in the Fr1da study was €28.17 (95% CI: 19.96; 39.63), of which €18.70 (10.82; 30.28) was incurred by the pediatric practice,

€9.35 (8.18; 10.45) by the coordination center and laboratory, and €0.11 (0.10; 0.13) by the local diabetes clinic (Table 1).

Overall, 280 (0.31%) of 90,632 children were diagnosed with presymptomatic type 1 diabetes. The average cost per diagnosed child was €9,117 (95% CI: 6,460; 12,827) (Table 1).

Estimated cost of screening for presymptomatic type 1 diabetes in standard care in Germany

In a simulated standard care scenario for Germany, assuming the same prevalence of presymptomatic type 1 diabetes of 0.31% as in the Fr1da study, the average cost per child for screening was estimated at €21.73 (95% CI: 16.76; 28.19), including €9.34 (8.29; 10.42) for laboratory costs, €12.25 (7.24; 18.52) for pediatrician costs, and €0.14 (0.12; 0.15) for local diabetes clinics to perform metabolic staging and education in children diagnosed with presymptomatic type 1 diabetes (Table 2). In this model, 50% of the costs incurred in the Fr1da study for obtaining informed consent were included, autoantibody-negative results in the initial screening sample were not communicated to families, and all children with presymptomatic type 1 diabetes underwent staging and education. The estimated average cost per diagnosed child was €7,035 (95% CI: 5,426; 9,124) (Table 2).

Alternative models were based on the standard care scenario but calculated higher (plus 100%) or lower (minus 50%) pediatrician time costs, or estimated lower or higher costs for the 3-Screen ELISA (Table 2). The average cost per child for screening for presymptomatic type 1 diabetes ranged from €15.70 (95% CI: 13.28; 18.51) up to €33.80 (23.72; 47.43) in these models. The analysis showed that screening costs were more sensitive to changes in physician time costs than to changes in ELISA test kit costs.

Conclusions

In this study, we provide detailed information on the costs associated with a public health screening for presymptomatic type 1 diabetes in Germany. We report these costs as observed in the Fr1da study, totaling €28.17 per child studied, and specifically as incurred by participating pediatricians, the study coordination center and laboratory, and local diabetes clinics. In addition, we estimate the total costs that would be expected for screening as part of standard care in the German health care system to be €21.73 per child screened. We believe that our data provide useful reference values for the planning and implementation of screening tests for presymptomatic type 1 diabetes in the general population and for assessing the cost-effectiveness of targeted prevention strategies.

Our study has two major strengths. First, the Fr1da study is the largest population-based screening study to date for presymptomatic type 1 diabetes without prior selection for genetic risk or family history (24, 25). Second, the present study used various data sources for a micro-costing approach within the Fr1da study. This includes detailed information on the cost of acquiring, processing, and analyzing samples and communicating results, as well as the cost of metabolic staging of children diagnosed with presymptomatic type 1 diabetes, combined with specific education for affected families. To our knowledge, such a granular cost analysis is unprecedented in the field of type 1 diabetes screening, and it allowed us to detail the direct medical costs associated with public health screening from a health care system perspective.

Besides the Fr1da study, another large-scale population-based screening program for the early detection of presymptomatic type 1 diabetes in children is currently underway in the USA; the Autoimmunity Screening for Kids (ASK) program in Denver, Colorado. In the ASK program, the cost per screened child was recently estimated to be $47 in the observed data and $141 in routine care (20), which is overall higher than the costs for public health screening in the Fr1da study. However, when comparing the costs observed in the two studies, it should be noted that the study

design and scope of the underlying data differ. In the Fr1da study, screening was implemented in a routine care setting in collaboration with outpatient pediatric practices, considered only children aged 2 to 5 years, and included more than 90,000 children at the time of analysis (25). The ASK program covered a broader age range (2–17 years) and had around 10,000 participants at the time of the economic analysis. Compared to the ASK cost study by Mc Queen et al. (20), we used a more detailed cost assessment in our study, but most importantly, the cost of health care services are much higher in the USA than in Germany or other European countries (39). The significant cost difference between the observed and routine care scenarios in the ASK screening results from the large difference between the negotiated fee for laboratory services of $15 in the study and the assumed commercial price of $138 in routine care. For comparison, the negotiated material cost for the Fr1da study for the 3-Screen ELISA was €1.20 per sample tested. Negotiated costs for laboratory services are specific to the two studies, and a 'real-world' price for the required laboratory services is not yet available. However, due to scaling effects, the cost of test kits is expected to decrease in the long term as screening for presymptomatic type 1 diabetes becomes standard care in many health systems. In a simulated standard care scenario, we varied the material costs for the ELISA up to €3.60 per test and sample. The tripling of ELISA costs increased the projected cost per child screened from €21.73 to €24.13, or by 11%.

