

1 **Supplementary methods**

2

3 **Abbreviations**

4 ASV – amplicon sequence variant

5 AUC – area under the curve

6 AUROC – area under the receiver-operator curve

7 CMV - cytomegalovirus

8 CRP – C-reactive protein

9 EBV – Epstein-Barr virus

10 ESBL – extended-spectrum beta lactamase

11 FACS – fluorescent-activated cell sorting

12 FMT – fecal microbiota transplantation

13 GAD – glutamate decarboxylase

14 HDLc – high density lipoprotein cholesterol

15 HLA – human leukocyte antigen

16 LDLc – low density lipoprotein cholesterol

17 LMM – linear mixed models analysis

18 LST – lymphocyte stimulation test

19 MMT – mixed meal test

20 MWU – Mann-Whitney U test

21 MRSA – methicillin-resistant *Staphylococcus aureus*

22 PBMCs - Peripheral blood mononuclear cells

23 PCR – polymerase chain reaction

24 PPI – preproinsulin

25 Qdot – quantum dot

26 ROC – receiver-operator curve

27 RT qPCR – reverse transcription quantitative PCR

28 T1D – type 1 diabetes

29 TG - triglycerides

30 TT – tetanus toxoid

31 UPLC-MS/MS - ultra high performance liquid chromatography coupled to tandem mass spectrometry

32

33 *Fecal donor recruitment and randomization*

34 Fecal donors completed questionnaires regarding dietary and bowel habits, travel history,
35 comorbidity including family history of diabetes mellitus and medication use. They were screened for
36 the presence of infectious diseases as described previously[1]. Furthermore, donors with 1st or 2nd
37 degree relatives with autoimmune diseases (including Coeliac disease, autoimmune thyroid disease,
38 type 1 diabetes and rheumatoid arthritis) were excluded. Blood was screened for human
39 immunodeficiency virus; human T-lymphotropic virus; Hepatitis A, B, and C; cytomegalovirus (CMV);
40 Epstein–Barr virus (EBV); strongyloides; amoebiasis, and lues. Presence of infection resulted in
41 exclusion, although previous and non-active infections with EBV and CMV were allowed. Donors
42 were also excluded if screening of their feces revealed the presence of pathogenic parasites (e.g.
43 blastocystis hominis, dientamoeba fragilis, giardia lamblia), multiresistent bacteria (*Shigella*,
44 *Campylobacter*, *Yersinia*, *MRSA*, *ESBL*, *Salmonella*, *enteropathogenic E. Coli* and *Clostridium difficile*)
45 or viruses (noro-, rota-, astro-, adeno (40/41/52)-, entero-, parecho- and sapovirus) as previously
46 recommended[2]. After an overnight fast, plasma samples were taken for biochemistry and
47 metabolomics and a morning fecal sample was collected.

48 *FMT procedure*

49 Seven healthy lean donors (of whom 3 were used twice) donated for the allogenic gut microbiota
50 transfer to new onset type 1 diabetes (T1D) patients, and the same donor was used for the three
51 consecutive FMT's in an individual T1D patient.

52 After admission, a duodenal tube was placed by gastroscopy or CORTRAK enteral access system. Each
53 patient then underwent complete colon lavage with 2-4L of Klean prep® (macrogol) by duodenal
54 tube until the researcher judged that the bowel was properly lavaged (i.e. no solid excrement, but
55 clear fluid) for approximately 3h. Then, between 200 and 300 grams of feces was processed by
56 dilution in 500 ml of 0.9% saline solution and filtered through unfolded cotton gauzes. The filtrate
57 was used for transplantation two hours after the last administration of Klean prep® by duodenal tube
58 in around 30 minutes using 50cc syringes. After a short observation period the patient was sent
59 home.

60

61 *Study visits*

62 All study visits were performed at Amsterdam UMC, location AMC. Participants were asked to fill out
63 an online nutritional diary for the duration of one week before each study visit to monitor caloric
64 intake including the amount of dietary carbohydrates, fats, proteins and fibers. During the study
65 visits blood pressure, weight and daily insulin use were documented. Fasting blood samples were
66 taken at each visit and upon centrifugation stored at -80°C for subsequent analyses. Whole blood
67 sodium heparin tubes were kept on room temperature and processed within 24 hours for
68 immunological analyses (described under immunology).

