SUPPLEMENTARY DATA

Supplementary Table 1. Formulas for IGF1 age and sex-based percentile calculations. Fifth-order polynomial equations were robustly fit over historical IGF1 data (31) in order to solve for Y, IGF1 percentile, using X, raw IGF1 (ng/mL). Substitute appropriate constants according to age and sex bin of subject: Y = B0 + B1*X + B2*X^2 + B3*X^3 + B4*X^4 + B5*X^5. Goodness of fit represented as robust standard deviation of the residuals (RSDR).

Age and Sex Bin	B0	B1	B2	B3	B4	B5	RSDR
0-2 y	13.53	-1.894	7.709e-2	-8.257e-4	3.705e-6	-6.048e-9	0.8
2-4 y	24.62	-2.249	6.079e-2	-4.99e-4	1.76e-6	-2.29e-9	0.5
4-6 y	24.18	-1.754	3.812e-2	-2.498e-4	7.028e-7	-7.308e-10	0.5
6-7 y	39.81	-2.254	3.895e-2	-2.238e-4	5.625e-7	-5.278e-10	0.3
7-8 y	55.04	-2.383	3.216e-2	-1.506e-4	3.088e-7	-2.355e-10	0.9
8-9 y, M	71.02	-2.611	3.004e-2	-1.201e-4	2.005e-7	-1.138e-10	0.9
8-9 y, F	48.84	-1.706	1.832e-2	-6.782e-5	1.105e-7	-6.751e-11	0.3
9-10 y, M	77.01	-2.425	2.363e-2	-7.535e-5	8.327e-8	-8.734e-12	1.1
9-10 y, F	69.31	-2.014	1.835e-2	-5.851e-5	7.92e-8	-3.782e-11	1.1
10-11 y, M	87.57	-2.169	1.476e-2	-1.022e-5	-1.003e-7	1.715e-10	1.0
10-11 y, F	71.99	-1.762	1.352e-2	-3.613e-5	4.027e-8	-1.522e-11	1.2
11-12 y, M	99.58	-2.314	1.587e-2	-2.629e-5	-2.422e-8	6.704e-11	1.1
11-12 y, F	55.6	-1.186	7.853e-3	-1.823e-5	1.866e-8	-7.154e-12	0.5
12-13 y, M	85.85	-1.969	1.424e-2	-3.59e-5	3.616e-8	-1.073e-11	1.1
12-13 y, F	56.66	-0.952	4.984e-3	-9.056e-6	7.167e-9	-2.099e-12	0.9
13-14 y, M	85.12	-1.543	8.808e-3	-1.772e-5	1.459e-8	-3.828e-12	0.9
13-14 y, F	89.56	-1.095	4.105e-3	-4.767e-6	1.28e-9	5.209e-13	1.2
14-15 y, M	76.95	-1.102	4.969e-3	-7.889e-6	5.261e-9	-1.204e-12	0.9
14-15 y, F	100.1	-0.9434	2.09e-3	1.872e-6	-7.285e-9	4.388e-12	1.1
15-16 y, M	97.3	-1.074	3.414e-3	-2.157e-6	-2.305e-9	2.202e-12	1.1
15-16 y, F	95.38	-0.9569	2.497e-3	3.219e-7	-5.109e-9	3.342e-12	1.0
16-17 y, M	95.39	-1.009	2.823e-3	1.339e-8	-5.562e-9	3.889e-12	1.0
16-17 y, F	90.46	-0.8734	1.783e-3	3.256e-6	-9.935e-9	6.012e-12	1.1
17-18 y, M	14.11	0.6103	-9.78e-3	4.596e-5	-8.037e-8	4.791e-11	1.1
17-18 y, F	21.3	0.5058	-9.067e-3	4.326e-5	-7.555e-8	4.476e-11	1.2
18-19 y, M	8.195	0.7015	-1.07e-2	5.09e-5	-9.116e-8	5.583e-11	1.2
18-19 y, F	-4.779	1.015	-1.349e-2	6.219e-5	-1.116e-7	6.924e-11	1.1

SUPPLEMENTARY DATA

19-20 y	-7.826	1.142	-1.567e-2	7.587e-5	-1.438e-7	9.451e-11	1.3
20-30 y	82.48	-2.293	1.99e-2	-5.803e-5	6.193e-8	-1.216e-11	1.3
30-40 y	80.52	-2.368	2.17e-2	-6.648e-5	7.413e-8	-1.463e-11	1.2
40-50 y	75.83	-2.359	2.271e-2	-7.135e-5	7.746e-8	-7.634e-12	1.1
50-60 y	80.33	-2.68	2.804e-2	-1.012e-4	1.451e-7	-6.067e-11	1.1
60-70 y	73.41	-2.663	3.031e-2	-1.205e-4	2.002e-7	-1.132e-10	0.9

SUPPLEMENTARY DATA

Supplementary Table 2. Formulas for IGF2 age-based percentile calculations. Semilog lines were fit over historical IGF2 data (31) in order to solve for Y, IGF2 percentile, using X, raw IGF2 (ng/mL). Substitute appropriate constants according to age bin of subject: Y = Y-intercept + Slope*log(X). Goodness of fit represented as absolute sum of squares.

Age Bin	Slope	Y-intercept	Absolute Sum of Squares
1-3 y	235.4	-603.4	1.9e-3
3-5 y	246.4	-636	3.3
5-7 y	246	-640	4.7e-3
7-9 y	248.5	-650	1.9e-2
9-11 y	255.7	-671.4	1.3e-2
11-13 y	256.2	-674.2	2.0e-3
13-15 y	258.6	-682.4	1.1e-3
15-20 y	248.1	-653.8	1.3e-3
20-30 y	233.8	-612	4.9e-4
30-40 y	239.8	-629.3	1.3e-2
40-50 y	221.1	-572	1.2e-3
50-60 y	212.7	-547.6	3.7e-3
60-70 y	210.1	-535.4	1.0e-3

SUPPLEMENTARY DATA

Supplementary Table 3. Multiplicity adjusted p-values for Figure 1.