Because of wide variation in test characteristics, proportion of positive results, and treatment options for individuals who test positive, it is difficult to compare the costs of different public health screening programs. In Germany, the extended newborn screening that screens for 14 different diseases would be one possible comparator. In 2017, the frequency of a child having a positive screening result was 1/999 (~0.1%) (40), as compared to ~0.3% in the Frida study (25). The costs of the newborn screening at the physician site, including information, capillary blood draw and shipping, are €14.83 (38). The costs of laboratory sample analysis were €11.55 until

2016 (12 diseases) and increased to €16.38 and €24.70 after the introduction of screening for cystic fibrosis and severe combined immunodeficiency, respectively.

Further research needs to determine whether the costs of early diagnosis of type 1 diabetes through screening in children are outweighed by associated reductions in future health care costs and improvements in quality of life and life expectancy. Screening for presymptomatic type 1 diabetes combined with education and care for affected families is very likely to reduce the incidence of DKA at onset of type 1 diabetes (18, 19, 25). This would prevent the occurrence of life-threatening conditions and have a positive impact on long-term health outcomes in patients with type 1 diabetes (11-13). In addition, there are other benefits from diagnosing individuals at an early stage of type 1 diabetes. Screening and identifying such individuals is the prerequisite for targeted strategies to treat presymptomatic type 1 diabetes in the future (21, 23).

It is important to acknowledge that the costs associated with screening for presymptomatic type 1 diabetes presented here are specific to Germany. Our sensitivity analyses show that results are sensitive to time costs of healthcare professionals. Previous studies have shown that respective costs are much higher in the USA compared with Germany and other European countries. However, variation within European countries is much smaller (39). This must be taken into account when transferring the results of this study to other countries and health care systems.

Our study has limitations that must be considered. For the cost analysis of the Fr1da study, we excluded campaign costs, although there was substantial spending on public advertising and commercials, in pediatric practices, and online. Two main reasons for this decision were lack of valid data and that these costs would only be relevant in a study setting, not in standard care. Furthermore, we did not consider overhead and fixed costs such as costs for the building or general equipment, which may result in an underestimation of laboratory costs. In addition, time cost

estimates are based on pediatricians' self-reported time spent on screening-related procedures, and despite appropriate adjustments, actual time costs may be over- or underestimated. Furthermore, time spent by nurses was also estimated by physicians. This increases the uncertainty around these estimates. If the screening were established in standard care, it would be more likely that the time spent per child screened could be less than in the Fr1da study. Finally, we did not include follow-up monitoring of children diagnosed with presymptomatic type 1 diabetes in our cost analyses but focused on the one-time expenditure per child for screening and staging.

In conclusion, our study provides a cost estimate for public health screening for presymptomatic type 1 diabetes that considers detailed insights into the costs of each associated procedure. By presenting our micro-costing approach in a transparent manner, the estimates can be easily adapted to other countries and scenarios. This information can help improve the effectiveness of screening and provides information for health policy planners seeking to implement similar screening elsewhere. In addition, the study results are important for assessing the cost-effectiveness of targeted type 1 prevention strategies.

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Table 1

Cost of screening for presymptomatic type 1 diabetes as observed in the Fr1da study

	Total costs	Pediatric practice	Coordination center and laboratory
Costs (€)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cost per child screened	€28.17 (19.96; 39.63)	€18.70 (10.82; 30.28)	€9.35 (8.18; 10.46)
Sample acquisition	€19.96 (12.16; 30.97)	€16.96 (9.25; 28.05)	€2.99 (2.25; 3.68)
Sample analysis and result communication	€8.10 (6.33; 11.03)	€1.74 (0.35; 4.66)	€6.36 (5.47; 7.20)
Metabolic staging and Education *	€0.11 (0.10; 0.13)		
Cost per case diagnosed †	€9,117 (6,460; 12,827)	€6,052 (3,503; 9,801)	€3,028 (2,649; 3,385)

