The Application of Genomics in Diabetes: Barriers to Discovery and Implementation

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The emerging availability of genomic and electronic health data in large populations is a powerful tool for research that has drawn interest in bringing precision medicine to diabetes. In this article, we discuss the potential application of genomics to the prediction, prevention, and treatment of diabetes, and we use examples from other areas of medicine to illustrate some of the challenges involved in conducting genomics research in human populations and implementing findings in practice. At this time, a major barrier to the application of genomics in diabetes care is the lack of actionable genomic findings. Whether genomic information should be used in clinical practice requires a framework for evaluating the validity and clinical utility of this approach, an improved integration of genomic data into electronic health records, and the clinical decision support and educational resources for clinicians to use these data. Efforts to identify optimal approaches in all of these domains are in progress and may help to bring diabetes into the era of genomic medicine.

Many anticipated that the completion of the Human Genome Project over 10 years ago would mark the beginning of a new era of genomic medicine, in which new approaches to discovery research, disease prediction, and treatment would develop from an improved understanding of the genetic causes of human disease. In some areas of medicine, genomic discoveries have led to important new treatments. Genetic association studies have demonstrated that loss-of-function mutations in *PCSK9* result in low levels of LDL cholesterol and a reduced risk of coronary heart disease (1,2), This discovery led to a new class of drugs with dramatic lipid-lowering effects (3,4). In oncology, there has been a shift from using older drugs with broad cytotoxic effects to therapies that target specific mutations in driver genes (5), resulting in impressive reductions in mortality for some cancers (6).

Beyond the discovery of new drug targets, genomic information can be used to predict the occurrence of disease and to identify subgroups of patients for whom existing therapies or interventions will have the greatest efficacy or the least adverse effects. These are key elements of an approach that is now called precision medicine (7). Successes in oncology and other technological developments—the rapidly decreasing cost of whole-genome sequencing (8), improvements in informatics, and the widespread adoption of electronic health records (9–11)—have galvanized interest in applying various forms of big data, including genomics, to diseases such as diabetes (12). In this article, we discuss the application of genomics to diabetes, with a focus on some of the challenges involved in conducting genomics research in human populations and implementing findings in practice.

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GENOMICS IN THE PREDICTION, PREVENTION, AND DIAGNOSIS OF DIABETES

The incidence and prevalence of diabetes have doubled over the past two decades (13), and there are now about 30 million adults in the U.S. living with this condition, 95% of whom have type 2 diabetes (14). Genome-wide association (GWA) studies test hundreds of thousands or even millions of common (minor allele frequency [MAF] >5%) and low-frequency (MAF 1–5%) variants across both protein coding (exonic) and noncoding (intronic) regions of the genome. Large GWA studies have identified more than 50 genetic loci associated with various glycemic traits and at least 90 loci associated with type 2 diabetes (15–18). These genetic variants, which may explain as much as 10% of the variance in disease susceptibility, have advanced our understanding of the biology of diabetes, but each genetic locus confers only a small increase in risk. For example, the common variant from these GWA studies most strongly associated with type 2 diabetes, an intronic variant in *TCF7L2* (rs7903146), is associated with a 37% increased relative risk per copy of the variant allele (19). Rare variants (MAF <1%) and variants that are common only in specific ancestral populations have been associated with a greater increase in diabetes risk, but they account for less of the overall burden of diabetes (20–22).

Genetic risk scores (GRSs) that combine information from multiple genetic variants have been evaluated as a tool for the prediction of type 2 diabetes. Meigs et al. (23) found that a GRS with 18 variants was significantly associated with the risk of developing type 2 diabetes in the Framingham Heart Study (FHS) (odds ratio [OR] 1.12 per variant allele) and that persons in the highest out of three risk categories had an OR of 2.6 for developing type 2 diabetes compared with persons in the lowest risk category. However, this GRS did not improve the prediction of diabetes beyond traditional nongenetic risk factors (23), and the same was true for an updated GRS that included 65 variants (24). To put this into perspective, a prognostic marker with an OR of 3.0 that correctly identifies 80% of persons who will develop diabetes would incorrectly classify 60% of

persons who will not develop diabetes (25); this degree of discrimination is not useful clinically (26).