Figure	Dunn's multiple comparisons test	Mean rank diff.	Significant?	Adjusted p-value
1C	AAb- Control vs. AAb- Relative	-5.804	ns	>0.9999
	AAb- Control vs. AAb+	84.67	****	<0.0001
	AAb- Control vs. Recent Onset	19.77	ns	>0.9999
	AAb- Control vs. Established	23.58	ns	>0.9999
	AAb- Relative vs. AAb+	90.48	****	<0.0001
	AAb- Relative vs. Recent Onset	25.57	ns	>0.9999
	AAb- Relative vs. Established	29.39	ns	0.6349
	AAb+ vs. Recent Onset	-64.91	**	0.0010
	AAb+ vs. Established	-61.09	**	0.0019
	Recent Onset vs. Established	3.818	ns	>0.9999
1D	AAb- Control vs. AAb- Relative	-61.75	**	0.0010
	AAb- Control vs. AAb+	24.54	ns	>0.9999
	AAb- Control vs. Recent Onset	-0.8724	ns	>0.9999
	AAb- Control vs. Established	-50.33	**	0.0082
	AAb- Relative vs. AAb+	86.28	****	<0.0001
	AAb- Relative vs. Recent Onset	60.88	**	0.0020
	AAb- Relative vs. Established	11.41	ns	>0.9999
	AAb+ vs. Recent Onset	-25.41	ns	>0.9999

SUPPLEMENTARY DATA

	AAb+ vs. Established	-74.87	****	<0.0001
	Recent Onset vs. Established	-49.46	*	0.0145
1E	AAb- Relative vs. 1 AAb+	50.03	***	0.0002
	AAb- Relative vs. 2-3 AAb+	48.09	***	0.0001
	AAb- Relative vs. Recent Onset	13.32	ns	0.8028
	1 AAb+ vs. 2-3 AAb+	-1.939	ns	>0.9999
	1 AAb+ vs. Recent Onset	-36.72	*	0.0120
	2-3 AAb+ vs. Recent Onset	-34.78	**	0.0098
1F	AAb- Relative vs. 1 AAb+	36.87	**	0.0099
	AAb- Relative vs. 2-3 AAb+	55.53	****	<0.0001
	AAb- Relative vs. Recent Onset	31.94	**	0.0024
	1 AAb+ vs. 2-3 AAb+	18.66	ns	0.9982
	1 AAb+ vs. Recent Onset	-4.926	ns	>0.9999
	2-3 AAb+ vs. Recent Onset	-23.58	ns	0.2141

SUPPLEMENTARY DATA

Supplementary Table 4. Multiplicity adjusted p-values for Supplementary Figure 1.

Figure	Dunn's multiple comparisons test	Mean rank diff.	Significant?	Adjusted p-value
S1A	AAb- Control vs. AAb- Relative	7.020	ns	>0.9999
	AAb- Control vs. AAb+	76.81	****	<0.0001
	AAb- Control vs. Recent Onset	28.27	ns	0.6455
	AAb- Control vs. Established	40.00	ns	0.0737
	AAb- Relative vs. AAb+	69.79	***	0.0004
	AAb- Relative vs. Recent Onset	21.25	ns	>0.9999
	AAb- Relative vs. Established	32.98	ns	0.3728
	AAb+ vs. Recent Onset	-48.54	*	0.0365
	AAb+ vs. Established	-36.81	ns	0.2447
	Recent Onset vs. Established	11.73	ns	>0.9999
S1B	AAb- Control vs. AAb- Relative	-62.82	***	0.0008
	AAb- Control vs. AAb+	25.00	ns	>0.9999
	AAb- Control vs. Recent Onset	0.1076	ns	>0.9999
	AAb- Control vs. Established	-47.77	*	0.0152
	AAb- Relative vs. AAb+	87.82	****	<0.0001
	AAb- Relative vs. Recent Onset	62.93	**	0.0012
	AAb- Relative vs. Established	15.05	ns	>0.9999
	AAb+ vs. Recent Onset	-24.89	ns	>0.9999

SUPPLEMENTARY DATA

	AAb+ vs. Established	-72.77	****	<0.0001
	Recent Onset vs. Established	-47.88	*	0.0208
S1C	AAb- vs. 1 AAb+	49.88	***	0.0002
	AAb- vs. 2-3 AAb+	29.69	*	0.0491
	AAb- vs. Recent Onset	11.71	ns	>0.9999
	1 AAb+ vs. 2-3 AAb+	-20.19	ns	0.8467
	1 AAb+ vs. Recent Onset	-38.18	**	0.0079
	2-3 AAb+ vs. Recent Onset	-17.98	ns	0.6206
S1D	AAb- vs. 1 AAb+	40.22	**	0.0036
	AAb- vs. 2-3 AAb+	54.18	****	<0.0001
	AAb- vs. Recent Onset	33.02	**	0.0016
	1 AAb+ vs. 2-3 AAb+	13.96	ns	>0.9999
	1 AAb+ vs. Recent Onset	-7.204	ns	>0.9999
	2-3 AAb+ vs. Recent Onset	-21.16	ns	0.3588

SUPPLEMENTARY DATA

Supplementary Table 5. Percentages of IGF1 and IGF2 measurements compared to reference ranges for age and sex, per group. Subjects from UF cross-sectional cohort. IGF1 and IGF2 levels were below the fifth percentile in a higher percentage of 1 AAb+ and 2-3 AAb+ subjects as compared to all other groups.

Characteristic	**IGF1**		**IGF2**	
	n below 5th percentile	**% of total subjects**	**n below 5th percentile**	**% of total subjects**
AAb- Control	2	2.90%	6	8.70%
AAb- Relative	6	10.91%	0	0.00%
1 AAb+	8	36.36%	3	12.00%
2-3 AAb+	9	33.33%	7	25.93%
Recent Onset	5	8.20%	1	1.64%
Established	7	10.45%	2	2.94%

SUPPLEMENTARY DATA

Supplementary Table 6. Multiplicity adjusted p-values for Supplementary Figure 2.

