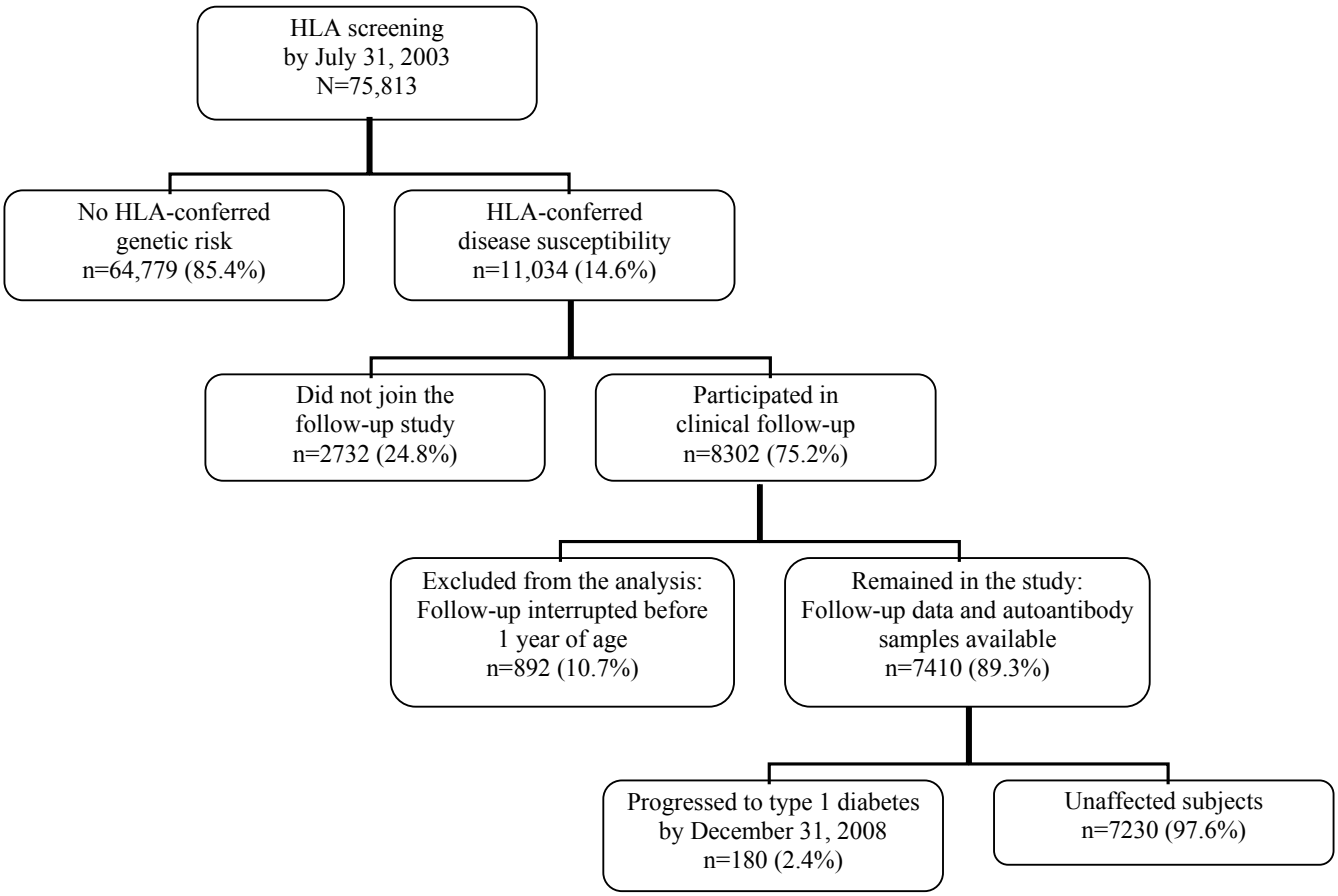
Supplementary Fig. 1. The DIPP Study cohort.