* Probabilistic cost per child screened for metabolic staging and education were completely accounted as costs for the local diabetes clinics. † The costs per case diagnosed for the local diabetes clinic were €37.11 (95% CI: 32.26; 41.98). CI = confidence interval

Table 2

Cost of screening for presymptomatic type 1 diabetes as estimated for standard care in Germany

Simulated standard care scenarios	Total costs	Pediatric practice	Coordination center and laboratory
Costs (€)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Cost per child screened * (Model A)	€21.73 (16.76; 28.19)	€12.25 (7.24; 18.52)	€9.34 (8.29; 10.42)
Cost per case diagnosed †	€7,035 (5,426; 9,124)	€3,967 (2,344; 5,996)	€3,024 (2,684; 3,373)
Model A plus 100% pediatrician time costs	€33.80 (23.72; 47.43)	€24.21 (14.61; 37.28)	€9.45 (8.41; 10.53)
Model A minus 50% pediatrician time costs	€15.70 (13.28; 18.51)	€6.27 (4.07; 8.87)	€9.29 (8.26; 10.38)
Model A with lower 3-Screen ELISA costs (€1.4 per test)	€21.93 (19.96; 28.39)	€12.25 (7.24; 18.52)	€9.54 (8.49; 10.62)
Model A with higher 3-Screen ELISA costs (€3.6 per test)	€24.13 (19.16; 30.59)	€12.25 (7.24; 18.52)	€11.74 (10.69; 12.82)

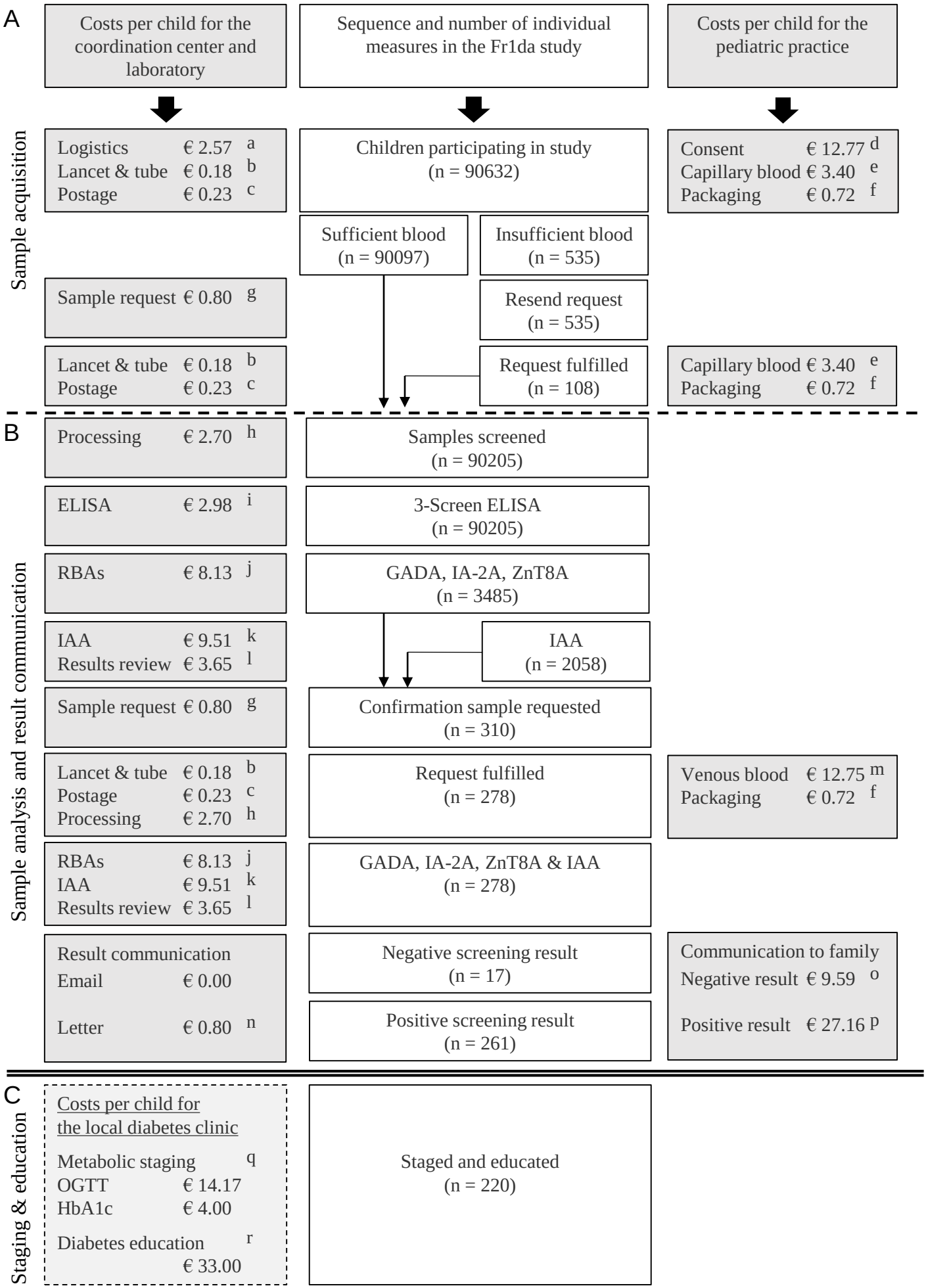
* Probabilistic costs for staging were €0.14 (95% CI: 0.12; 0.15) in the simulated standard care scenario and completely accounted as costs for the local diabetes clinics. † The costs per case diagnosed for the local diabetes clinic were €44.02 (95% CI: 38.19; 49.80). CI = confidence interval