Figure	Dunn's multiple comparisons test	Mean rank diff.	Significant?	Adjusted p-value
S2A	AAb- Control vs. AAb- Relative	-8.621	ns	>0.9999
	AAb- Control vs. AAb+	-48.82	*	0.0205
	AAb- Control vs. Recent Onset	-18.47	ns	>0.9999
	AAb- Control vs. Established	-50.99	**	0.0052
	AAb- Relative vs. AAb+	-40.20	ns	0.1459
	AAb- Relative vs. Recent Onset	-9.848	ns	>0.9999
	AAb- Relative vs. Established	-42.37	ns	0.0579
	AAb+ vs. Recent Onset	30.36	ns	0.6289
	AAb+ vs. Established	-2.167	ns	>0.9999
	Recent Onset vs. Established	-32.52	ns	0.3245
S2B	AAb- Control vs. AAb- Relative	-18.06	ns	>0.9999
	AAb- Control vs. AAb+	10.40	ns	>0.9999
	AAb- Control vs. Recent Onset	19.84	ns	>0.9999
	AAb- Control vs. Established	0.1971	ns	>0.9999
	AAb- Relative vs. AAb+	28.46	ns	0.8714
	AAb- Relative vs. Recent Onset	37.90	ns	0.1914
	AAb- Relative vs. Established	18.26	ns	>0.9999
	AAb+ vs. Recent Onset	9.437	ns	>0.9999

SUPPLEMENTARY DATA

	AAb+ vs. Established	-10.20	ns	>0.9999
	Recent Onset vs. Established	-19.64	ns	>0.9999
S2C	AAb- Control vs. AAb- Relative	18.71	ns	>0.9999
	AAb- Control vs. AAb+	22.21	ns	>0.9999
	AAb- Control vs. Recent Onset	45.92	*	0.0311
	AAb- Control vs. Established	32.42	ns	0.2901
	AAb- Relative vs. AAb+	3.499	ns	>0.9999
	AAb- Relative vs. Recent Onset	27.21	ns	0.9262
	AAb- Relative vs. Established	13.71	ns	>0.9999
	AAb+ vs. Recent Onset	23.71	ns	>0.9999
	AAb+ vs. Established	10.21	ns	>0.9999
	Recent Onset vs. Established	-13.50	ns	>0.9999
S2D	AAb- Control vs. AAb- Relative	-20.97	ns	>0.9999
	AAb- Control vs. AAb+	27.17	ns	0.8976
	AAb- Control vs. Recent Onset	33.23	ns	0.3237
	AAb- Control vs. Established	-6.997	ns	>0.9999
	AAb- Relative vs. AAb+	48.13	*	0.0382
	AAb- Relative vs. Recent Onset	54.20	**	0.0081
	AAb- Relative vs. Established	13.97	ns	>0.9999
	AAb+ vs. Recent Onset	6.070	ns	>0.9999
	AAb+ vs. Established	-34.16	ns	0.3119

	Recent Onset vs. Established	-40.23	ns	0.0886
S2E	AAb- vs. 1 AAb+	-28.18	ns	0.0808
	AAb- vs. 2-3 AAb+	-16.70	ns	0.7643
	AAb- vs. Recent Onset	-5.574	ns	>0.9999
	1 AAb+ vs. 2-3 AAb+	11.48	ns	>0.9999
	1 AAb+ vs. Recent Onset	22.60	ns	0.2776
	2-3 AAb+ vs. Recent Onset	11.12	ns	>0.9999
S2F	AAb- vs. 1 AAb+	11.60	ns	>0.9999
	AAb- vs. 2-3 AAb+	17.35	ns	0.7057
	AAb- vs. Recent Onset	20.79	ns	0.1185
	1 AAb+ vs. 2-3 AAb+	5.750	ns	>0.9999
	1 AAb+ vs. Recent Onset	9.189	ns	>0.9999
	2-3 AAb+ vs. Recent Onset	3.439	ns	>0.9999
S2G	AAb- vs. 1 AAb+	8.928	ns	>0.9999
	AAb- vs. 2-3 AAb+	-3.700	ns	>0.9999
	AAb- vs. Recent Onset	14.53	ns	0.6205
	1 AAb+ vs. 2-3 AAb+	-12.63	ns	>0.9999
	1 AAb+ vs. Recent Onset	5.600	ns	>0.9999
	2-3 AAb+ vs. Recent Onset	18.23	ns	0.5900
S2H	AAb- vs. 1 AAb+	22.70	ns	0.2955
	AAb- vs. 2-3 AAb+	32.86	*	0.0183

	AAb- vs. Recent Onset	30.51	**	0.0038
	1 AAb+ vs. 2-3 AAb+	10.16	ns	>0.9999
	1 AAb+ vs. Recent Onset	7.803	ns	>0.9999
	2-3 AAb+ vs. Recent Onset	-2.355	ns	>0.9999

