Supplementary Table 1. R^2 and F-statistics for instruments used to proxy PPARG, ABCC8, and GLP1R perturbation

Target	R^2	***F*-statistic**
PPARG	0.00070 -0.00119	285.82-487.14
ABCC8	0.00014-0.00027	59.11-111.98
GLP1R	0.00014-0.00022	56.32-88.82

Range of R^2 and *F*-statistics correspond to estimates of these metrics across instruments constructed using independent (r^2<0.001) and weakly correlated (r^2<0.20) SNPs.

Supplementary Table 2. Estimates of the smallest detectable OR per unit change in drug target-mediated inverse rank-normal transformed HbA_{1c} reduction (mmol/mol) where there is 80% power to detect an effect (α=0.05)

Cancer endpoint	**PPARG**	**ABCC8**	**GLP1R**
Breast cancer	1.40-1.55	2.03-2.65	2.22-2.72
ER+ Breast cancer	1.49-1.68	2.28-3.11	2.53-3.20
ER- Breast cancer	1.83-2.21	3.55-5.71	4.14-5.96
Colorectal cancer	1.58-1.82	2.60-3.73	2.92-3.85
Colon cancer	1.74-2.06	3.18-4.92	3.67-5.11
Rectal cancer	2.00-2.54	4.42-7.73	5.31-8.13
Prostate cancer	1.55-1.77	2.49-3.50	2.78-3.61
Advanced prostate cancer	2.09-2.62	4.67-8.34	5.64-8.78
Overall cancer risk	1.66-1.94	2.88-4.28	3.28-4.44

Ranges correspond to differences in power estimates across instruments constructed using independent (r^2<0.001) and weakly correlated (r^2<0.20) SNPs.

Supplementary Table 3. Posterior probabilities under differing hypotheses relating the associations between T2D variants in or within proximity to the *PPARG* locus and ALT levels

Configuration	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
	8.33×10^{-63}	9.24×10^{-23}	7.43×10^{-42}	8.15×10^{-2}	0.92

H_0 = neither T2D nor ALT has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only ALT has a genetic association in the region, H_3 = both T2D and ALT are associated but have different causal variants, H_4= both T2D and ALT are associated and share a single causal variant.

Supplementary Table 4. Posterior probabilities under differing hypotheses relating the associations between T2D variants in or within proximity to the *PPARG* locus and AST levels

Configuration	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
	1.58×10^{-50}	1.76×10^{-10}	1.46×10^{-41}	0.16	0.84

H_0 = neither T2D nor AST has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only AST has a genetic association in the region, H_3 = both T2D and AST are associated but have different causal variants, H_4= both T2D and AST are associated and share a single causal variant.

Supplementary Table 5. Posterior probabilities under differing hypotheses relating the associations between T2D variants in or within proximity to the *ABCC8* locus and BMI levels

Configuration	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
	8.07×10^{-43}	2.70×10^{-2}	1.09×10^{-42}	3.56×10^{-2}	0.94

H_0 = neither T2D nor BMI has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only BMI has a genetic association in the region, H_3 = both T2D and BMI are associated but have different causal variants, H_4= both T2D and BMI are associated and share a single causal variant.

Supplementary Table 6. Posterior probabilities under differing hypotheses relating the associations between T2D in or within proximity to the *GLP1R* locus and BMI levels

T2D SNP	**BMI SNP**	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
Marginal	Marginal	2.21×10^{-5}	0.88	2.91×10^{-6}	0.12	2.27×10^{-3}
rs10305420*	Marginal	2.40×10^{-6}	0.89	2.91×10^{-7}	0.11	2.16×10^{-3}
rs147718699†	Marginal	5.15×10^{-5}	0.89	6.31×10^{-6}	0.11	3.08×10^{-3}
rs2115200†	Marginal	4.86×10^{-5}	0.89	5.90×10^{-6}	0.11	2.94×10^{-3}
rs34179517†	Marginal	1.66×10^{-7}	0.89	2.01×10^{-8}	0.11	4.93×10^{-3}

Marginal = SNP associations that are unconditioned (on either the sentinel SNP or additional conditionally independent genome-wide significant SNP for each respective trait), * = Sentinel SNP, † = Conditionally independent and significant ($P<5 \times 10^{-8}$) SNP, H_0 = neither T2D nor BMI has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only BMI has a genetic association in the region, H_3 = both T2D and BMI are associated but have different causal variants, H_4= both T2D and BMI are associated and share a single causal variant.

Supplementary Table 7. Iterative leave-one-out analysis for Mendelian randomisation analysis of genetically-proxied PPARG perturbation and risk of prostate cancer

SNP removed	**OR (95% CI)**
rs143888770	1.74 (1.02-2.97)
rs150535373	1.75 (1.03-2.99)
rs17819328	1.81 (1.02-3.24)
rs4135247	1.51 (0.70-3.29)
rs4135300	1.81 (1.08-3.04)
rs598747	1.87 (1.19-2.94)
rs7637403	1.77 (1.18-2.66)

OR (95% CI) are scaled to represent the effect of genetically-proxied perturbation of PPARG equivalent to a 1 unit decrease in IRNT HbA_{1c}.

