SUPPLEMENTARY DATA

The 1,374 regulated transcripts identified in cross-sectional studies consists of: 1) 575 LRS-associated probe sets where the 138 up-regulated and 437 down-regulated transcripts are annotated as being inflammatory and regulatory, respectively; 2) 128 RO T1D-associated probe sets where the 36 up-regulated and 92 down-regulated transcripts are annotated as being inflammatory and regulatory, respectively; 3) 156 HRS-associated probe sets where the 84 up-regulated and 72 down-regulated transcripts are annotated as being regulatory and inflammatory, respectively; and 4) 647 uHC-associated probe sets where the 532 up-regulated and 115 down-regulated transcripts are annotated as being regulatory and inflammatory, respectively (These are Tabulated in Online Supplemental Table 1).

In order to comprehensively measure the inflammatory state, ontology-based inflammatory index (*I.I.*) algorithms were tested that utilized ratios between the mean log intensity of inflammatory versus regulatory probe sets for each of the cross-sectional data subsets. Scoring strategies utilizing all 1,374 probe sets more effectively separated the four cohorts than ones utilizing smaller data subsets, including the 128 probe sets associated with the RO T1D cohort. Since the majority of siblings that progress to T1D possess DR3 and/or DR4 haplotypes, additional weighting of probe sets associated with the RO T1D and HRS groups was evaluated. While all tested algorithms were able to capture temporal changes in the inflammatory state (see tables below), optimal cross-sectional group separation was observed with the following scoring strategy:

$$IA_k = \frac{\sum_{i=1}^{n_k}(E_i - \overline{E_{i,uHC}})}{n_k} \qquad \text{1a}$$

Where, IA_k is the mean inflammatory activity, relative to uHC, of a given sample associated with the k^{th}-cohort-specific regulated genes (k=1, 2, 3, or 4, representing the LRS, RO T1D, HRS, and uHC cohorts, respectively). E is the expression ($\log_2$ intensity) of the sample. $\overline{E_{uHC}}$ is the mean expression ($\log_2$ intensity) of uHC cohort. n_k is the number of genes associated with inflammatory activity specific to the k^{th} cohort LRS (n_1=138), RO T1D (n_2=36), HRS (n_3=72), uHC (n_4=115) as described above and in Figure 5.

$$RA_k = \frac{\sum_{j=1}^{m_k}(E_j - \overline{E_{j,uHC}})}{m_k} \qquad \text{1b}$$

RA_k is the mean regulatory activity, relative to uHC, of a given sample associated with the k^{th}-cohort-specific regulated genes (k=1, 2, 3, or 4 representing the LRS, RO T1D, HRS, and uHC cohorts, respectively). m_k is the number of genes associated with regulatory activity specific to the k^{th} cohort LRS (m_1=437), RO T1D (m_2=92), HRS (m_3=84), uHC (m_4=532) as described above and in Figure 5.

The *I.I.* for a sample, based upon each cross-sectional data subset k ($I.I._k$), is determined by:

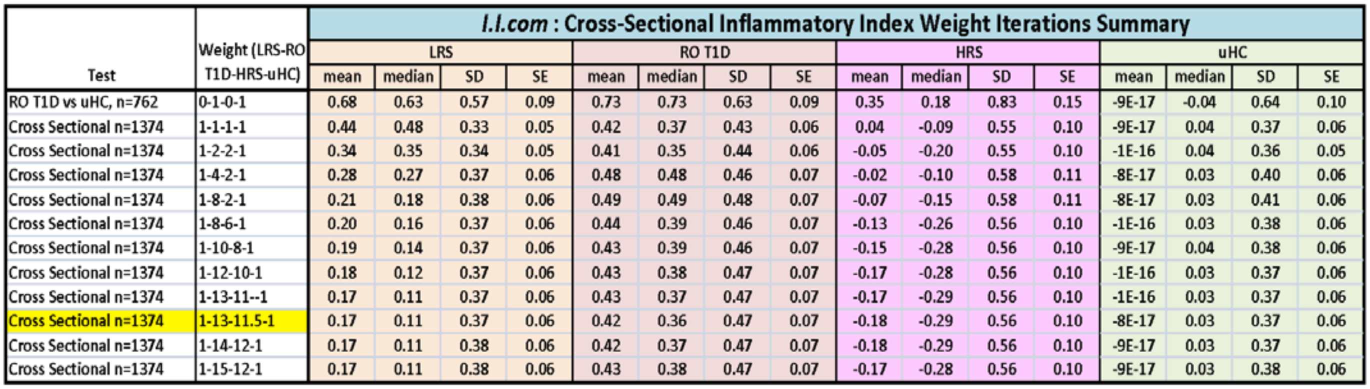
$$I.I._k = IA_k - RA_k \qquad 2$$

After which, $I.I._{com}$, a composite score for a sample based upon the individual $I.I._k$ for each of the four cross-sectional data subsets is determined by:

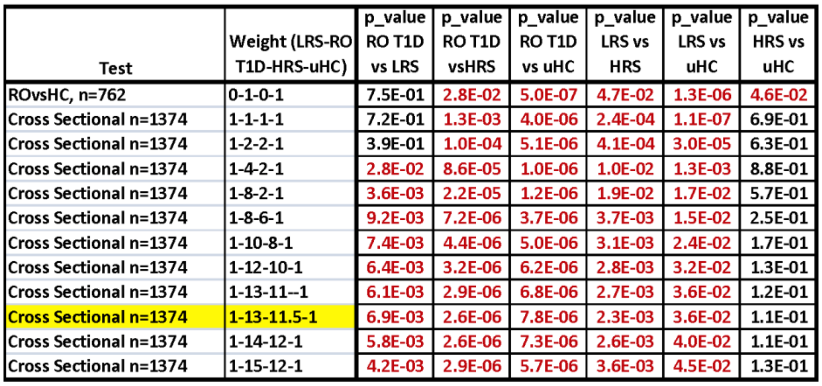
$$I.I._{com} = \frac{\sum_{k=1}^{4}(W_k * I.I._k)}{\sum_{k=1}^{4} W_k} \qquad 3$$

Where W_k is the optimized weight for each of the four cross-sectional cohorts, defined by: W = [1.0, 13.0, 11.5, 1.0] to ascribe higher weight to genes of the RO T1D and HRS cohorts.

It is important to note that for the subjects illustrated in Figure 5, independent evaluation of the slopes associated with IA_k and RA_k revealed that $I.I._{com}$ for any given subject was influenced by changes in both inflammatory and regulatory activity; however the relative contribution of each varied between subjects.