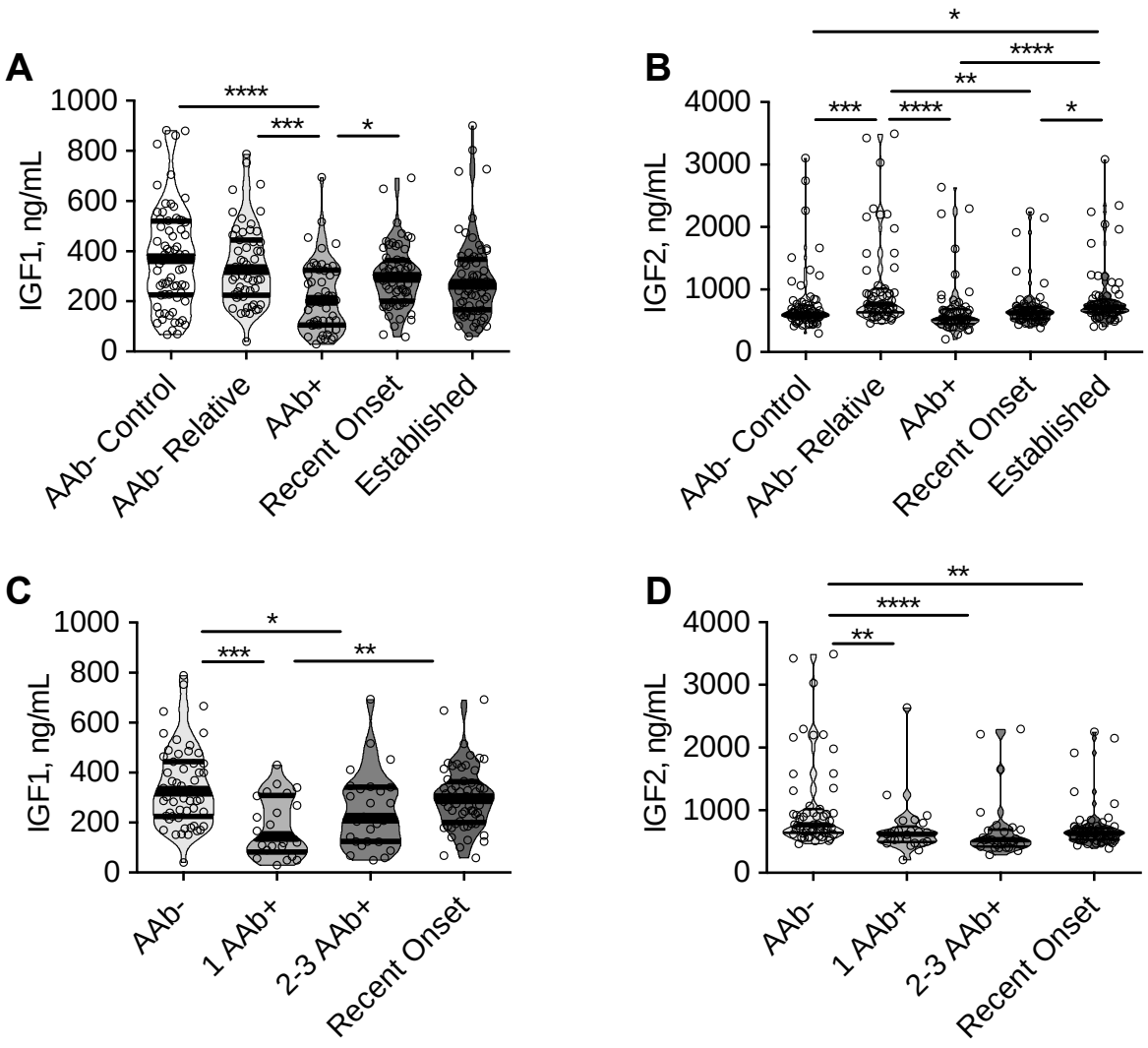
SUPPLEMENTARY DATA

Supplementary Table 7. Circulating IGFs can discriminate type 1 diabetes stages without the need for IGFBP measurements. A multinomial logistic regression model was established using R version 3.4.1. Only individuals with complete IGF1, IGF2, and IGFBP data, as well as reported race/ethnicity were included in the analysis. As height and weight information were voluntarily provided, missing BMI percentile data were imputed with predictive means matching using the MICE package. An automated forward variable selection method from the LEAPS package was used to generate a multinomial logistic regression model evaluating age, BMI percentile, sex, ethnicity, and log-transformed IGF1, IGF2, IGFBP1, IGFBP3, IGFBP6, and IGFBP7 concentrations as explanatory variables for a model to predict the cohort of the subject as the response variable. The variables included in the best additive model are shown here. The relevance of each explanatory variable in modeling differences between groups was determined by calculating relative risk ratios (RRR) with 95% CI, with the logically previous group in progression to disease as the referent.

	AAb- Relatives vs. 1 AAb+		**1 AAb+ vs. 2-3 AAb+**		**2-3 AAb+ vs. Recent Onset**	
Characteristic	**RRR (95% CI)**	**p value**	**RRR (95% CI)**	**p value**	**RRR (95% CI)**	**p value**
Log.IGF1	0.06 (0.02 - 0.20)	< 0.0001	1.81 (0.61 – 5.36)	0.28	4.32 (1.58 – 11.85)	< 0.01
Log.IGF2	0.17 (0.04 – 0.67)	< 0.05	0.61 (0.14 – 2.76)	0.52	2.52 (0.62 – 10.19)	0.19
Age	1.17 (0.98 - 1.41)	0.09	1.08 (0.90 - 1.30)	0.39	0.83 (0.71 - 0.96)	< 0.05
Log.IGFBP7	0.16 (0.02 – 1.34)	0.09	0.78 (0.09 – 6.57)	0.82	1.02 (0.18 – 5.67)	0.98

SUPPLEMENTARY DATA

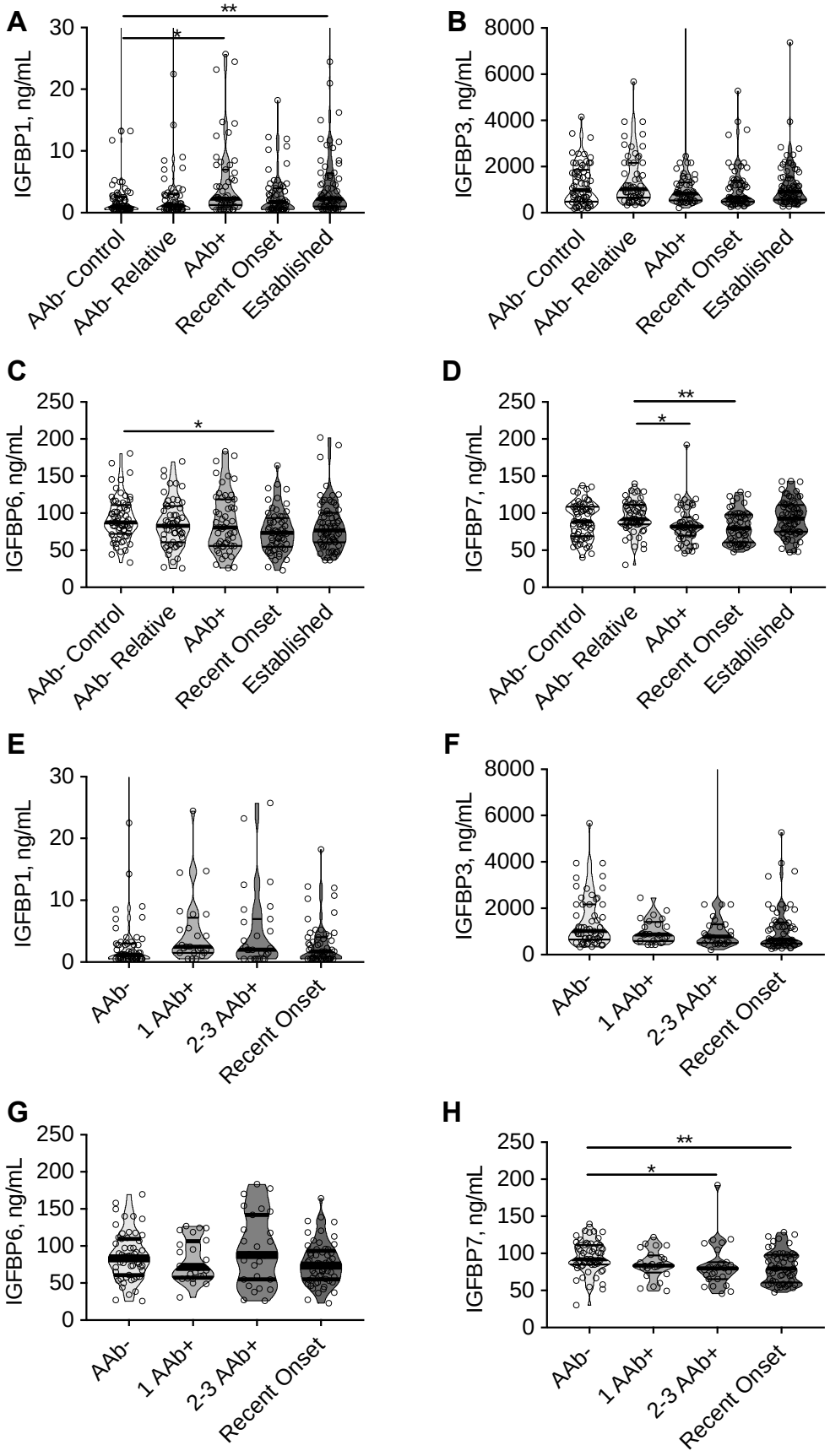
Supplementary Figure 1. Raw total IGF1 and IGF2 levels are significantly decreased in serum of AAb+ subjects at high risk for type 1 diabetes onset. Subjects from UF cross-sectional cohort. Violin plots showing (A) raw IGF1 levels show decreased IGF1 in AAb+ subjects as compared to AAb- controls, AAb- relatives, and subjects with recent-onset type 1 diabetes. (B) Raw IGF2 levels are decreased in AAb+ subjects and subjects with recent-onset disease as compared to AAb- relatives and established type 1 diabetes. Upon stratification of AAb+ group by number of AAb, (C) raw IGF1 levels and (D) raw IGF2 levels remain significantly decreased for those with any number of AAb. Kruskal-Wallis with Dunn's multiple comparisons test: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ****, $p < 0.0001$.



