Brief Report

Variation in *TCF7L2* Influences Therapeutic Response to Sulfonylureas

A GoDARTs Study

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OBJECTIVE—There is considerable interindividual variation in sulfonylurea response in type 2 diabetes. Transcription factor 7-like 2 (*TCF7L2*) variants have been identified to be strongly associated with type 2 diabetes risk, probably due to decreased β-cell function. We hypothesized that variation in *TCF7L2* would influence response to sulfonylureas but not metformin. We studied the effect of *TCF7L2* rs12255372 and rs7903146 genotypes on glycemic response.

RESEARCH DESIGN AND METHODS—The DARTS/MEMO (Diabetes Audit and Research Tayside/Medicines Monitoring Unit) collaboration database includes prescribing, biochemistry, and clinical phenotype of all patients with diabetes within Tayside, Scotland, from 1992. Of these, the *TCF7L2* genotype was determined in 4,469 patients with type 2 diabetes recruited to GoDARTS (Genetics of Diabetes Audit and Research Tayside) between 1997 and July 2006. A total of 901 incident sulfonylurea users and 945 metformin users were identified. A logistic regression was used with treatment failure defined as an A1C >7% within 3–12 months after treatment initiation. Covariates included the *TCF7L2* genotype, BMI, sex, age diagnosed, drug adherence, and drug dose. A1C pretreatment was available in a subset of patients (sulfonylurea $n = 579$; metformin $n = 755$).

RESULTS—Carriers of the risk allele were less likely to respond to sulfonylureas with an odds ratio (OR) for failure of 1.95 (95% CI 1.23–3.06; $P = 0.005$), comparing rs12255372 T/T vs. G/G. Including the baseline A1C strengthened this association (OR 2.16 [95% CI 1.21–3.86], $P = 0.009$). A similar, although slightly weaker, association was seen with rs7903146. No association was seen between metformin response and either single nucleotide polymorphism, after adjustment for baseline A1C.

CONCLUSIONS—*TCF7L2* variants influence therapeutic response to sulfonylureas but not metformin. This study establishes that genetic variation can alter response to therapy in type 2 diabetes. ***Diabetes*** **56:2178–2182, 2007**

Sulfonylureas are widely used to treat type 2 diabetes. There is considerable interindividual variation in the hypoglycemic response to sulfonylureas. Physiological studies have shown response is in part predicted by stimulated C-peptide, as a marker of endogenous β-cell reserve (1,2). Therefore, variation in sulfonylurea response may be explained by variation in genes involved in regulating β-cell function. Apart from in some monogenic forms of diabetes (3–5), there has been limited success in pharmacogenetic studies of sulfonylurea response: The results for the effect of the E23K variant of *KCNJ11* (6–8) on response are conflicting, and although in physiological studies variants in *ABCC8* (encoding SUR1) have been shown to influence insulin secretory response to intravenous tolbutamide (9), the impact of these variants on glycemic response has not been studied.

Recently, two intronic single nucleotide polymorphisms (SNPs) within the transcription factor 7-like 2 (*TCF7L2*) gene, rs12255372 and rs7903146, were found to substantially contribute to the risk of type 2 diabetes (10). This finding has been robustly replicated in a number of studies across multiple populations (11–23) and has been shown to influence progression to diabetes (11,18,20). *TCF7L2* is involved in the Wnt signaling pathway, yet the mechanism linking this with diabetes is not known. *TCF7L2* is expressed in the mature and developing pancreatic β-cells (17), and insulin secretion is reduced in those with the risk alleles (11,13,16), suggesting a predominant direct or indirect role of *TCF7L2* on β-cell function.

Given the robust influence of *TCF7L2* variants on risk of type 2 diabetes and their probable role in β-cell function, we hypothesized that carriers of the diabetes risk alleles at rs12255372 and rs7903146 would have a poorer hypoglycemic response to sulfonylureas due to decreased β-cell function compared with individuals lacking these alleles. On the other hand, these variants would have minimal impact on metformin response, which acts predominantly by improving insulin action rather than secretion. Therefore, we studied the influence of variation within *TCF7L2* on the early response to sulfonylureas and metformin in 1,846 patients with type 2 diabetes in Tayside, Scotland.

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SNP, single nucleotide polymorphism.