69

70 *Description per study visit*

71 All visits took place after an overnight fast with subjects taking no long acting insulin the night before
72 as previously described (Moran et al., 2013). At each visit blood, fecal and urine sampling and
73 biometric measurements took place. At baseline all patients first underwent gastroduodenoscopy. A
74 small dose of midazolam (2.5 or 5mg) was administered for patient's comfort. Duodenal biopsies
75 were immediately collected in sterile tubes, snap-frozen in liquid nitrogen and stored at -80°C,
76 followed by nasoduodenal tube placement. Then at least 2 hours later, a standardized 2h mixed meal
77 test (MMT)(Nestlé sustacal boost®) was performed as previously described[3] to study residual Beta-

78 cell function. At 2, 9 and 12 months, patients again underwent a mixed-meal test for residual Beta-
79 cell C-peptide secretion. After the 2 hour MMT, a duodenal tube was placed by means of CORTRAK
80 enteral access, bowel cleansing for 6 hours was performed and the fecal transplant procedures were
81 repeated. At 6 months, patients underwent gastroduodenoscopy and biopsies were taken from the
82 duodenum and again thereafter, the mixed-meal test was performed. Of note, the similar daily
83 schedule was used in all patients to minimize variation in measurements between subjects.

84

85 *Mixed meal test*

86 Starting the evening before each mixed meal test, T1D patients interrupted their long-acting insulin
87 injections as previously published [3]. After an overnight fast and without taking their short-acting
88 morning insulin dose, a mixed meal test was performed with Boost High Protein (Nestlé Nutrition,
89 Vervey, Switzerland) at 6 ml/kg body weight with a maximum of 360 ml per person as previously
90 described[4]. Subsequent blood sampling for stimulated C-peptide was performed at -10, 0, 15, 30,
91 45, 60, 90 and 120 minutes. Area under the curve (AUC) was derived according to the trapezoidal
92 rule.

93

94 *Adaptive T-cell Immunity*

95 Whole blood samples were processed within 24 hours after sampling. Peripheral blood mononuclear
96 cells (PBMC's) were used for measurement of immune response. Granulocytes were isolated for
97 DNA-extraction and human leukocyte antigen (HLA) typing.

98

99 *Isolation of Peripheral blood mononuclear cells (PBMC's)*

100 PBMC's were isolated using Ficoll-density gradient centrifugation (ficoll 5.7%, amidotrizoaat 9%,
101 *Pharmacy Leiden University Medical Centre*). After centrifuging, the interphase containing PBMC's
102 was harvest and washed 3 times using PBS. PBMC's were suspended in 2 ml Iscove's modified

103 Dulbecco's Medium (IMDM, *Lonza*) supplemented with L-glutamine, penicillin-streptomycin (Pen
104 Strep) and 15% Human serum and counted.

105

106 *Lymphocyte Stimulation Test (LST)*

107 T-cell proliferation in response to antigenic stimulation was performed as described previously
108 (Kracht, *Nature Medicine* 2017). Cells were incubated in conditioned medium alone or in the
109 presence of autoantigen proteins glutamate decarboxylase (GAD65), preproinsulin (PPI), insulinoma
110 antigen-1 (IA-2) and a defective ribosomal product of proinsulin mRNA (DRIP) generated by stressed
111 Beta cells[5]. For controls, cells were stimulated with Interleukin-2 (IL-2) or cultured with tetanus
112 toxoid (TT). Cells were incubated for 5 days, after which ³H-thymidine (50μl, 10 μCi/ml) was added
113 for the last 18 hours of the culture.

114

115 *Fluorescent-activated cell sorting (FACS) analyses and Quantum dot (Qdot)*

116 For phenotyping and quantification of autoreactive CD8+ T-cell s, PBMC were stained with
117 fluorescent antibodies according to a standard, independently validated protocol as described
118 previously [6]. Stained cells were measured using FACS-Canto (phenotyping) and LSR-II (Q-dot)
119 machines (Becton&Dickinson). Phenotyping data were analyzed using FlowJo software (TreeStar)
120 using the gating strategy (supplementary figure 1) or as described previously for Qdot analyses [6].

121

122 *Plasma metabolites*

123 Fasting plasma targeted metabolite measurements were done by Metabolon (Durham, NC), using
124 ultra high performance liquid chromatography coupled to tandem mass spectrometry (UPLC-
125 MS/MS), as previously described [7]. Raw data was normalized to account for inter-day differences.
126 Then, the levels of each metabolite were rescaled to set the median equal to 1 across all samples.
127 Missing values, generally due to the sample measurement falling below the limit of detection, were
128 then imputed with the minimum observed value for the respective metabolite.