Figure legends

Figure 1 Flowchart of the sequence and number of individual measures in screening children for presymptomatic type 1 diabetes, and associated cost items and average costs per child, as observed in the Fr1da study for (A) sample acquisition, (B) sample analysis and result communication, and (C) staging and education. Costs incurred are listed separately for the Fr1da study coordination center and laboratory (boxes on the left), the pediatric practice (boxes on the right), and the local diabetes clinic (box bottom left). It is indicated how often the respective measure was carried out (boxes in the middle). Index letters to the right of each cost item refer to information in Supplementary Table S3 on the calculation of costs per measure.

3-Screen ELISA = 3-Screen Islet Cell Antibody ELISA (RSR Ltd., Cardiff, UK) measuring autoantibodies to GAD (GADA) and/or insulinoma-associated antigen-2 (IA-2A) and/or zinc transporter-8 (ZnT8A); RBAs = radio binding assays; IAA = insulin autoantibodies; OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin

Figure 1


A
Costs per child for the coordination center and laboratory
Sequence and number of individual measures in the Fr1da study
Costs per child for the pediatric practice
Sample acquisition
Logistics € 2.57 a
Lancet & tube € 0.18 b
Postage € 0.23 c
Children participating in study (n = 90632)
Consent € 12.77 d
Capillary blood € 3.40 e
Packaging € 0.72 f
Sufficient blood (n = 90097)
Insufficient blood (n = 535)
Sample request € 0.80 g
Resend request (n = 535)
Lancet & tube € 0.18 b
Postage € 0.23 c
Request fulfilled (n = 108)
Capillary blood € 3.40 e
Packaging € 0.72 f
B
Sample analysis and result communication
Processing € 2.70 h
Samples screened (n = 90205)
ELISA € 2.98 i
3-Screen ELISA (n = 90205)
RBAs € 8.13 j
GADA, IA-2A, ZnT8A (n = 3485)
IAA € 9.51 k
Results review € 3.65 l
IAA (n = 2058)
Sample request € 0.80 g
Confirmation sample requested (n = 310)
Lancet & tube € 0.18 b
Postage € 0.23 c
Processing € 2.70 h
Request fulfilled (n = 278)
Venous blood € 12.75 m
Packaging € 0.72 f
RBAs € 8.13 j
IAA € 9.51 k
Results review € 3.65 l
GADA, IA-2A, ZnT8A & IAA (n = 278)
Result communication
Email € 0.00
Letter € 0.80 n
Negative screening result (n = 17)
Positive screening result (n = 261)
Communication to family
Negative result € 9.59 o
Positive result € 27.16 p
C
Staging & education
Costs per child for the local diabetes clinic
Metabolic staging q
OGTT € 14.17
HbA1c € 4.00
Diabetes education r
€ 33.00
Staged and educated (n = 220)

Supplementary Material

Supplement to Karl et al., Costs of Public Health Screening of Children for Presymptomatic Type 1 Diabetes in Bavaria, Germany

Table of Contents

Table S1. Overview of the amount of resources/estimated units per child screened in the Fr1da study