Supplementary Table 1: Comparison between those children who carried the high risk HLA genotype and those with moderate risk genotypes. T1D, Type 1 diabetes; ICA, islet cell antibodies; DAA, diabetes-associated autoantibodies. *P<0.001, †P=0.004, ‡P=0.03, §P=0.04.

	High risk	Moderate risk
	n (%)	
Total	1575 (21.3)	5835 (78.7)
Males	829 (52.6)	3068 (52.6)
Progression to T1D	80 (5.1)	100 (1.7)*
T1D affected family members at index child's birth	53 (3.4)	124 (2.1)†
Participation in the intervention study	82 (5.2)	137 (2.3)*
ICA-based seroconversion	325 (20.6)	848 (14.5)*
Positivity for ≥2 DAAs[a]	141 (43.4)	250 (29.5)*
Persistent autoantibody positivity[a]	194 (59.7)	487 (56.4)*
Persistently positive for ≥2 DAAs[a]	109 (33.5)	174 (20.5)*
	Years	
Age at diagnosis	5.1 (1.0–12.0)	4.9 (0.9–12.5)
Age at seroconversion	3.5 (0.3–13.3)	4.0 (0.2–13.7)‡
Age at maximal DAA status	4.2 (0.5–13.3)	5.0 (0.5–13.7)§
Delay from seroconversion to diagnosis	2.8 (0.1–9.0)	2.8 (0.0–10.9)

[a] % of ICA-positive subjects. Details regarding the DAA combinations; see Supplementary Table 3.

Supplementary Table 2. 5-year predictive characteristics of the four diabetes-associated autoantibodies (DAA): Islet cell antibodies (ICA), insulin antibodies (IAA), glutamic acid antibodies (GADA), and islet antigen-2 antibodies (IA-2A). T1D+/ All+, progressors/all subjects positive for the given specificity; $CI_{95\%}$, 95% confidence interval; prefix "p", persistently positive autoantibody; PPV and NPV, positive and negative predictive value. In the case of defined autoantibody categories, each individual is included in only one category.

Combinations of autoantibodies	**T1D+/All+, n**	**Sensitivity, % ($CI_{95\%}$)**	**Specificity, % ($CI_{95\%}$)**	**PPV, % ($CI_{95\%}$)**	**NPV, % ($CI_{95\%}$)**	**Cumulative risk, % ($CI_{95\%}$)**
Total number of subjects	147/6747					
ICA the only positive DAA	3/222	2.0 (0.4–5.8)	96.7 (96.2–97.1)	1.4 (0.3–3.9)	97.8 (97.4–98.1)	1.4 (0–2.9)
Double positivity	12/33	8.2 (4.3–13.8)	99.7 (99.5–99.8)	36.4 (20.4–54.9)	98.0 (97.6–98.3)	36.4 (20.0–52.8)
ICA, IAA	9/17	6.1 (2.8–11.3)	99.9 (99.8–99.9)	52.9 (27.8–77.0)	97.9 (97.6–98.3)	52.9 (29.2–76.7)
ICA, GADA	0/10	0 (0–2.5)	99.8 (99.7–99.9)	0 (0–30.8)	97.8 (97.4–98.2)	0 (0–0)
ICA, IA-2A	3/6	2.0 (0.4–5.8)	100 (99.9–100)	50.0 (11.8–88.2)	97.9 (97.5–98.2)	50.0 (10.0–90.0)
Triple positivity	32/52	21.8 (15.4–29.3)	99.7 (99.5–99.8)	61.5 (47.0–74.7)	98.3 (97.9–98.6)	61.5 (48.3–74.8)
ICA, IAA, GADA	12/22	8.2 (4.3–13.8)	99.8 (99.7–99.9)	54.5 (32.2–75.6)	98.0 (97.6–98.3)	54.5 (33.7–75.4)
ICA, IAA, IA-2A	13/20	8.8 (4.8–14.6)	99.9 (99.8–100)	65.0 (40.8–84.6)	98.0 (97.6–98.3)	65.0 (44.1–85.9)