129

130 *Biochemistry*

131 Glucose and C-reactive protein (CRP, Roche, Switzerland) were determined in fasted plasma samples.
132 C-peptide was measured by radioimmunoassay (Millipore, Amsterdam, The Netherlands). Total
133 cholesterol, high density lipoprotein cholesterol (HDLc), and triglycerides (TG) were determined in
134 EDTA-containing plasma using commercially available enzymatic assays (Randox, Antrim, UK and
135 DiaSys, Germany). All analyses were performed using a Selectra autoanalyzer (Sopachem, The
136 Netherlands). Low density lipoprotein cholesterol (LDLc) was calculated using the Friedewald formula.
137 Calprotectin was determined in feces using a commercial ELISA (Bühlmann, Switzerland). Hba1c was
138 measured by HPLC (Tosoh G8, Tosoh Bioscience)

139

140 *Fecal sample shotgun sequencing and metagenomic pipeline*

141 Fecal microbiota were analysed using shotgun sequencing on donor and patient samples taken at 0,
142 6 and 12 months after initiation of study. DNA extraction from fecal samples for shotgun
143 metagenomics was performed as previously described[8]. Subsequently, shotgun metagenomic
144 sequencing was performed (Clinical Microbiomics, Copenhagen, Denmark). Before sequencing, the
145 quality of the DNA samples was evaluated using agarose gel electrophoresis, NanoDrop 2000
146 spectrophotometry and Qubit 2.0 fluorometer quantitation. The genomic DNA was randomly
147 sheared into fragments of around 350 bp. The fragmented DNA was used for library construction
148 using NEBNext Ultra Library Prep Kit for Illumina (New England Biolabs). The prepared DNA libraries
149 were evaluated using Qubit 2.0 fluorometer quantitation and Agilent 2100 Bioanalyzer for the
150 fragment size distribution. Real time quantitative PCR (qPCR) was used to determine the
151 concentration of the final library before sequencing. The library was sequenced on an Illumina HiSeq
152 platform to produce 2 x 150 bp paired-end reads. Raw reads were quality filtered using Trimmomatic
153 (v0.38), removing adapters, trimming the first 5 bp, and then quality trimming reads using a sliding

154 window of 4 bp and a minimum Q-score of 15. Reads that were shorter than 70 bp after trimming
155 were discarded. Surviving paired reads were mapped against the human genome (GRCh37_hg19)
156 with bowtie2 (v2.3.4.3) in order to remove human reads. Finally, the remaining quality filtered, non-
157 human reads were sub-sampled to 20 million reads per sample and processed using Metaphlan2[9]
158 (v2.7.7) to infer metagenomic microbial species composition and Humann2[10] (v0.11.2) to extract
159 gene counts and functional pathways. In brief, reads were mapped using bowtie2 against microbial
160 pangenomes; unmapped reads were translated and mapped against the full Uniref90 protein
161 database using diamond (v0.8.38). Pathway collection was performed using the MetaCyc database.

162

163 *Small intestinal microbiota analyses*

164 Biopsies were added to a bead-beating tube with 300 μ l Stool Transport and Recovery (STAR) buffer,
165 0.25 g of sterilized zirconia beads (0.1 mm). 6 μ l of Proteinase K (20mg/ml; QIAGEN, Venlo, The
166 Netherlands) was added and incubated for 1hr at 55 °C. The biopsies were then homogenized by
167 bead-beating three times (60 s \times 5.5 ms) followed by incubation for 15 min at 95 °C at 1000 rpm.
168 Samples were then centrifuged for 5 min at 4 °C and 14,000 g and supernatants transferred to sterile
169 tubes. Pellets were re-processed using 200 μ l STAR buffer and both supernatants were pooled. DNA
170 purification was performed with a customized kit (AS1220; Promega) using 250 μ l of the final
171 supernatant pool. DNA was eluted in 50 μ l of DNase- RNase-free water and its concentration
172 measured using a DS-11 FX+ Spectrophotometer/Fluorometer (DeNovix Inc., Wilmington, USA) with
173 the Qubit™ dsDNA BR Assay kit (Thermo Scientific, Landsmeer, The Netherlands). The V5-V6 region
174 of 16S ribosomal RNA (rRNA) gene was amplified in duplicate PCR reactions for each sample in a total
175 reaction volume of 50 μ l. A first step PCR using the 27F and the 1369R primer were used for primary
176 enrichment. 1 μ l of 10uM primer, 1 μ l dNTPs mixture, 0.5 μ l Phusion Green Hot Start II High-Fidelity
177 DNA Polymerase (2 U/ μ l; Thermo Scientific, Landsmeer, The Netherlands), 10 μ l 5 \times Phusion Green HF
178 Buffer, and 36.5 μ l DNase- RNase-free water. The amplification program included 30 s of initial
179 denaturation step at 98°C, followed by 5 cycles of denaturation at 98 oC for 30 s, annealing at 52 °C