Supplementary Table 8. Posterior probabilities under differing hypotheses relating the associations between T2D in or within proximity to the *PPARG* locus and prostate cancer risk

T2D SNP	**PCa SNP**	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
Marginal	Marginal	6.68×10^{-41}	0.74	2.26×10^{-41}	0.25	8.14×10^{-3}
rs17036160*	Marginal	3.84×10^{-51}	0.81	8.80×10^{-52}	0.18	8.87×10^{-3}
rs7650482†	Marginal	7.79×10^{-41}	0.81	1.78×10^{-41}	0.18	8.89×10^{-3}
rs9872031†	Marginal	7.79×10^{-41}	0.81	1.78×10^{-41}	0.18	8.89×10^{-3}

Marginal = SNP associations that are unconditioned (on either the sentinel SNP or additional conditionally independent genome-wide significant SNP for each respective trait), * = Sentinel SNP, † = Conditionally independent and significant ($P<5\times10^{-8}$) SNP, H_0 = neither T2D nor prostate cancer risk has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only prostate cancer risk has a genetic association in the region, H_3 = both T2D and prostate cancer risk are associated but have different causal variants, H_4= both T2D and prostate cancer risk are associated and share a single causal variant.

Supplementary Table 9. Iterative leave-one-out analysis for Mendelian randomisation analysis of genetically-proxied PPARG perturbation and risk of ER+ breast cancer

SNP removed	**OR (95% CI)**
rs143888770	0.58 (0.38-0.87)
rs150535373	0.56 (0.38-0.82)
rs17819328	0.53 (0.34-0.83)
rs4135247	0.63 (0.33-1.19)
rs4135300	0.55 (0.37-0.83)
rs598747	0.57 (0.36-0.89)
rs7637403	0.57 (0.38-0.88)

OR (95% CI) are scaled to represent the effect of genetically-proxied perturbation of PPARG equivalent to a unit decrease in IRNT HbA_{1c}.

Supplementary Table 10. Posterior probabilities under differing hypotheses relating the associations between T2D in or within proximity to the *PPARG* locus and ER+ breast cancer risk

T2D SNP	**BCa SNP**	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
Marginal	Marginal	6.50×10^{-41}	0.72	2.08×10^{-41}	0.23	4.74×10^{-2}
rs17036160*	Marginal	3.60×10^{-51}	0.76	9.29×10^{-52}	0.20	4.92×10^{-2}
rs7650482†	Marginal	7.32×10^{-41}	0.76	1.88×10^{-41}	0.19	4.81×10^{-2}
rs9872031†	Marginal	7.32×10^{-41}	0.76	1.88×10^{-41}	0.19	4.81×10^{-2}

Marginal = SNP associations that are unconditioned (on either the sentinel SNP or additional conditionally independent genome-wide significant SNP for each respective trait), * = Sentinel SNP, † = Conditionally independent and significant ($P<5 \times 10^{-8}$) SNP, H_0 = neither T2D nor ER+ breast cancer risk has a genetic association in the region, H_1 = only T2D has a genetic association in the region, H_2 = only ER+ breast cancer risk has a genetic association in the region, H_3 = both T2D and ER+ breast cancer risk are associated but have different causal variants, H_4= both T2D and ER+ breast cancer risk are associated and share a single causal variant.

Supplementary Table 11. Posterior probabilities under differing hypotheses relating the associations between T2D in or within proximity to drug target loci and positive controls or cancer risk using different priors for H_4