Index Figure 1	**Time spent (minutes), Pediatric practice** [§]	**Mean**	**SD**	**Distribution**	**Explanation** (see Supplementary Material, Online survey for paediatricians)	**Source**
d	Consent (physician time)	5.14	1.90	Gamma moments	Survey question #3	A
e	Capillary blood draw					
	% by pediatrician	23.08%		Beta	Survey question #4	A
	Physician time	4.00	1.75	Gamma moments	Survey question #4.1	A
	% by nurse	76.92%		Beta	Survey question #4	A
	Nurse time	3.73	0.97	Gamma	Survey question #4.1	A
f	Packaging					
	% by pediatrician	5.88%		Beta	Survey question #5	A
	Physician time	4.90	2.00	Gamma moments	Survey question #5.1	A
	% by nurse	94.12%		Beta	Survey question #5	A
	Nurse time	4.90	2.00	Gamma	Survey question #5.1	A
m	Venous blood draw					
	% by pediatrician	87.88%		Beta	Survey question #7	A

	Physician time	6.61	2.80	Gamma moments	Survey question #7.1	A
	% by nurse	12.12%		Beta	Survey question #7	A
	Nurse time	7.35	0.76	Gamma	Survey question #7.1	A
o	Communication of negative screening result					
	% overall	18.06%	23.00%	Beta moments	Survey question #8	A
	% by pediatrician	88.55%		Beta	Survey question #8.1	A
	Physician time	4.32	2.31	Gamma moments	Survey question #8.2	A
	% by nurse	11.45%		Beta	Survey question #8.1	A
	Nurse time	2.08	1.11	Gamma	Survey question #8.2	A
p	Communication of positive screening result					
	% by pediatrician	97.76%		Beta	Survey question #9	A
	Physician time	11.18	3.07	Normal	Survey question #9.1	A
	% by nurse	2.24%		Beta	Survey question #9	A
	Nurse time	3.00	0.75	Normal	Survey question #9.1	A

Index Figure 1	Time spent (minutes), Coordination center and laboratory	Mean	SD	Distribution	Explanation	Source
a	Logistics					
	Data management time (per child)	1.67	0.33	Normal	A data manager worked 8 hours (sd = 1.6 hours) per week from February 2015 to May 2019 for the Fr1da study	C
	Packing packages with forms and other materials for pediatricians	0.12	0.02	Normal	The time it took to pack one package (12 minutes [sd = 2.4 minute]) that include starter packages for 100 children	C
	Hotline time (per child included)	1.11	0.22	Normal	Fr1da offered a hotline for participating pediatricians that has been active for 90 minutes (sd = 18 minute) per day for 1581 weekdays from February 2015 to May 2019	C
h	Processing					
	Centrifuging	3.25	0.45	Normal	The time per centrifuge (240 min) divided by the number of samples per day (73.91).	B
	Data entering	2.00	0.40	Normal	Basic information had to be entered for every sample received	B
	Follow-up calls (per sample)	0.20	0.02	Normal	The time spent on follow-up calls per day (15 min) divided by the number of samples per day (73.91)	B
i	3-Screen ELISA	3.79	0.38	Normal	The time per ELISA duration (280 min) divided by the number of samples per day (73.91).	B
	Interpretation of ELISA results	0.07	0.01	Normal	Results of every sample that had been tested with ELISA were reviewed by a laboratory staff member	B

j	GADA, IA-2A, ZnT8A (RBAs)	5.68	0.57	Normal	The time per RIA duration (420 min) divided by the number of samples per day (73.91).	B
k	IAA	6.49	0.65	Normal	The time per IAA (480 min) divided by the number of samples per day (73.91).	B
l	Results review	1.00	-	-	For every sample that had been tested positive for at least one autoantibody a medical expert and two technical staff members had to review the result	B

Index Figure 1	**Materials used (number per child)**	**Units**	**SD**	**Distribution**	**Explanation**	**Source**
a	Cardboard used per package sent to pediatricians	0.01	-	-	Packages to doctors were send in cardboard packaging and included material for 100 children	C
a	Flyer and consent form	1.00	-	-	Flyers and consent forms that were send to the pediatricians offices	C
a	Postage (materials to pediatricians) per child	0.01	-	-	The postage for one package with materials (e.g. flyer, consent forms, lancets) for 100 children	C
b	Blood collection devices	1.00	-	-	Lancets & tubes	C
c	Postage (samples to laboratory), mean units	0.23	0.15	Normal	One package can contain more than one sample. Therefore, one package is divided by the number of samples sent per week	C
g	Postage (resend request)	1.00	-	-	Postage for one resend request	C
h	Lab materials	1.00	-	-	Pipette tips and serum tubes	C
h	Barcodes	5.00	-	-	For every sample the laboratory used five barcodes	C
i	3-Screen ELISA	1.00	-	-	Number of tests per sample	C