180 for 40 s, elongation at 72 °C for 90 s, and a final extension step at 72 °C for 7 min. On the PCR product
181 a nested PCR was performed using the master mix containing 1 µl of a unique barcoded primer,
182 784F-n and 1064R-n (10 µM each per reaction), 1 µl dNTPs mixture, 0.5 µl Phusion Green Hot Start II
183 High-Fidelity DNA Polymerase (2 U/µl; Thermo Scientific, Landsmeer, The Netherlands), 10 µl 5×
184 Phusion Green HF Buffer, and 36.5 µl DNase- RNAse-free water. The amplification program included
185 30 s of initial denaturation step at 98°C, followed by 5 cycles of denaturation at 98 °C for 10 s,
186 annealing at 42 °C for 10 s, elongation at 72 °C for 10 s, and a final extension step at 72 °C for 7 min.
187 The PCR product was visualised in 1% agarose gel (~280 bp) and purified with CleanPCR kit (CleanNA,
188 Alphen aan den Rijn, The Netherlands). The concentration of the purified PCR product was measured
189 with Qubit dsDNA BR Assay Kit (Invitrogen, California, USA) and 200 ng of microbial DNA from each
190 sample were pooled for the creation of the final amplicon library which was sequenced (150 bp,
191 paired-end) on the Illumina HiSeq. 2500 platform (GATC Biotech, Constance, Germany).

192 Raw reads were demultiplexed using the Je software suite (v2.0.) allowing no mismatches in the
193 barcodes. After removing the barcodes, linker and primers, reads were mapped against the human
194 genome using bowtie2 in order to remove human reads. Surviving microbial forward and reverse
195 reads were pipelined separately using DADA2[11] (v1.12.1). Amplicon Sequence Variants (ASVs)
196 inferred from the reverse reads were reverse-complemented and matched against ASVs inferred
197 from the forwards reads. Only non-chimeric forward reads ASVs that matched reverse-
198 complemented reverse reads ASVs were kept. ASV sample counts were inferred from the forward
199 reads. ASV taxonomy was assigned using DADA2 and the SILVA (v132) database. The resulting ASV
200 table and taxonomy assignments were integrated using the phyloseq R package (v1.28.0) and
201 rarefied to 60000 counts per sample.

202

203 *Duodenal gene expression*

204 Fresh biopsy samples were snap frozen, stored at -80°C and processed as previously published
205 (Pellegrini et al., 2017). Prior to RNA extraction, biopsies were transferred into 500 µl lysis buffer

206 (mirVana Isolation Kit, Ambion, Austin, TX), homogenized with Tissue Ruptor (Qiagen, Hilden,
207 Germany) and frozen again. Total RNA was extracted with mirVana Kit following manufacturer's
208 instruction and quantified by spectrophotometer lecture (Epoch, Gen5 software; BioTek, Winooski,
209 VT). OD A260/A280 ratio ≥ 2.0 and *GAPDH* Ct < 28 in Taqman single assay identified acceptable quality
210 RNA samples. For reverse transcription PCR, after DNase treatment (Turbo DNase, Invitrogen), 5 μ g
211 of RNA were retro-transcribed in a 21 μ l reaction volume with SuperScript IV RT (Invitrogen)
212 following manufacturer's instructions. Predesigned TaqMan Arrays Human Inflammation Panel and
213 Human Cell Junction Panel (Applied Biosystems, Foster City, CA) were used for gene expression
214 study. A list of genes is reported in supplementary table 1. PCR runs and fluorescence detection were
215 carried out in a 7900 Real-Time PCR System (Applied Biosystems) at the following temperature
216 conditions: 50° C for 2 minutes, 95° C for 10 minutes and 40 cycles of 95° C for 15 seconds and 60° C
217 for 1 minute. Results were expressed as fold changes ($2^{-\Delta\text{Ct}}$ method) over a mean of expression of
218 the selected best reference genes: 5 housekeeping (HK) genes for Human Inflammation panel I (β -
219 *actin*, β -2 *Microglobulin*, *GAPDH*, *RPLP0* and *UBC*) and 4 housekeeping genes for Human Cell Junction
220 Panel (β -2 *Microglobulin*, *GAPDH*, *RPLP0* and *UBC*).