SUPPLEMENTARY DATA

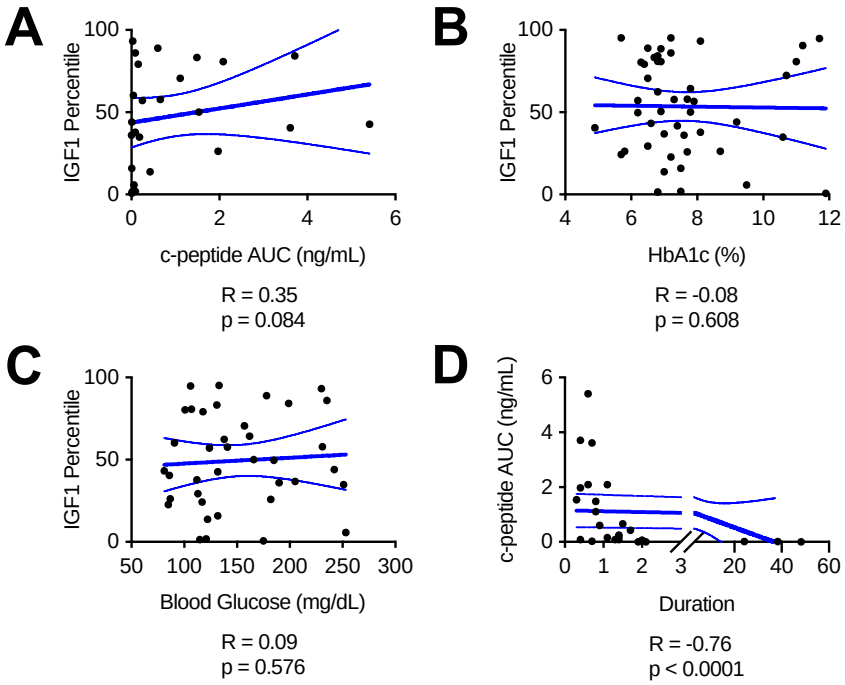
Supplementary Figure 2. High-affinity IGFBP levels are generally unchanged in serum of AAb+ subjects and subjects with recent-onset type 1 diabetes. Subjects from UF cross-sectional cohort. Violin plots showing (A) IGFBP1 increased in AAb+ subjects as compared to AAb- controls. (B) IGFBP3 appears relatively stable during disease pathogenesis. (C) IGFBP6 decreased in subjects with recent-onset disease as compared to AAb- controls. (D) IGFBP7 decreased in subjects with recent-onset type 1 diabetes and AAb+ subjects as compared to AAb- relatives. Upon stratification of AAb+ group by number of AAb, (E) IGFBP1, (F) IGFBP3 and (G) IGFBP6 levels did not significantly change between at-risk groups. (H) IGFBP7 decreased in subjects with multiple AAb+ as compared to AAb- relatives. Kruskal-Wallis with Dunn's multiple comparisons test: *, $p < 0.05$; **, $p < 0.01$.