TABLE 1
Baseline demography

		rs12255372				rs7903146			
	All	GG	GT	TT	ANOVA	CC	CT	TT	ANOVA
Patients started on sulfonylureas									
n	901	382	415	104		380	409	112	
Age at Rx (years)	63.8 ± 9.6	63.8 ± 9.6	63.9 ± 9.8	63.7 ± 8.9	0.99	63.8 ± 9.8	64.1 ± 9.6	62.9 ± 8.7	0.53
Age at diagnosis (years)	61.3 ± 9.6	61.5 ± 9.4	61.3 ± 9.8	60.9 ± 9.7	0.84	61.6 ± 9.6	61.3 ± 9.7	60.2 ± 9.3	0.40
BMI average (kg/m^2)	28.3 ± 4.6	28.3 ± 4.5	28.4 ± 4.7	27.6 ± 4.7	0.26	28.4 ± 4.6	28.3 ± 4.6	27.7 ± 4.4	0.37
BMI at diagnosis (kg/m^2)*	28.1 ± 4.6	27.9 ± 4.6	28.5 ± 4.8	26.8 ± 3.5	**0.020**	28.1 ± 4.7	28.4 ± 4.7	27.0 ± 3.5	**0.049**
BMI at start of treatment†	28.0 ± 4.5	28.0 ± 4.6	28.2 ± 4.6	27.0 ± 3.3	0.09	28.2 ± 4.8	28.1 ± 4.6	27.1 ± 3.3	0.13
Sex (% male)	58	57	59	63	0.55	58	57	63	0.63
Dose (% maximum)	28 ± 15	28 ± 14	29 ± 16	29 ± 15	0.75	28 ± 15	29 ± 15	28 ± 14	0.84
Adherence (%)	80 ± 18	80 ± 18	79 ± 18	83 ± 15	0.092	79 ± 18	80 ± 17	82 ± 15	0.31
Metformin									
n	945	434	420	91		422	424	99	
Age at Rx (years)	60.0 ± 9.5	60.4 ± 9.7	59.5 ± 9.0	61.2 ± 10.5	0.17	60.5 ± 9.6	59.5 ± 9.2	60.6 ± 9.9	0.24
Age at diagnosis (years)	57.7 ± 9.4	58.2 ± 9.5	56.9 ± 8.9	59.2 ± 10.4	**0.041**	58.3 ± 9.4	57.0 ± 9.1	58.4 ± 9.9	0.11
BMI average (kg/m^2)	32.8 ± 5.6	33.4 ± 5.7	32.4 ± 5.4	31.4 ± 5.5	**0.002**	33.3 ± 5.7	32.6 ± 5.4	31.2 ± 5.5	**0.003**
BMI at diagnosis (kg/m^2)‡	33.1 ± 6.0	34.0 ± 6.3	32.4 ± 5.6	31.8 ± 5.6	**<0.001**	34.0 ± 6.3	32.6 ± 5.6	31.5 ± 5.5	**0.001**
BMI at start of treatment§	32.9 ± 5.8	33.6 ± 5.9	32.5 ± 5.6	31.3 ± 5.7	**0.001**	33.5 ± 6.0	32.6 ± 5.5	31.2 ± 5.6	**0.001**
Sex (% male)	52	47	56	48	**0.026**	49	54	53	0.28
Dose (% maximum)	19 ± 7	19 ± 7	19 ± 6	19 ± 5	0.38	19 ± 7	19 ± 7	19 ± 7	0.50
Adherence (%)	92 ± 12	91 ± 13	92 ± 11	92 ± 11	0.26	91 ± 14	92 ± 11	93 ± 11	0.16

Data are means ± SD unless otherwise indicated. $P < 0.05$ are bold. *n = 643; †n = 800; ‡n = 761; §n = 893. Rx, treatment.

RESEARCH DESIGN AND METHODS

Patients were identified from an ongoing study of the Genetics of Diabetes Audit and Research Tayside (GoDARTS) (4,469 cases) recruited in Tayside, Scotland, between 1 October 1997 and 1 July 2006 who could be linked to the MEMO (Medicines Monitoring Unit) databases. The DARTS/MEMO collaboration includes validated prescribing, biochemistry, and phenotypic historical data from 1992 to present (24), and prospective longitudinal data are collected on each person with type 2 diabetes recruited into the genetic study.