j	GADA, IA-2A, ZnT8A (RBAs)	1.00	-	-	Number of tests per sample	C
k	IAA	1.00	-	-	Number of tests per sample	C
n	Postage (positive result communication to pediatrician)	1.00	-	-	Postage for the communication of one positive result (negative results were communicated via email)	C
Index Figure 1	**Measures carried out (number per child), Local diabetes clinics**	**Units**			**Explanation**	**Source**
q	OGTT	1.00	-	-	To stage one child at the local diabetes clinic a OGTT is performed	C
q	HbA1c	1.00	-	-	To stage one child at the local diabetes clinic HbA1c% is measured	C
r	Education	1.00	-	-	Every participating family receives one initial education	C
	Number of samples	**Mean**	**SD**	**Distribution**	**Explanation**	**Source**
	Samples sent per week (pediatrician to laboratory)	3.50	1.81	Gamma	Survey question #1	A
	Samples received per day by laboratory	73.91	22.18	Normal	Documentation of the Fr1da coordination center	C

Note. 3-Screen ELISA = 3-Screen Islet Cell Antibody ELISA (RSR Ltd., Cardiff, UK) measuring autoantibodies to GAD (GADA) and/or insulinoma-associated antigen-2 (IA-2A) and/or zinc transporter-8 (ZnT8A); RBA = radio binding assay; IAA = insulin autoantibodies; OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin; [§] all pediatrician time estimates are 75% of what the actual questionnaire responses were; A = online survey among 134 participating pediatricians; B = information based Fr1da staff member documentation; C = Fr1da coordination center and laboratory

Table S2. Estimated costs per unit of resources

Costs per unit	Observed		Distribution	Explanation	Source
	Mean	*SD*			
Pediatrician time costs	€2.48	€0.05	Normal	Annual revenue of pediatrician in a practice: €352,000 Standard deviation of annual revenue: 2.0% Average working day pear year: 214 Average hours per week: 49 Minus the average annual income of a nurse plus employer contributions [§]	(1)
Nurse time costs	€0.39	€0.08	Normal	Annual income: €32,749.62 Standard deviation of annual income: 20% Working day according pediatrician working days: 214 Average hours per week: 40 Plus employer contributions for pension insurance (9.3%), health insurance (7.3%), unemployment insurance (1.2%), nursing care insurance (1.6%).	(2)
Laboratory staff member time costs	€0.46	€0.09	Normal	Annual income: €39,310.85 Standard deviation of annual income: 20% Working day according pediatrician working days: 214 Average hours per week: 40 Plus employer contributions for pension insurance (9.3%), health insurance (7.3%), unemployment insurance (1.2%), nursing care insurance (1.6%).	(3)
Expert time costs	€2.48	€0.05	Normal	Equal to the pediatrician time costs.	(1)
Scientific staff member time costs	€0.71	€0.14	Normal	Annual income: €59950.67 Standard deviation of annual income: 2.0% Working day according pediatrician working days: 214 Average hours per week: 40 Plus employer contributions for pension insurance (9.3%), health insurance (7.3%), unemployment insurance (1.2%), nursing care insurance (1.6%)."	(4)

Cardboard	€1.77	-	-	Costs for cardboard for one package that contains material for 100 children	(5)
Costs for printing one set of forms	€0.14	-	-	Costs for printing one set of forms	(5)
Postage for large materials to pediatricians	€6.25	-	-	Postage for one package sent to a pediatrician practice that includes material for 100 children	(5)
Postage for smaller packages	€0.80	-	-	Postage for any other kind of smaller package or letter (e.g. resend requests, samples to laboratory)	(5)
3-Screen ELISA	€1.20	-	-		RSR Ltd.
GADA, IA-2A, ZnT8A (RBAs)	€5.50	-	-		(5)
IAA	€6.50	-	-		(5)
Blood collection devices	€0.18	-	-		(5)
Follow-up calls	€0.09	-	-		
Barcodes	€0.14	-	-		(5)
Other lab material	€0.04	-	-		(5)