SUPPLEMENTARY DATA



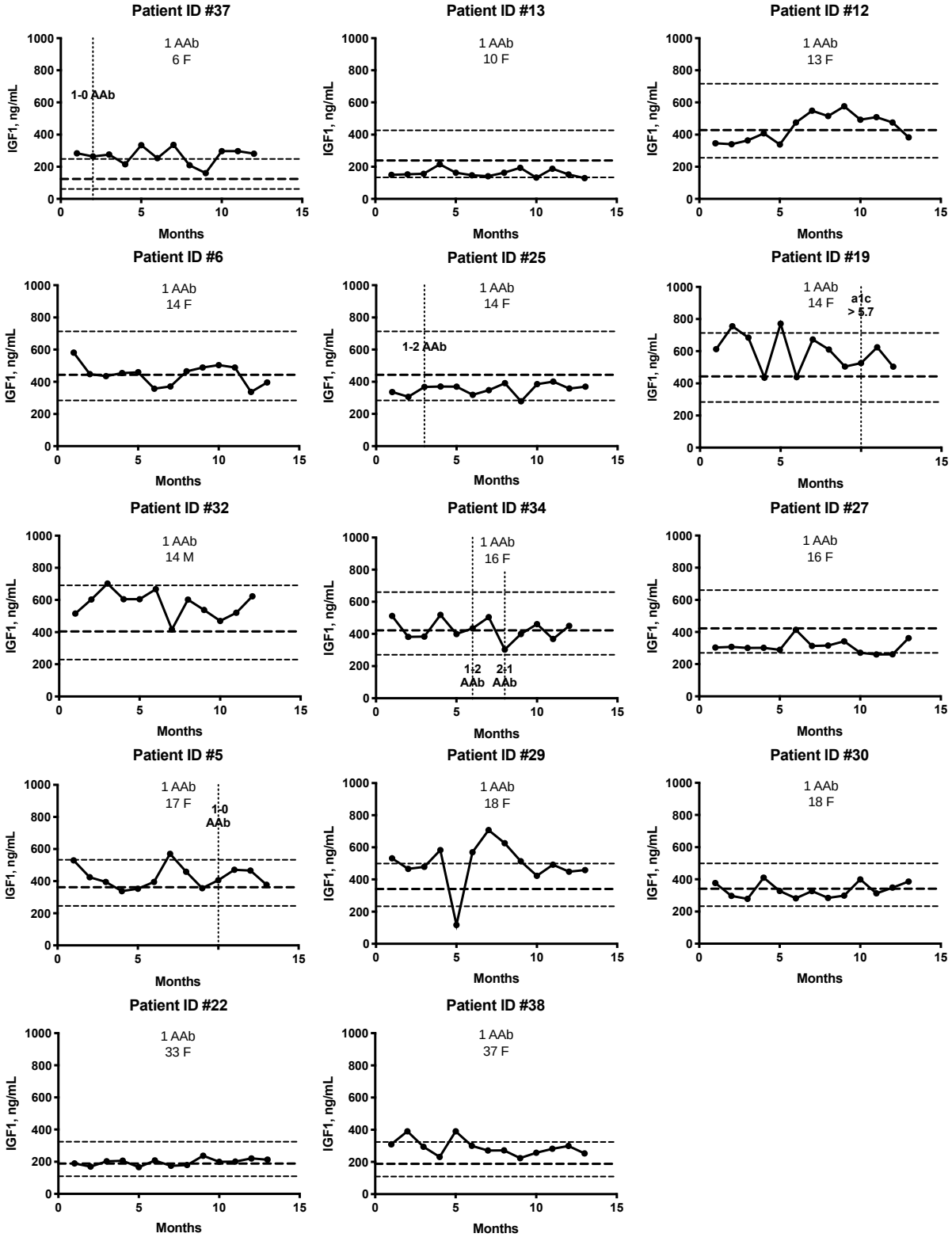
SUPPLEMENTARY DATA

Supplementary Figure 3. IGF1 levels show trends for association with endogenous β-cell function. In previously fasted subjects with type 1 diabetes from BRI, (A) IGF1 percentile shows a trend for a positive correlation with C-peptide AUC and does not associate with (B) HbA1c or (C) fasting blood glucose levels. (D) C-peptide AUC is significantly and negatively correlated with disease duration in this cohort. Data are overlaid with best fit lines (solid) and 95% CI (dashed lines). Spearman correlation.



SUPPLEMENTARY DATA

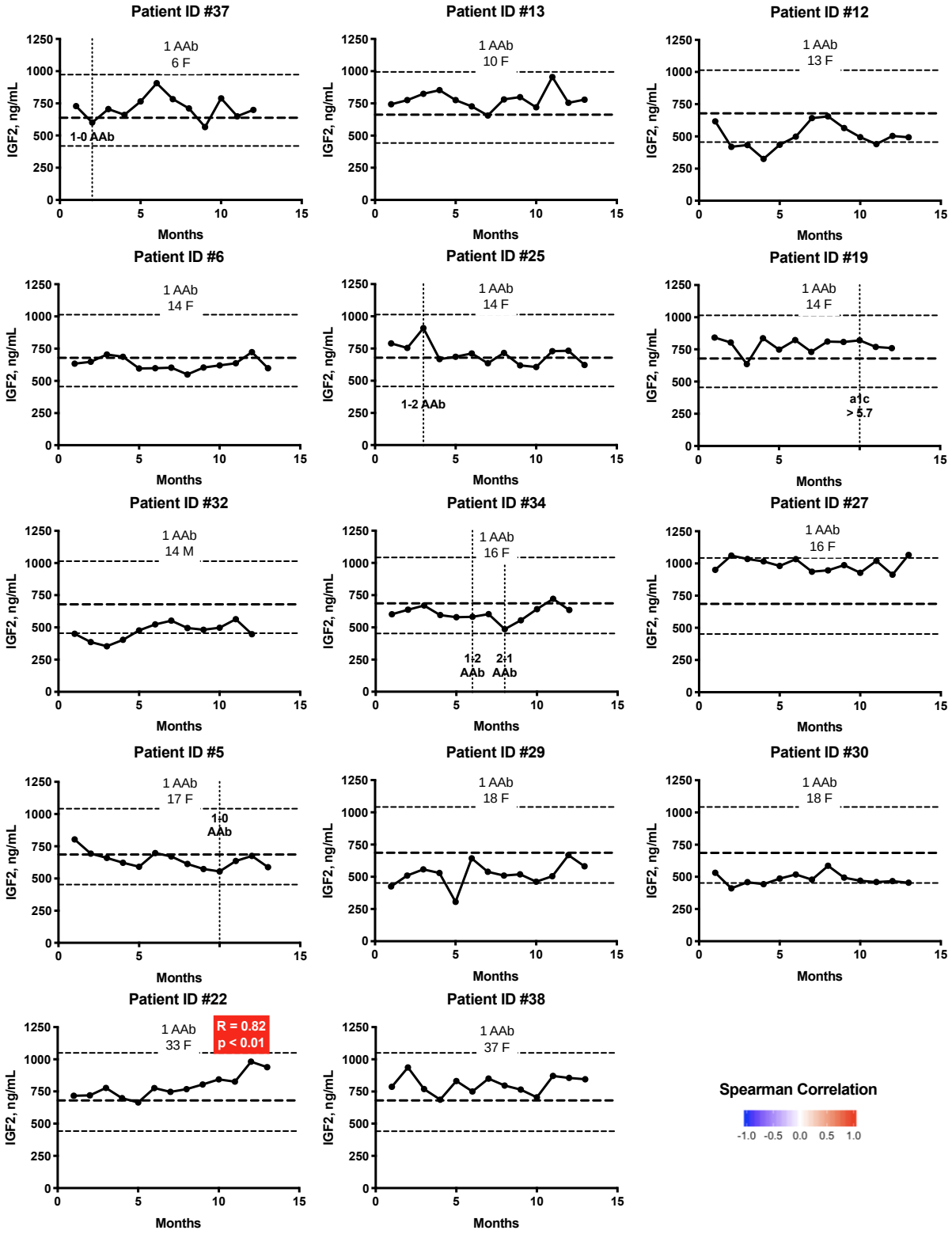
Supplementary Figure 4. Longitudinal follow-up of subjects with a single AAb at enrollment shows IGF1 stability over time. Subjects from longitudinal T1DBIT cohort. Raw IGF1 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged in order of increasing age. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines.