For this study, patients were selected to have type 2 diabetes on the basis of an age of diagnosis after the age of 40 years, with no progression to insulin dependency within 6 months of diagnosis. Patients were excluded who were diagnosed with diabetes after age 90 years. Prescription data were available between January 1992 and April 2004. All incident users of sulfonylureas and metformin were identified; to be eligible, all study participants had to have received no diabetes treatment for at least 6 months before their index prescription for sulfonylurea or metformin and were thus considered treatment naïve. We therefore identified 1,168 patients who subsequently encashed at least two sulfonylurea prescriptions and 1,263 patients who encashed at least two metformin prescriptions. The study was approved by the Tayside Medical Ethics Committee, and informed consent was obtained from all subjects.

Definition of response. For inclusion in the study, patients were required to have at least one A1C recorded within 3–12 months after commencing sulfonylureas (n = 901) or metformin (n = 945). A "treat to target" approach was taken, with failure defined as the failure to reach an A1C ≤7% within the 3- to 12-month period after incident drug prescription. In a further analysis, the A1C within the 6 months before commencing sulfonylureas (n = 579) or metformin (n = 755) was included as a covariate. Where A1C was measured more than once before treatment, the A1C level nearest to drug initiation was taken. The A1C was Diabetes Control and Complications Trial aligned.

Drug adherence and dose. We used population-based drug dispensing records to calculate the percentage of maximum possible adherence for each patient (25). Dose was expressed as a percentage of the maximal prescribed dose in the British National Formulary (to allow comparison between sulfonylurea drugs) (26).

Determination of BMI. The BMI (average) was taken as the mean of the BMI measures recorded throughout the study period. The BMI at diagnosis was taken as the mean of the BMI measures within 1 year, either side of diagnosis. The BMI at treatment initiation was taken as the mean of the BMI measures within 1 year, either side of treatment initiation.

Genotyping. We genotyped rs12255372 and rs7903146 of *TCF7L2* using TaqMan allelic discrimination assays as previously described (22). Both variants were in Hardy-Weinberg equilibrium and were in tight linkage disequilibrium as previously reported (R^2 = 0.9). Genotyping success rate for each SNP was ~98%, and duplicate genotyping concordance was >99%.

Statistical analysis. Comparison of baseline characteristics by genotype was by ANOVA. Genotype frequencies were analyzed by χ^2 test for trend (1 d.f.). A logistic regression analysis was used to investigate response, with failure of treatment (minimum A1C after starting treatment >7%) as the dependent variable. Covariates were selected if there was a significant difference in baseline characteristics by genotype or if there was a simple correlation with response with $P < 0.1$. With respect to genotype, a codominant model was assumed, with the GG (rs12255372) and CC (rs7903146) genotype as the reference.

RESULTS

Baseline characteristics of incident sulfonylurea and metformin users according to genotype at rs12255372 and rs7903146 is shown in Table 1. In keeping with previous studies, those with two copies of the T-allele of rs12255372 or rs7903146 (TT) had a lower BMI at diagnosis of diabetes in both the sulfonylurea- and metformin-treated groups. This was more marked in the metformin-treated group, who were more obese, and could be seen in BMI at treatment initiation and in a BMI averaged over the whole study period.

Across the whole cohort, 42% of sulfonylurea users and 49% of metformin users did not achieve a target A1C <7% within 1 year of treatment initiation. The genotype frequencies at rs12255372 and rs7903146 according to the early therapeutic response to sulfonylureas or metformin are shown in Table 2. Genotype influenced response to sulfonylureas, with more treatment failure in the TT homozygotes of either SNP. Fifty-seven percent of the TT homozygotes failed to reach target compared with only

TABLE 2
Genotype frequencies by treatment response

	rs1225372				rs7903146			
Failure to reach target?	GG	GT	TT	*P*	CC	CT	TT	*P*
Sulfonylurea								
No	230 (60)	246 (59)	45 (43)	0.006	232 (60)	236 (58)	43 (47)	0.035
Yes	152 (40)	169 (41)	59 (57)		148 (40)	173 (42)	59 (53)	
Metformin								
No	225 (52)	213 (51)	42 (46)	0.61	229 (54)	207 (49)	44 (44)	0.12
Yes	209 (48)	207 (49)	49 (54)		193 (46)	217 (51)	55 (56)	

Data are *n* (%).