ICA, GADA, IA-2A	7/10	4.8 (1.9–9.6)	100 (99.9–100)	70.0 (34.8–93.3)	97.9 (97.6–98.2)	70.0 (41.6–98.4)
All four DAA positive	71/120	48.3 (40.0–56.7)	99.3 (99.0–99.5)	59.2 (49.8–68.0)	98.9 (98.6–99.1)	59.2 (50.4–68.0)
Positive for at least ICA	118/427	80.3 (72.9–86.4)	95.3 (94.8–95.8)	27.6 (23.4–32.1)	99.5 (99.3–99.7)	27.6 (23.4–31.9)
≥ 2 positive DAA	115/205	78.2 (70.7–84.6)	98.6 (98.3–98.9)	56.1 (49.0–63.0)	99.5 (99.3–99.7)	56.1 (49.3–62.9)
≥ 3 positive DAA	103/172	70.1 (62.0–77.3)	99.0 (98.7–99.2)	59.9 (52.1–67.3)	99.3 (99.1–99.5)	59.9 (52.6–67.2)
Only ICA persistently positive	6/127	4.1 (1.5–8.7)	98.2 (97.8–98.5)	4.7 (1.8–10.0)	97.9 (97.5–98.2)	4.7 (1.0–8.4)
Persistent double positivity	26/42	17.7 (11.9–24.8)	99.8 (99.6–99.9)	61.9 (45.6–76.4)	98.2 (97.8–98.5)	61.9 (47.2–76.6)
pICA, pIAA	9/11	6.1 (2.8–11.3)	100 (99.9–100)	81.8 (48.2–97.7)	98.0 (97.6–98.3)	81.8 (59.0–100)
pICA, pGADA	2/7	1.4 (0.2–4.8)	99.9 (99.8–100)	28.6 (3.7–71.0)	97.8 (97.5–98.2)	28.6 (0–62.0)
pICA, pIA-2A	15/24	10.2 (5.8–16.3)	99.9 (99.7–99.9)	62.5 (40.6–81.2)	98.0 (97.7–98.4)	62.5 (43.1–81.9)
Persistent triple positivity	37/63	25.2 (18.4–33)	99.6 (99.4–99.7)	58.7 (45.6–71.0)	98.4 (98.0–98.6)	58.7 (46.6–70.9)
pICA, pIAA, pGADA	9/15	6.1 (2.8–11.3)	99.9 (99.8–100)	60.0 (32.3–83.7)	98.0 (97.6–98.3)	60.0 (35.2–84.8)
pICA, pIAA, pIA-2A	16/24	10.9 (6.4–17.1)	99.9 (99.8–99.9)	66.7 (44.7–84.4)	98.1 (97.7–98.4)	66.7 (47.8–85.5)
pICA, pGADA, pIA-2A	12/24	8.2 (4.3–13.8)	99.8 (99.7–99.9)	50.0 (29.1–70.9)	98.0 (97.6–98.3)	50.0 (30.0–70.0)
All four DAA persistently positive	41/68	27.9 (20.8–35.9)	99.6 (99.4–99.7)	60.3 (47.7–72.0)	98.4 (98.1–98.7)	60.3 (48.7–71.9)
Persistently positive for at least ICA	110/300	74.8 (67.0–81.6)	97.1 (96.7–97.5)	36.7 (31.2–42.4)	99.4 (99.2–99.6)	36.7 (31.2–42.1)
≥ 2 DAA persistently positive	104/173	70.7 (62.7–78.0)	99.0 (98.7–99.2)	60.1 (52.4–67.5)	99.3 (99.1–99.5)	60.1 (52.8–67.4)
≥ 3 DAA persistently positive	78/131	53.1 (44.7–61.3)	99.2 (99.0–99.4)	59.5 (50.6–68.0)	99.0 (98.7–99.2)	59.5 (51.1–67.9)

Supplementary Table 3. Predictive characteristics of the four diabetes-associated autoantibodies (DAA) among children with the high-risk HLA genotype (A) and the moderate-risk genotypes (B). Antibodies against islet cells (ICA), insulin (IAA), glutamic acid (GADA), and islet antigen-2 (IA-2A). T1D+/ All+, progressors/all subjects positive for the given specificity; $CI_{95\%}$, 95% confidence interval; prefix "p", persistently positive autoantibody; PPV and NPV, positive and negative predictive value. In the case of defined autoantibody categories, each individual is included in only one category.