OGTT	€14.17	-	-	Costs per OGTT were drawn from the uniform valuation standard of the EBM	(6)
HbA1c	€4.00	-	-	Costs per HbA1c measurement were drawn from the uniform valuation standard of the EBM	(6)
Diabetes Education	€33.00	-	-	Costs per education were drawn from the uniform valuation standard of the EBM	(6)

Note. 3-Screen ELISA = 3-Screen Islet Cell Antibody ELISA (RSR Ltd., Cardiff, UK) measuring autoantibodies to GAD (GADA) and/or insulinoma-associated antigen-2 (IA-2A) and/or zinc transporter-8 (ZnT8A); RBA = radio binding assay; IAA = insulin autoantibodies; OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin; EBM = uniform evaluation standard of the National Association of Statutory Health Insurance Physicians (KBV); [§] To estimate the time costs per minute for a pediatrician in Germany, we relied on the "Zi-Praxis-Panel" (1). The panel conducts an annual survey of physicians in private practice in Germany. The survey collected data from 5,519 physicians including 107 pediatricians and analyzed detailed information on physician income/revenue and expenditures. As a result, we were able to determine the actual income of pediatricians in the survey. We divided these incomes by reported minutes worked, assuming a reported workload of 49 hours per week, 251 days worked, and 37 days absent due to vacations and illness. To avoid double-counting, the income of a nurse has been deducted from the annual revenue of the practice. Physicians in private practice are usually self-employed. Nurses and healthcare staff are usually employed and therefore employer contributions (overhead costs) apply.

Table S3. Cost items and average costs per measure in the Fr1da study

Index Figure 1	**Cost item**	**Costs per measure**	**Probabilistic 95% confidence interval**		**Calculation**	
		Mean	LCI	UCI	Number of units per child (see Table S1)	Costs per unit (see Table S2)
a	Logistics	€2.57	€1.93	€3.17	Units of cardboard	Costs per cardboard packaging
					Units of forms per family	Costs per form
					Time it takes to pack one material package / 100	Laboratory staff member time costs
					Time it takes to manage the data of one child	Scientific staff member time costs
b	Lancet & tube	€0.18	-	-	Number of blood collection devices	Costs of one blood collection device
c	Postage	€0.23	€0.03[§]	€0.53	1 / Samples per week (physician to laboratory)	Postage for one small package
d	Consent	€12.77	€5.14	€24.37	Time it takes a pediatrician to inform families and obtain their consent	Pediatrician time cost
e	Capillary blood	€3.40	€1.66	€6.00	(% of capillary blood samples performed by a pediatrician * time it takes a pediatrician to perform a capillary blood draw)	Pediatrician time cost
					(% of capillary blood draws performed by a nurse * time it takes a nurse to perform a capillary blood draw)	Nurse time cost

f	Packaging	€0.72	€0.10	€1.25	(% of packaging performed by a pediatrician * time it takes to pack samples)	Pediatrician time cost
					(% of packaging performed by a nurse * time it takes to pack samples) / samples per week (physician to laboratory)	Nurse time cost
g	Sample request	€0.80	-	-	Resend request	Postage for one resend request
h	Processing	€2.70	€1.97	€3.53	Time spent on follow-up calls per sample	Laboratory staff member time costs
					Time spent on centrifuging / samples received per day by laboratory	Laboratory staff member time costs
					Number of barcodes	Costs of one barcode
					Number of other lab materials	Costs of one unit of pipette tips and serum tubes
					Data entering	Laboratory staff member time costs
i	3-Screen ELISA	€2.98	€2.23	€3.82	Time spent on ELISA / samples received per day by laboratory	Laboratory staff member time costs
					Number of ELISA tests utilized per sample	Costs of one measurement of ELISA
					Time spent on interpreting ELISA result	Laboratory staff member time costs
j	GADA, IA-2A, ZnT8A (RBAs)	€8.13	€7.07	€9.30	Time spent on RBAs / samples received per day by laboratory	Laboratory staff member time costs
					Number of RBAs utilized per sample	Costs of one measurement of RBAs