40% of the GG individuals. The heterozygote group displayed an intermediate failure rate, and this corresponded to a per-allele odds ratio (OR) for treatment failure of 1.28 ($P = 0.014$) for rs12255372 and 1.27 ($P = 0.017$) for rs7903146. There was no significant effect of genotype on metformin response.

A logistic regression was used to account for baseline differences and other confounding factors (Table 3). For sulfonylurea response, the rs12255372 TT homozygotes were more likely not to be treated to target as the GG homozygotes (OR 1.94), with a slightly weaker association with rs7903146 (OR 1.73). The per-allele OR for treatment failure was 1.28 ($P = 0.02$) for rs12255372 and 1.26 ($P = 0.03$) for rs7903146. For metformin, there was also an increase in treatment failure by genotype, although this only achieved statistical significance when comparing TT vs. CC for rs7903146 (OR 1.58, $P = 0.046$).

Because *TCF7L2* is likely to be influencing baseline glycemic control, a further logistic regression analysis was done on 579 sulfonylurea-treated and 755 metformin-treated patients in whom the A1C was known within 6 months before treatment initiation (Table 3). The baseline characteristics of this subgroup are shown in supplementary Tables 1 and 2 (available in an online appendix at http://dx.doi.org/10.2337/db07-0440). Including the A1C pretreatment in the model abolished any effect of genotype on treatment response to metformin. However, inclusion of pretreatment A1C strengthened the association between sulfonylurea response and genotype at rs1225372 (TT vs. GG, OR 2.16) and at rs7903146 (TT vs. CC, 1.90). This can also be seen if the both cohorts are analyzed together using treatment (sulfonylurea or metformin) and pretreatment A1C as covariates: In a logistic regression, there was a significant interaction between treatment and genotype (rs1225372 TT vs. GG, $P = 0.04$)

In a complementary approach, a linear regression model was used with the minimum A1C achieved within the year following sulfonylurea initiation as the dependent variable (supplementary Table 3). Using this model, the predicted A1C on treatment by genotype at rs1225372 was GG 7.0 (95% CI 6.86–7.14) vs. TT 7.33 (7.06–7.60) ($P = 0.032$). Similar results were seen for rs7903146.

Finally, to include the time taken to achieve target A1C <7%, we used Cox proportional hazards to analyze the effect of genotype on response. The Kaplan-Meier plots for response by rs1225372 genotype, adjusted for pretreatment A1C, are shown in Fig. 1, with the TT group more likely not to achieve target than the GG group (hazard ratio 1.54, $P = 0.03$) for sulfonylurea treatment but with no effect of genotype on metformin response ($P = 0.82$).

DISCUSSION

We show that variation in *TCF7L2* influences initial treatment success with sulfonylurea therapy in patients with type 2 diabetes. This is seen for both SNPs that have been reported to be associated with diabetes risk and is in addition to the effect of dose, adherence, sex, and baseline glycemia (determined by A1C pretreatment). With respect to rs1225372, the 12% of the diabetic population with two copies of the T-allele were twice as likely not to achieve an A1C <7% within 1 year of treatment initiation than the 42% of the population with two copies of the G-allele, even accounting for baseline difference in pretreatment A1C. This results in the majority of TT (57%) homozygotes not achieving target A1C, an absolute difference of 17% compared with the GG homozygotes.

There was a weak association between metformin treatment success and *TCF7L2* genotype; however, this effect was abolished by inclusion of pretreatment A1C as a covariate in the model. While this could reflect a reduction in power or suggest that metformin may be less effective in the TT homozygotes, it may reflect an effect of these variants on glycemia rather than a genotypic influence on response per se. In support of this, we have recently shown that in the overall Go-DARTs population, the rs7903146 TT homozygote case and control subjects had a higher A1C, with the TT homozygote case subjects being more likely to require oral medication or insulin than the CC homozygotes (22).

The association between *TCF7L2* variants and sulfonylurea response, but not metformin response, supports the growing body of evidence that *TCF7L2* is involved in direct or indirect (e.g., incretin mediated [10]) regulation of β-cell function (11,13,16). Detailed physiological and pharmacokinetic studies of patients selected on the basis of their *TCF7L2* genotype are required to further investigate the mechanism for decreased sulfonylurea response in the TT homozygotes.