A

Combinations of autoantibodies	**T1D+/All+, n**	**Sensitivity, % ($CI_{95\%}$)**	**Specificity, % ($CI_{95\%}$)**	**PPV, % ($CI_{95\%}$)**	**NPV, % ($CI_{95\%}$)**	**Cumulative risk, % ($CI_{95\%}$)**
Total number of subjects	80/1575					
ICA the only positive DAA	0/184	0 (0–4.5)	87.7 (85.9–89.3)	0 (0–2.0)	94.2 (92.9–95.4)	0 (0–0)
Double positivity	8/42	10.0 (4.4–18.8)	97.7 (96.8–98.4)	19.0 (8.6–34.1)	95.3 (94.1–96.3)	25.4 (9.4–41.4)
ICA, IAA	6/18	7.5 (2.8–15.6)	99.2 (98.6–99.6)	33.3 (13.3–59.0)	95.2 (94.1–96.2)	39.4 (13.2–65.6)
ICA, GADA	1/21	1.3 (0–6.8)	98.7 (97.9–99.2)	4.8 (0.1–23.8)	94.9 (93.7–96.0)	8.3 (0–24.0)
ICA, IA-2A	1/3	1.3 (0–6.8)	99.9 (99.5–100)	33.3 (0.8–90.6)	95.0 (93.8–96.0)	50.0 (0–100)
Triple positivity	22/39	27.5 (18.1–38.6)	98.9 (98.2–99.3)	56.4 (39.6–72.2)	96.2 (95.1–97.1)	74.0 (55.4–92.6)
ICA, IAA, GADA	12/20	15.0 (8.0–24.7)	99.5 (98.9–99.8)	60.0 (36.1–80.9)	95.6 (94.5–96.6)	72.0 (48.5–95.5)
ICA, IAA, IA-2A	8/8	10.0 (4.4–18.8)	100 (99.8–100)	100 (63.1–100)	95.4 (94.2–96.4)	100 (100–100)
ICA, GADA, IA-2A	2/11	2.5 (0.3–8.7)	99.4 (98.9–99.7)	18.2 (2.3–51.8)	95.0 (93.8–96.0)	25.0 (0–55.0)
All four DAA positive	40/60	50.0 (38.6–61.4)	98.7 (97.9–99.2)	66.7 (53.3–78.3)	97.4 (96.4–98.1)	85.5 (72.0–99.0)
Positive for at least ICA	70/325	87.5 (78.2–93.8)	84.6 (82.7–86.5)	23.7 (19.0–29.0)	99.2 (98.5–99.6)	35.4 (27.0–43.8)
≥ 2 positive DAA	70/141	87.5 (78.2–93.8)	95.3 (94.0–96.3)	49.6 (41.1–58.2)	99.3 (98.7–99.7)	74.7 (62.4–87.1)
≥ 3 positive DAA	62/99	77.5 (66.8–86.1)	97.5 (96.6–98.3)	62.6 (52.3–72.1)	98.8 (98.1–99.3)	81.3 (70.1–92.5)
Only ICA persistently positive	2/85	2.5 (0.3–8.7)	94.4 (93.2–95.6)	2.4 (0.3–8.2)	94.8 (93.5–95.8)	3.4 (0–8.0)
Persistent double positivity	14/26	17.5 (9.9–27.6)	99.2 (98.6–99.6)	53.8 (33.4–73.4)	95.7 (94.6–96.7)	100 (100–100)
pICA, pIAA	6/7	7.5 (2.8–15.6)	99.9 (99.6–100)	85.7 (42.1–99.6)	95.3 (94.1–96.3)	100 (100–100)
pICA, pGADA	2/11	2.5 (0.3–8.7)	99.4 (98.9–99.7)	18.2 (2.3–51.8)	95.0 (93.8–96.0)	23.8 (0–52.8)