k	IAA	€9.51	€8.27	€10.95	Time spent on IAA-RBAs / samples received per day by laboratory	Laboratory staff member time costs
					Number of RBAs utilized per sample	Costs of one measurement of IAA
l	Results review	€3.65	€3.31	€3.99	Time spent on interpretation of a laboratory result	Expert time costs
					Time spent on interpretation of a laboratory result	Laboratory staff member time cost
					Time spent on interpretation of a laboratory result	Scientific staff member time costs
m	Venous blood	€12.75	€5.80	€22.39	% of venous blood draws performed by a pediatrician * time it takes a pediatrician to perform a venous blood draw	Pediatrician time cost
					% of venous blood draws performed by a nurse * time it takes a nurse to perform a venous blood draw	Nurse time cost
n	Result communication (letter)	€0.80	-	-	Positive result letter	Postage for one letter
	Communication to family (negative result) (observed)[§]	€1.73	€0.36	€4.88	% of negative results communicated by a pediatrician * time it takes a pediatrician to communicate a negative result	Pediatrician time cost
					% of negative results communicated by a nurse * time it takes a nurse to communicate a negative result	Nurse time cost
o	Communication to family	€9.59	€2.53	€23.70	% of negative results communicated by a pediatrician * time it takes a	Pediatrician time cost

	(negative result) (routine)				pediatrician to communicate a negative result	
					% of negative results communicated by a nurse * time it takes a nurse to communicate a negative result	Nurse time cost
p	Communication to family (positive result)	€27.16	€26.76	€27.41	% of positive results communicated by a pediatrician * time it takes a pediatrician to communicate a positive result	Pediatrician time cost
					% of positive results communicated by a nurse * time it takes a nurse to communicate a positive result	Nurse time cost
q	Metabolic staging	€18.17	-	-	Number of OGTTs necessary for staging	Costs of one OGTT
					Number of Hba1c measurements necessary for staging	Costs of one HbA1c measurement
r	Diabetes Education	€33.00	-	-	Number of education sessions	Costs of one education session

Note. LCI = lower 95% confidence interval; UCI = upper 95% confidence interval; 3-Screen ELISA = 3-Screen Islet Cell Antibody ELISA (RSR Ltd., Cardiff, UK) measuring autoantibodies to GAD (GADA) and/or insulinoma-associated antigen-2 (IA-2A) and/or zinc transporter-8 (ZnT8A); RBA = radio binding assay; IAA = insulin autoantibodies; OGTT = oral glucose tolerance test; HbA1c = glycated hemoglobin; [§] costs observed for negative result communication are not displayed in Figure 1 because negative result communication was generally assumed in 16.1% of *all* negative results, e.g. also including ELISA negative results. [§] Due to the distribution parameters (mean = €0.23, sd = €0.15), some of the simulated values where < 0. These values have been replaced by the deterministic mean of €0.23.

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Online survey for pediatricians participating in the Fr1da study

1. On average, how many children participate in Fr1da in your practice per week?

   Please give an integral number: |__|__|__|

2. What is the proportion of families that deny their participation in Fr1da after receiving information?

   Please give an integral number: |__|__|__| %

3. On average, how much time does information and consent per family take?

   Please give the time in minutes: |__|__|__|min

4. Usually, who performs the capillary blood draw that is necessary for participation in the Fr1da study?

   0 Physician

   0 Nurse

   4.1. On average, how much time does a capillary blood draw take?

   Please give the time in minutes: |__|__|__|min

5. Usually, who takes care of the packaging and shipping of the samples?

   0 Physician

   0 Nurse

   5.1. On average, how much time does the packaging and shipping of the samples take?

   Please give the time in minutes: |__|__|__|min

6. Usually, who informs families that a venous blood draw is needed for the child and asks for another appointment?

   0 Physician

   0 Nurse

   6.1. On average, how much time does this conversation with families take?

   Please give the time in minutes: |__|__|__|min

7. Usually, who performs the venous blood draw that is sometime requested by the in the Fr1da study coordination center?

0 Physician

0 Nurse

7.1. On average, how much time does a venous blood draw take?

Please give the time in minutes: |__|__|__|min

8. What is the proportion of families that you inform of a negative screening result (i.e. no diagnosis of presymptomatic type 1 diabetes)?

Please give an integral number: |__|__|__| %

8.1. Usually, if the families are informed of a negative screening result, who informs the families?

0 Physician

0 Nurse

8.2. On average, how much time does the communication of a negative screening result take?

Please give the time in minutes: |__|__|__|min

9. Usually, who informs the families of a positive screening result (i.e. diagnosis of presymptomatic type 1 diabetes)?

0 Physician

0 Nurse

9.1. On average, how much time does the communication of a positive screening result take?

Please give the time in minutes: |__|__|__|min

Fr1da Study Group

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