In line with previous studies, we show an association of genotype on BMI (11,20,22,23). This is particularly striking in the more obese metformin-treated group. Because retrospective data are available following recruitment in our study, it is possible to investigate the association between genotype and BMI at diagnosis of diabetes. The BMI difference by genotype is largest at diagnosis, with the effect reducing by treatment initiation or when averaged over the whole study period. This is in keeping with the *TCF7L2* risk variants effecting β-cell function, causing diabetes to present at a lower level of obesity or insulin resistance.

There are limitations to this study. This is an observational study rather than a randomized interventional study and is therefore prone to prescriber bias. However, the

TABLE 3
Logistic regression analysis with treatment failure as the dependent variable

	rs1225372					rs7903146			
	Without baseline A1C		With baseline A1C			Without baseline A1C		With baseline A1C	
	OR (95% CI)	*P*	OR (95% CI)	*P*		OR (95% CI)	*P*	OR (95% CI)	*P*
Sulfonylurea (*n*)	901		579			901		579	
GT	1.06 (0.79–1.43)	0.69	1.14 (0.78–1.68)	0.50	CT	1.13 (0.84–1.52)	0.42	1.23 (0.84–1.81)	0.29
TT	1.94 (1.23–3.06)	**0.005**	2.16 (1.21–3.86)	**0.009**	TT	1.73 (1.11–2.70)	**0.015**	1.90 (1.09–3.33)	**0.024**
Sex (male = 1; female = 0)	0.68 (0.51–0.90)	**0.008**	0.60 (0.41–0.87)	**0.007**		0.68 (0.51–0.91)	**0.009**	0.60 (0.42–0.87)	**0.007**
Age diagnosed (years)	0.99 (0.98–1.01)	0.30	0.99 (0.97–1.00)	0.13		0.99 (0.98–1.01)	0.34	0.99 (0.97–1.00)	0.15
Dose (per 5% of maximum)	1.20 (1.14–1.27)	**<0.001**	1.18 (1.10–1.27)	**<0.001**		1.21 (1.14–1.27)	**<0.001**	1.18 (1.11–1.27)	**<0.001**
Adherence (per 5%)	1.06 (1.02–1.11)	**0.003**	1.04 (0.99–1.10)	0.13		1.07 (1.02–1.11)	**0.001**	1.05 (0.99–1.11)	0.12
A1C pretreatment (%)	—	—	1.38 (1.24–1.52)	**<0.001**		—	—	1.30 (1.18–1.44)	**<0.001**
Metformin (*n*)	945		755			945		755	
GT	1.06 (0.80–1.39)	0.70	0.96 (0.70–1.33)	0.81	CT	1.26 (0.95–1.67)	0.10	1.17 (0.85–1.61)	0.34
TT	1.41 (0.89–2.25)	0.15	1.09 (0.63–1.91)	0.75	TT	1.58 (1.01–2.50)	**0.047**	1.19 (0.69–2.02)	0.53
Sex (male = 1; female = 0)	0.98 (0.75–1.29)	0.91	1.10 (0.81–1.49)	0.54		0.98 (0.75–1.28)	0.89	1.09 (0.81–1.48)	0.57
Age diagnosed (years)	0.99 (0.98–1.01)	0.32	0.99 (0.97–1.01)	0.19		0.99 (0.98–1.01)	0.39	0.99 (0.97–1.01)	0.23
BMI average (kg/m^2)	1.01 (0.98–1.03)	0.84	1.00 (0.97–1.01)	0.91		1.01 (0.98–1.03)	0.59	1.00 (0.98–1.03)	0.82
Dose (per 5% of maximum)	1.29 (1.19–1.41)	<0.001	1.31 (1.18–1.45)	**<0.001**		1.29 (1.19–1.41)	<0.001	1.31 (1.17–1.45)	**<0.001**
Adherence (per 5%)	1.01 (0.95–1.06)	0.84	0.98 (0.92–1.04)	0.56		1.00 (0.95–1.06)	0.91	0.98 (0.92–1.04)	0.51
A1C pretreatment	—	—	1.38 (1.24–1.52)	**<0.001**		—	—	1.38 (1.24–1.53)	**<0.001**

$P < 0.05$ are bold.