SUPPLEMENTARY DATA

Supplementary Figure 5. Longitudinal follow-up of subjects with a single AAb at enrollment shows IGF2 stability over time. Subjects from longitudinal T1DBIT cohort. Raw IGF2 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged in order of increasing age. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines. Spearman r and p values shown in upper right-hand corner.

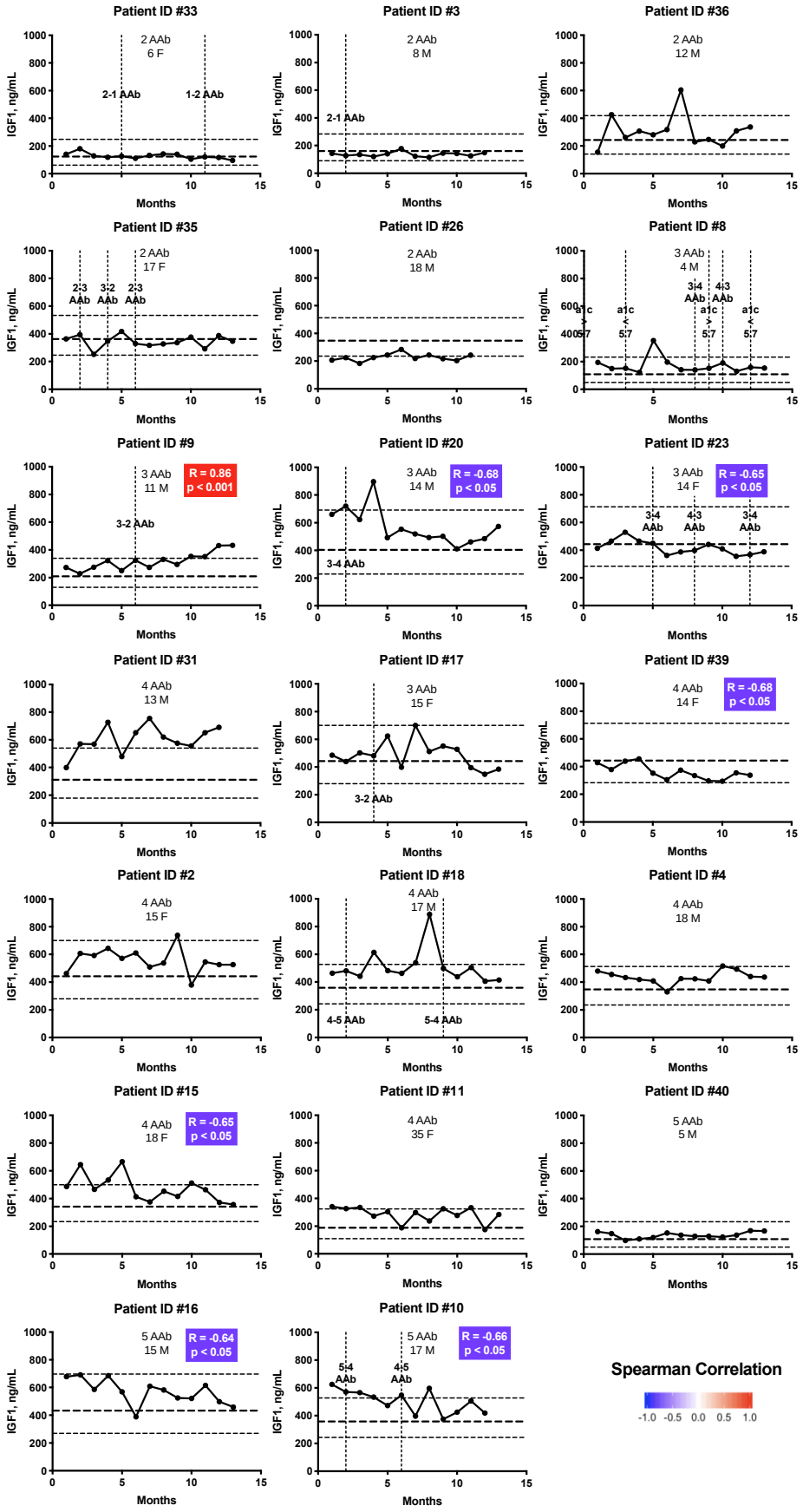
SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 6. Longitudinal follow-up of subjects with multiple AAb at enrollment shows IGF1 typically stable or decreasing over time. Subjects from longitudinal T1DBIT cohort. Raw IGF1 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged in order of number of AAb at enrollment, followed by increasing age. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines. Spearman r and p values shown in upper right-hand corner.