pICA, pIA-2A	6/8	7.5 (2.8–15.6)	99.9 (99.5–100)	75.0 (34.9–96.8)	95.3 (94.1–96.3)	100 (100–100)
Persistent triple positivity	27/52	33.8 (23.6–45.2)	98.3 (97.5–98.9)	51.9 (37.6–66.0)	96.5 (95.5–97.4)	65.5 (47.3–83.7)
pICA, pIAA, pGADA	9/13	11.3 (5.3–20.3)	99.7 (99.3–99.9)	69.2 (38.6–90.9)	95.5 (94.3–96.4)	20.0 (0–55.1)
pICA, pIAA, pIA-2A	9/9	11.3 (5.3–20.3)	100 (99.8–100)	100 (66.4–100)	95.5 (94.3–96.4)	63.3 (39.6–87.1)
pICA, pGADA, pIA-2A	9/30	11.3 (5.3–20.3)	98.6 (97.9–99.1)	30.0 (14.7–49.4)	95.4 (94.2–96.4)	63.5 (35.1–91.9)
All four DAA persistently positive	25/31	31.3 (21.3–42.6)	99.6 (99.1–99.9)	80.6 (62.5–92.5)	96.4 (95.4–97.3)	94.7 (84.7–100)
Persistently positive for at least ICA	68/194	85.0 (75.3–92.0)	91.6 (90.0–92.9)	35.1 (28.4–42.2)	99.1 (98.5–99.6)	53.8 (42.7–64.8)
≥ 2 DAA persistently positive	66/109	82.5 (72.4–90.1)	97.1 (96.1–97.9)	60.6 (50.7–69.8)	99.0 (98.4–99.5)	82.4 (71.1–93.8)
≥ 3 DAA persistently positive	52/83	65.0 (53.5–75.3)	97.9 (97.1–98.6)	62.7 (51.3–73.0)	98.1 (97.3–98.7)	80.5 (68.0–93.0)

B

Combinations of autoantibodies	T1D+/All+, n	Sensitivity, % ($CI_{95\%}$)	Specificity, % ($CI_{95\%}$)	PPV, % ($CI_{95\%}$)	NPV, % ($CI_{95\%}$)	Cumulative risk, % ($CI_{95\%}$)
Total number of subjects	100/5835					
ICA the only positive DAA	1/598	1.0 (0–5.4)	89.6 (88.8–90.4)	0.2 (0–0.9)	98.1 (97.7–98.5)	0.4 (0–1.1)
Double positivity	6/86	6.0 (2.2–12.6)	98.6 (98.3–98.9)	7.0 (2.6–14.6)	98.4 (98.0–98.7)	11.3 (1.6–21.1)
ICA, IAA	4/38	4.0 (1.1–9.9)	99.4 (99.2–99.6)	10.5 (2.9–24.8)	98.3 (98.0–98.7)	17.8 (0–36.0)
ICA, GADA	1/39	1.0 (0–5.4)	99.3 (99.1–99.5)	2.6 (0.1–13.5)	98.3 (97.9–98.6)	2.6 (0–7.5)
ICA, IA-2A	1/9	1.0 (0–5.4)	99.9 (99.7–99.9)	11.1 (0.3–48.2)	98.3 (97.9–98.6)	16.7 (0–46.5)
Triple positivity	20/48	20.0 (12.7–29.2)	99.5 (99.3–99.7)	41.7 (27.6–56.8)	98.6 (98.3–98.9)	57.2 (39.1–75.4)
ICA, IAA, GADA	3/16	3.0 (0.6–8.5)	99.8 (99.6–99.9)	18.8 (4.0–45.6)	98.3 (98.0–98.6)	24.2 (0–48.7)
ICA, IAA, IA-2A	12/19	12.0 (6.4–20.0)	99.9 (99.7–100)	63.2 (38.4–83.7)	98.5 (98.1–98.8)	75.4 (52.5–98.4)