Test	Weight (LRS-RO T1D-HRS-uHC)	*I.I.com* : Cross-Sectional Inflammatory Index Weight Iterations Summary															
		LRS				RO T1D				HRS				uHC			
		mean	median	SD	SE	mean	median	SD	SE	mean	median	SD	SE	mean	median	SD	SE
RO T1D vs uHC, n=762	0-1-0-1	0.68	0.63	0.57	0.09	0.73	0.73	0.63	0.09	0.35	0.18	0.83	0.15	-9E-17	-0.04	0.64	0.10
Cross Sectional n=1374	1-1-1-1	0.44	0.48	0.33	0.05	0.42	0.37	0.43	0.06	0.04	-0.09	0.55	0.10	-9E-17	0.04	0.37	0.06
Cross Sectional n=1374	1-2-2-1	0.34	0.35	0.34	0.05	0.41	0.35	0.44	0.06	-0.05	-0.20	0.55	0.10	-1E-16	0.04	0.36	0.05
Cross Sectional n=1374	1-4-2-1	0.28	0.27	0.37	0.06	0.48	0.48	0.46	0.07	-0.02	-0.10	0.58	0.11	-8E-17	0.03	0.40	0.06
Cross Sectional n=1374	1-8-2-1	0.21	0.18	0.38	0.06	0.49	0.49	0.48	0.07	-0.07	-0.15	0.58	0.11	-8E-17	0.03	0.41	0.06
Cross Sectional n=1374	1-8-6-1	0.20	0.16	0.37	0.06	0.44	0.39	0.46	0.07	-0.13	-0.26	0.56	0.10	-1E-16	0.03	0.38	0.06
Cross Sectional n=1374	1-10-8-1	0.19	0.14	0.37	0.06	0.43	0.39	0.46	0.07	-0.15	-0.28	0.56	0.10	-9E-17	0.04	0.38	0.06
Cross Sectional n=1374	1-12-10-1	0.18	0.12	0.37	0.06	0.43	0.38	0.47	0.07	-0.17	-0.28	0.56	0.10	-1E-16	0.03	0.37	0.06
Cross Sectional n=1374	1-13-11--1	0.17	0.11	0.37	0.06	0.43	0.37	0.47	0.07	-0.17	-0.29	0.56	0.10	-1E-16	0.03	0.37	0.06
Cross Sectional n=1374	1-13-11.5-1	0.17	0.11	0.37	0.06	0.42	0.36	0.47	0.07	-0.18	-0.29	0.56	0.10	-8E-17	0.03	0.37	0.06
Cross Sectional n=1374	1-14-12-1	0.17	0.11	0.38	0.06	0.42	0.37	0.47	0.07	-0.18	-0.29	0.56	0.10	-9E-17	0.03	0.37	0.06
Cross Sectional n=1374	1-15-12-1	0.17	0.11	0.38	0.06	0.43	0.38	0.47	0.07	-0.17	-0.28	0.56	0.10	-9E-17	0.03	0.38	0.06



Test	Weight (LRS-RO T1D-HRS-uHC)	p_value RO T1D vs LRS	p_value RO T1D vsHRS	p_value RO T1D vs uHC	p_value LRS vs HRS	p_value LRS vs uHC	p_value HRS vs uHC
ROvsHC, n=762	0-1-0-1	7.5E-01	2.8E-02	5.0E-07	4.7E-02	1.3E-06	4.6E-02
Cross Sectional n=1374	1-1-1-1	7.2E-01	1.3E-03	4.0E-06	2.4E-04	1.1E-07	6.9E-01
Cross Sectional n=1374	1-2-2-1	3.9E-01	1.0E-04	5.1E-06	4.1E-04	3.0E-05	6.3E-01
Cross Sectional n=1374	1-4-2-1	2.8E-02	8.6E-05	1.0E-06	1.0E-02	1.3E-03	8.8E-01
Cross Sectional n=1374	1-8-2-1	3.6E-03	2.2E-05	1.2E-06	1.9E-02	1.7E-02	5.7E-01
Cross Sectional n=1374	1-8-6-1	9.2E-03	7.2E-06	3.7E-06	3.7E-03	1.5E-02	2.5E-01
Cross Sectional n=1374	1-10-8-1	7.4E-03	4.4E-06	5.0E-06	3.1E-03	2.4E-02	1.7E-01
Cross Sectional n=1374	1-12-10-1	6.4E-03	3.2E-06	6.2E-06	2.8E-03	3.2E-02	1.3E-01
Cross Sectional n=1374	1-13-11--1	6.1E-03	2.9E-06	6.8E-06	2.7E-03	3.6E-02	1.2E-01
Cross Sectional n=1374	1-13-11.5-1	6.9E-03	2.6E-06	7.8E-06	2.3E-03	3.6E-02	1.1E-01
Cross Sectional n=1374	1-14-12-1	5.8E-03	2.6E-06	7.3E-06	2.6E-03	4.0E-02	1.1E-01
Cross Sectional n=1374	1-15-12-1	4.2E-03	2.9E-06	5.7E-06	3.6E-03	4.5E-02	1.3E-01