221

222 *Statistical analysis*

223 For baseline differences between groups, unpaired Student's t-test or the Mann-Whitney U test
224 (MWU) were used dependent on the distribution of the data. Accordingly, data are expressed as
225 mean \pm the standard deviation or the median with interquartile range. Post-prandial results (e.g. c-
226 peptide) are described as area under the curves (AUC) for the 2-hour post-prandial follow-up,
227 calculated by using the trapezoidal method. For correlation analyses, Spearman's Rank test was used
228 (as all parameters were non-parametric). For comparison of the primary end point a linear mixed
229 model (LMM) was used (lme4 package in R), where 'allocation' and 'time point' were fixed effects
230 and 'patient entry number' was a random effect. The p value for the interaction between 'allocation'
231 and 'time point' was reported. Additionally, parameters were compared between groups at various

232 time points using MWU with multiplicity correction. A p-value < 0.05 was considered statistically
233 significant.

234

235 *Missing values*

236 One study participant retracted informed consent after the first visit. This participant was not
237 included in our analyses. All other study participants completed all study visits, therefore missing
238 values are limited. Most missing data points were caused by laboratory problems such as inability to
239 extract DNA or failure to properly process or harvest immune cells. These missing data are
240 considered to be missing completely at random (MCAR). The exception to this is that one subject
241 refused the second gastroduodenoscopy, therefore his duodenal biopsies (small intestinal microbiota
242 and gene expression) after treatment are missing (1 in 20 cases or 5%). This subject has received
243 autologous FMT. We do not assume that having received autologous treatment rather than allogenic
244 (donor) faeces, metabolism or gene expression are in any way related to this person refusing the
245 second gastroscopy, therefore we consider these data to be 'missing at random'(MAR). Key variables
246 fasting C-peptide, C-peptide AUC, A1c and weight are complete (0% missing). The immunological
247 parameters mentioned in the text and figures (main figure 6 and supplementary figure 3) are all
248 based on complete data sets i.e. no missing values (CD4+ CM T cells, CD8+ T cells, CD8+CXCR3+ T
249 cells and CD4+CXCR3+ T cells). Most gene expression data in the manuscript and main and
250 supplemental figures (CCL22, CLDN12, CCL4, CD86, CCL19, CLDN 14, CCR5, CCL18, CD14) is 95%
251 complete (see above). For CCL13 one extra baseline measurement is missing, for CXCL12 one 'after
252 treatment' time point is missing, for CXCL1 two baseline and 1 after treatment time point is missing.
253 Some immunological analyses have suffered from missing data, e.g. the lymphocyte stimulation tests
254 (LST) analyses (1 to 4/20 (5-20%) of cases depending on the parameter). However, these data are not
255 mentioned in the figures (there was no statistically significant difference between the groups). The
256 fecal microbiota dataset is complete (complete case analysis). The missing values in the metabolite

257 data were imputed (see paragraph on metabolite analysis), therefore complete case analysis was
258 performed. No other data have been imputed.

259

260

261

262 *Machine learning and follow-up statistical analyses*

263 This technique was used on duodenal microbial composition (perform RT-qPCR on biopsies), on fecal
264 microbiota composition and metabolic pathway abundance (Shotgun sequencing), on plasma
265 metabolite levels and on duodenal gene expression levels data. To predict treatment groups, we
266 used the relative change (delta) of each parameter between 0 and 12 months. For duodenal
267 microbes and duodenal gene expression, we used delta 0 vs 6 months as no 12 months' time point
268 was available. For prediction of responders vs non-responders baseline values, delta 0 vs 6 months
269 and delta 0 vs 12 months were used. Each analysis produced a ranked list of the top 30 most
270 discriminative features. We selected the top parameters from each analysis that accurately (i.e.,
271 area under the receiver-operator curve (AUROC) ≥ 0.8) or moderately (AUROC > 0.7) predicted group
272 allocation for closer study, using an arbitrary cut off. This cut off was generally a relative importance
273 of around 30% or higher (for an example of this see figure 2C, from which the top 4 features were
274 selected). Then, we visualized the change in time of the selected parameters (Wilcoxon's signed rank
275 tests) and studied between-group differences (MWU) at each time point and finally, using
276 Spearman's rank test, we correlated these parameters with our primary end point and with other key
277 parameters that were identified in this way. For the most important analyses supplementary figures
278 showing the top 30 selected features are presented.