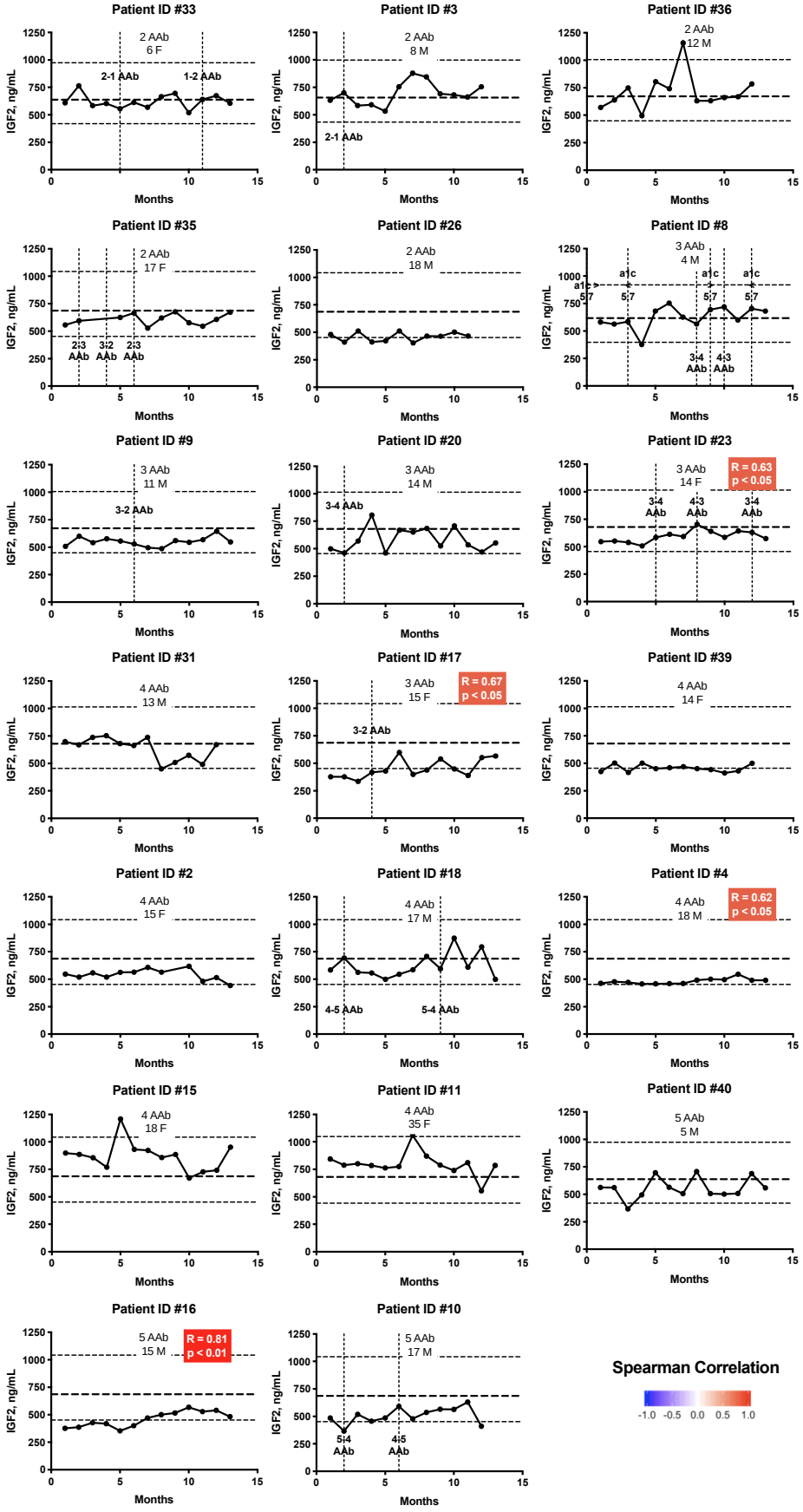
SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

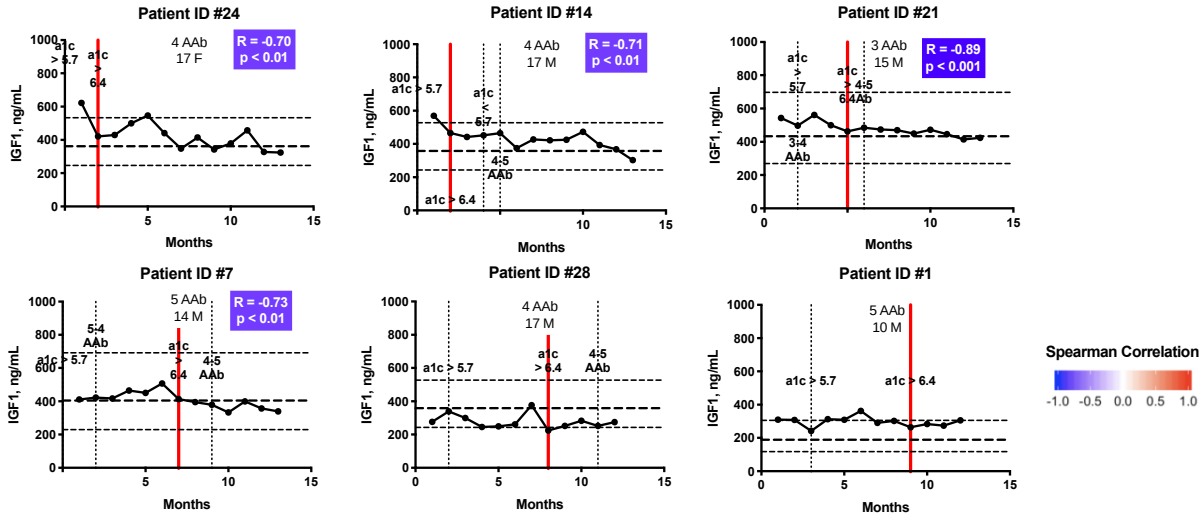
Supplementary Figure 7. Longitudinal follow-up of subjects with multiple AAb at enrollment shows IGF2 typically stable or increasing over time. Subjects from longitudinal T1DBIT cohort. Raw IGF2 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged in order of number of AAb at enrollment, followed by increasing age. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines. Spearman r and p values shown in upper right-hand corner.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 8. Longitudinal follow-up of multiple AAb subjects who develop type 1 diabetes during study shows IGF1 decreasing over time. Subjects from longitudinal T1DBIT cohort. Raw IGF1 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged from those diagnosed earlier to later in the study. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of diagnosis shown as vertical red line (a1c > 6.4) and pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines. Spearman r and p values shown in upper right-hand corner.



SUPPLEMENTARY DATA

Supplementary Figure 9. Longitudinal follow-up of multiple AAb subjects who develop type 1 diabetes during study shows variable trajectory of IGF2 over time. Subjects from longitudinal T1DBIT cohort. Raw IGF2 levels of individual T1DBIT subjects shown as solid lines. Subjects arranged from those diagnosed earlier to later in the study. 5%, 50%, and 95% reference ranges for age and sex are shown per person as horizontal dashed lines. Time of diagnosis shown as vertical red line (a1c > 6.4) and pre-type 1 diabetes (a1c > 5.7) or seroconversion events shown with vertical dashed black lines. Spearman r and p values shown in upper right-hand corner.