Drug target	**Outcome**	**SNP1***	**SNP2***	**p12 prior**	**H_0**	**H_1**	**H_2**	**H_3**	**H_4**
PPARG	ALT	Marginal	Marginal	5×10^{-5}	1.78×10^{-63}	1.98×10^{-23}	1.59×10^{-42}	0.02	0.98
PPARG	ALT	Marginal	Marginal	5×10^{-6}	1.54×10^{-62}	1.71×10^{-22}	1.37×10^{-41}	0.15	0.85
PPARG	AST	Marginal	Marginal	5×10^{-5}	3.64×10^{-51}	4.04×10^{-11}	3.34×10^{-42}	0.04	0.96
PPARG	AST	Marginal	Marginal	5×10^{-6}	2.73×10^{-50}	3.03×10^{-10}	2.51×10^{-41}	0.28	0.72
ABCC8	BMI	Marginal	Marginal	5×10^{-5}	4.05×10^{-49}	1.36×10^{-8}	8.11×10^{-43}	0.27	0.97
ABCC8	BMI	Marginal	Marginal	5×10^{-6}	3.26×10^{-48}	1.09×10^{-7}	6.53×10^{-42}	0.22	0.78
GLP1R	BMI	Marginal	Marginal	5×10^{-5}	2.19×10^{-5}	0.87	2.89×10^{-6}	0.12	0.01
GLP1R	BMI	rs10305420*	Marginal	5×10^{-5}	2.38×10^{-6}	0.88	2.89×10^{-7}	0.11	0.01
GLP1R	BMI	rs147718699†	Marginal	5×10^{-5}	5.09×10^{-5}	0.88	6.23×10^{-6}	0.11	0.02
GLP1R	BMI	rs2115200†	Marginal	5×10^{-5}	4.80×10^{-5}	0.88	5.84×10^{-6}	0.11	0.01
GLP1R	BMI	rs34179517†	Marginal	5×10^{-5}	1.62×10^{-7}	0.87	1.97×10^{-8}	0.11	0.02
GLP1R	BMI	Marginal	Marginal	5×10^{-6}	2.21×10^{-5}	0.88	2.92×10^{-6}	0.12	1.14×10^{-3}
GLP1R	BMI	rs10305420*	Marginal	5×10^{-6}	2.40×10^{-6}	0.89	2.92×10^{-7}	0.11	1.08×10^{-3}
GLP1R	BMI	rs147718699†	Marginal	5×10^{-6}	5.16×10^{-5}	0.89	6.32×10^{-6}	0.11	1.54×10^{-3}
GLP1R	BMI	rs2115200†	Marginal	5×10^{-6}	4.86×10^{-5}	0.89	5.91×10^{-6}	0.11	1.47×10^{-3}
GLP1R	BMI	rs34179517†	Marginal	5×10^{-6}	1.66×10^{-7}	0.89	2.02×10^{-8}	0.11	2.47×10^{-3}
PPARG	Prostate cancer risk	Marginal	Marginal	5×10^{-5}	6.47×10^{-41}	0.72	2.19×10^{-41}	0.24	0.04
PPARG	Prostate cancer risk	rs17036160*	Marginal	5×10^{-5}	3.71×10^{-51}	0.78	8.50×10^{-52}	0.18	0.04
PPARG	Prostate cancer risk	rs7650482†	Marginal	5×10^{-5}	7.52×10^{-41}	0.78	1.72×10^{-41}	0.18	0.04
PPARG	Prostate cancer risk	rs9872031†	Marginal	5×10^{-5}	7.52×10^{-41}	0.78	1.72×10^{-41}	0.18	0.04

PPARG	Prostate cancer risk	Marginal	Marginal	5×10^{-6}	6.70×10^{-41}	0.74	2.27×10^{-41}	0.25	4.09×10^{-3}
PPARG	Prostate cancer risk	rs17036160*	Marginal	5×10^{-6}	3.85×10^{-51}	0.81	8.84×10^{-52}	0.19	4.45×10^{-3}
PPARG	Prostate cancer risk	rs7650482†	Marginal	5×10^{-6}	7.83×10^{-41}	0.81	1.79×10^{-41}	0.19	4.47×10^{-3}
PPARG	Prostate cancer risk	rs9872031†	Marginal	5×10^{-6}	7.83×10^{-41}	0.81	1.79×10^{-41}	0.19	4.47×10^{-3}
PPARG	ER+ Breast cancer risk	Marginal	Marginal	5×10^{-5}	5.47×10^{-41}	0.61	1.75×10^{-41}	0.19	0.20
PPARG	ER+ Breast cancer risk	rs17036160*	Marginal	5×10^{-5}	3.01×10^{-51}	0.63	7.76×10^{-52}	0.16	0.21
PPARG	ER+ Breast cancer risk	rs7650482†	Marginal	5×10^{-5}	6.14×10^{-41}	0.64	1.58×10^{-41}	0.16	0.20
PPARG	ER+ Breast cancer risk	rs9872031†	Marginal	5×10^{-5}	6.14×10^{-41}	0.64	1.58×10^{-41}	0.16	0.20
PPARG	ER+ Breast cancer risk	Marginal	Marginal	5×10^{-6}	6.66×10^{-41}	0.74	2.13×10^{-41}	0.24	0.02
PPARG	ER+ Breast cancer risk	rs17036160*	Marginal	5×10^{-6}	3.69×10^{-51}	0.77	9.52 x 10-52	0.20	0.03
PPARG	ER+ Breast cancer risk	rs7650482†	Marginal	5×10^{-6}	7.50×10^{-41}	0.78	1.92×10^{-41}	0.20	0.02
PPARG	ER+ Breast cancer risk	rs9872031†	Marginal	5×10^{-6}	7.50×10^{-41}	0.78	1.92×10^{-41}	0.20	0.02

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index. SNP1 refers to drug target SNP, SNP2 refers to outcome SNP. Marginal = SNP associations that are marginal (on either the sentinel SNP or additional conditionally independent genome-wide significant SNP for each respective trait), * = Sentinel SNP, † = Conditionally independent and significant ($P<5x10^{-8}$) SNP, H_0 = neither drug target nor outcome has a genetic association in the region, H_1 = only drug target has a genetic association in the region, H_2 = only outcome has a genetic association in the region, H_3 = both drug target and outcome are associated but have different causal variants, H_4= both drug target and outcome are associated and share a single causal variant.

The PRACTICAL Consortium

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