ICA, GADA, IA-2A	5/13	5.0 (1.6–11.3)	99.9 (99.7–99.9)	38.5 (13.9–68.4)	98.4 (98.0–98.7)	53.8 (21.1–86.6)
All four DAA positive	58/116	58.0 (47.7–67.8)	99.0 (98.7–99.2)	50.0 (40.6–59.4)	99.3 (99.0–99.5)	72.5 (57.9–87.1)
Positive for at least ICA	85/848	85.0 (76.5–91.4)	86.7 (85.8–87.6)	10.0 (8.1–12.2)	99.7 (99.5–99.8)	19.8 (14.4–25.1)
≥ 2 positive DAA	84/250	84.0 (75.3–90.6)	97.1 (96.6–97.5)	33.6 (27.8–39.8)	99.7 (99.5–99.8)	56.5 (44.3–68.6)
≥ 3 positive DAA	78/164	78.0 (68.6–85.7)	98.5 (98.2–98.8)	47.6 (39.7–55.5)	99.6 (99.4–99.8)	69.0 (56.6–81.4)
Only ICA persistently positive	4/304	4.0 (1.1–9.9)	94.8 (94.2–95.3)	1.3 (0.4–3.3)	98.3 (97.9–98.6)	2.8 (0–5.5)
Persistent double positivity	23/56	23.0 (15.2–32.5)	99.4 (99.2–99.6)	41.1 (28.1–55.0)	98.7 (98.3–98.9)	68.8 (48.3–89.3)
pICA, pIAA	5/5	5.0 (1.6–11.3)	100 (99.9–100)	100 (47.8–100)	98.4 (98.0–98.7)	100 (100–100)
pICA, pGADA	0/15	0 (0–3.6)	99.7 (99.6–99.9)	0 (0–21.8)	98.3 (97.9–98.6)	0 (0–0)
pICA, pIA-2A	18/36	18.0 (11.0–26.9)	99.7 (99.5–99.8)	50.0 (32.9–67.1)	98.6 (98.2–98.9)	70.6 (49.7–91.4)
Persistent triple positivity	26/69	26.0 (17.7–35.7)	99.3 (99.0–99.5)	37.7 (26.3–50.2)	98.7 (98.4–99.0)	67.8 (43.1–92.5)
pICA, pIAA, pGADA	1/5	1.0 (0–5.4)	99.9 (99.8–100)	20.0 (0.5–71.6)	98.3 (97.9–98.6)	20.0 (0–55.1)
pICA, pIAA, pIA-2A	11/19	11.0 (5.6–18.8)	99.9 (99.7–99.9)	57.9 (33.5–79.7)	98.5 (98.1–98.8)	63.3 (39.6–87.1)
pICA, pGADA, pIA-2A	14/45	14.0 (7.9–22.4)	99.5 (99.2–99.6)	31.1 (18.2–46.6)	98.5 (98.2–98.8)	63.5 (35.1–91.9)
All four DAA persistently positive	30/49	30.0 (21.2–40.0)	99.7 (99.5–99.8)	61.2 (46.2–74.8)	98.8 (98.5–99.1)	71.2 (55.0–87.4)
Persistently positive for at least ICA	83/478	83.0 (74.2–89.8)	93.1 (92.4–93.8)	17.4 (14.1–21.1)	99.7 (99.5–99.8)	34.6 (25.8–43.5)
≥ 2 DAA persistently positive	79/174	79.0 (69.7–86.5)	98.3 (98.0–98.7)	45.4 (37.9–53.1)	99.6 (99.4–99.8)	67.5 (55.4–79.7)
≥ 3 DAA persistently positive	56/118	56.0 (45.7–65.9)	98.9 (98.6–99.2)	47.5 (38.2–56.9)	99.2 (99.0–99.4)	80.5 (68.0–93.0)