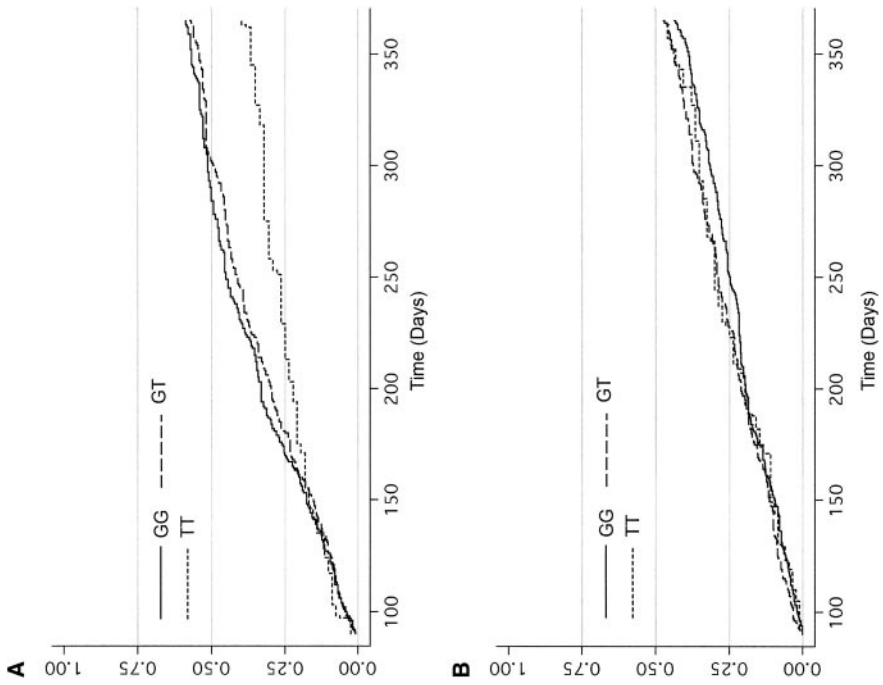

FIG. 1. Kaplan-Meier plots showing the proportion of patients, by genotype at rs1225372, who achieve a target A1C <7% after being initiated on treatment with a sulfonylurea (*A*) or metformin (*B*).

prescriber would have been blind to genotype, except where the genotype impacted on a clinical phenotype, which might influence management. In this study, we were able to account for differences in BMI, sex, and baseline A1C. Furthermore, the dose prescribed and a measure of adherence, based on prescription encashment, could also be accounted for. The potential difficulties with an observational study are highlighted by our finding that those who received a higher starting dose of sulfonylurea were less likely reach the A1C target. This probably reflects an anticipated lack of response, by the prescriber, on the basis of diabetes severity or other unmeasured factors. A further limitation is that this study was designed to look at the early response to therapy between 3 and 12 months after initiation. Three months after treatment initiation might be too early to see a full therapeutic effect, especially of metformin, and this short period may explain why the drug doses were relatively low. However, the decision to study early response was taken to minimize individual patient and physician factors, which are likely to confound the effect of genotype on longer-term response or failure, which would be better studied in the context of a carefully controlled clinical trial.

To date, pharmacogenetic studies on therapeutic response within diabetes have been limited. The most important example of genetic etiology impacting on clinical diabetes management has been in monogenic diabetes (3,5). We believe this current study is a robust example of pharmacogenetics within an unselected polygenic type 2 population. Compared with the monogenic examples, the

effect size of *TCF7L2* variation on response is modest, although a twofold greater likelihood of treatment failure in the 12% of the population who are TT homozygote at rs1225372 is striking. This highlights strong parallels between type 2 diabetes pharmacogenetics and genetics of disease risk, with individual risk alleles contributing only little to overall risk. However, with an increasing number of clear risk genes for type 2 diabetes resulting from whole-genome association studies (21), it may be possible to study the effect of combined genotypes on response, as has been done for type 2 diabetes risk (27), which may in due course allow the genotype to contribute to response prediction in the clinical management of patients. We believe that this study is a "proof of principle" that common genetic variation can influence therapeutic response in type 2 diabetes and that given robust candidate genes and a well-characterized therapeutic response phenotype, large population biobanks can be successfully used in population pharmacogenomic studies.

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