279

280 *Analysis of responders and non-responders irrespective of treatment group*

281 We investigated whether baseline characteristics of T1D patients can predict response to FMT
282 therapy at 12 months follow-up and which bacterial strains and plasma metabolites were associated
283 with this response. Clinical response was defined as <10% decline in Beta-cell function compared to
284 baseline at 12 months follow-up, which is significantly less than the expected natural 12 months
285 decline of 20% in beta cell function [4,12]. We chose responders at 12 months for our analyses
286 because our primary end point (MMT stimulated C-peptide) was significantly different at 12 (but not
287 at 6) months. At 12 months follow-up, clinical response sustained in 10 subjects of whom 3 had
288 received allogenic and 7 had received autologous FMT (see Figure 4A-B). We next used predictive
289 modelling to determine which parameters (either their baseline values or delta 0-12 month values)
290 were predictors of clinical response to FMT.

291

292 *Patient and public involvement*

293 This research was done without patient involvement. Patients were not invited to comment on the
294 study design and were not consulted to develop patient relevant outcomes or interpret the results.
295 Patients were not invited to contribute to the writing or editing of this document for readability or
296 accuracy.

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298 **References**

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- 300 1 van Nood E, Vrieze A, Nieuwdorp M, *et al.* Duodenal infusion of donor feces for recurrent
301 Clostridium difficile. *N Engl J Med* 2013;**368**:407–15. doi:10.1056/NEJMoa1205037
- 302 2 Cammarota G, Ianaro G, Tilg H, *et al.* European consensus conference on faecal microbiota
303 transplantation in clinical practice. *Gut* 2017;**66**:569–80. doi:10.1136/gutjnl-2016-313017
- 304 3 Moran A, Bundy B, Becker DJ, *et al.* Interleukin-1 antagonism in type 1 diabetes of recent
305 onset: two multicentre, randomised, double-blind, placebo-controlled trials. *Lancet (London,*

- 306 *England*) 2013;**381**:1905–15. doi:10.1016/S0140-6736(13)60023-9
- 307 4 Lachin JM, McGee PL, Greenbaum CJ, *et al.* Sample size requirements for studies of treatment
308 effects on beta-cell function in newly diagnosed type 1 diabetes. *PLoS One* 2011;**6**:e26471.
309 doi:10.1371/journal.pone.0026471
- 310 5 Kracht MJL, van Lummel M, Nikolic T, *et al.* Autoimmunity against a defective ribosomal
311 insulin gene product in type 1 diabetes. *Nat Med* 2017;**23**:501–7. doi:10.1038/nm.4289
- 312 6 Velthuis JH, Unger WW, Abreu JRF, *et al.* Simultaneous detection of circulating autoreactive
313 CD8+ T-cells specific for different islet cell-associated epitopes using combinatorial MHC
314 multimers. *Diabetes* 2010;**59**:1721–30. doi:10.2337/db09-1486
- 315 7 Koh A, Molinaro A, Stahlman M, *et al.* Microbially Produced Imidazole Propionate Impairs
316 Insulin Signaling through mTORC1. *Cell* 2018;**175**:947–961.e17. doi:10.1016/j.cell.2018.09.055
- 317 8 Vrieze A, Van Nood E, Holleman F, *et al.* Transfer of intestinal microbiota from lean donors
318 increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*
319 2012;**143**:913–6.e7. doi:10.1053/j.gastro.2012.06.031
- 320 9 Truong DT, Franzosa EA, Tickle TL, *et al.* MetaPhlan2 for enhanced metagenomic taxonomic
321 profiling. *Nat. Methods*. 2015;**12**:902–3. doi:10.1038/nmeth.3589
- 322 10 Franzosa EA, McIver LJ, Rahnavard G, *et al.* Species-level functional profiling of metagenomes
323 and metatranscriptomes. *Nat Methods* 2018;**15**:962–8. doi:10.1038/s41592-018-0176-y
- 324 11 Callahan BJ, McMurdie PJ, Rosen MJ, *et al.* DADA2: High-resolution sample inference from
325 Illumina amplicon data. *Nat Methods* 2016;**13**:581–3. doi:10.1038/nmeth.3869
- 326 12 Overgaard AJ, Weir JM, Jayawardana K, *et al.* Plasma lipid species at type 1 diabetes onset
327 predict residual beta-cell function after 6 months. *Metabolomics* 2018;**14**:158.
328 doi:10.1007/s11306-018-1456-3
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