Biologic pathways other than heritable changes in DNA sequence may also be important predictors of diabetes and account for some of the variability in diabetes susceptibility not explained by genetics or traditional environmental factors. For example, DNA methylation at CpG sites, a key epigenetic mechanism for the regulation of gene expression, has been associated with the risk of type 2 diabetes (27,28). Metabolomic profiles of amino acids and other small molecules may also play a role (29), particularly among younger adults (30). However, these new types of "omics" suffer from the traditional epidemiologic limitations of confounding and reverse causality and will require rigorous evaluation before their clinical validity and utility are understood.

Risk prediction tools are most useful when there are effective and safe prevention measures, which may include behavioral interventions or drug therapies. For high-risk adults, the Diabetes Prevention Program (DPP) lifestyle intervention reduces the risk of type 2 diabetes by more than half (31), and this intervention is now offered throughout the country at programs recognized by the Centers for Disease Control and Prevention. Although the highly effective DPP lifestyle intervention has few or no adverse effects, the identification of persons who benefit the most from the intervention could help to prioritize its deployment in resource-limited settings. Florez and colleagues (32,33) have evaluated whether several genetic variants associated with diabetes risk modified the effectiveness of the lifestyle intervention in the original DPP study, and they found little evidence of effect modification based on genetic risk. Some have argued that communicating genetic information on disease risk might help to motivate healthy behaviors, but current evidence does not support this claim (34). For example, in a small randomized controlled trial (RCT) of participants with type 2 diabetes who all underwent an intensive lifestyle intervention directed at weight loss, those who received information on their genetic risk for diabetes had the same self-reported motivation and adherence

to the intervention as those who did not (35).

If genetic tests are not helpful in the prediction and prevention of diabetes, they could have a role in discriminating between type 1 and type 2 diabetes. The epidemic of obesity (36) has made it more difficult to distinguish diabetes type because many children and young adults with type 1 diabetes are also obese (37). Misclassification poses significant risks; an incorrect diagnosis of type 2 diabetes may lead to inappropriate treatment with oral glucose-lowering drugs, and an incorrect diagnosis of type 1 diabetes may lead to unnecessary insulin treatment. In a recent cross-sectional study of type 1 and type 2 diabetes, Oram et al. (38) evaluated a GRS that included high-risk HLA genotypes and 31 genetic loci for type 2 diabetes. They found that this GRS improved the discrimination between strictly defined type 1 and type 2 diabetes when added to clinical factors and autoimmune antibody tests, and it also helped to predict who would require insulin treatment within 3 years of diagnosis (38). One advantage of a diagnostic tool based on genotype is that, unlike islet cell antibodies, the result does not change over time. However, before this type of genetic testing can be recommended for routine use in the clinic, further evaluation in prospective studies will be necessary to demonstrate not only accurate discrimination between type 1 and type 2 diabetes but also improved use of appropriate glucose-lowering treatment.

Most cases of diabetes have multiple genetic and environmental causes and are classified according to the presumed pathophysiologic defect—autoimmune destruction of β-cells leading to insulin deficiency for type 1 diabetes and varying degrees of insulin resistance and deficiency for type 2 diabetes. In other words, the vast majority of diabetes is polygenic, and despite the growth in knowledge about the various genetic causes of diabetes in recent years, classification of individual cases into meaningful subtypes based on the underlying genetics has been difficult. On the other hand, genetic testing may be useful for the diagnosis of certain forms of diabetes caused by defects in a single gene, such as *HNF1A* mutations for maturity-onset diabetes of the young (MODY)

(39) and activating *KCNJ11* mutations for neonatal diabetes (40), both of which are highly responsive to sulfonylurea therapy. These monogenic forms of diabetes account for ~1–2% of diabetes cases (41,42), and they typically present at a young age (<25 years) and follow an autosomal dominant pattern of inheritance. Targeted genotyping could also play a role in the diagnosis of type 2 diabetes in specific populations. For example, a rare missense variant in *HNF1A* (p.E508K) that increased the risk of diabetes fivefold was present among 2% in a study of Latinos in the southern U.S. with type 2 diabetes (20); additional studies are needed to determine whether this functional variant shares the sulfonylurea-responsiveness of the *HNF1A* variants that cause MODY.

PHARMACOGENOMICS OF THERAPIES FOR TYPE 2 DIABETES

Although, among persons with diabetes, the rates of microvascular (retinopathy, neuropathy, kidney disease) and cardiovascular complications have decreased by about half over the past two decades, they still occur more often among persons with diabetes than among individuals without diabetes (43). Reducing these risks is the major goal of glucose-lowering therapy. For type 1 diabetes, the long-term benefits of intensive insulin therapy are well established (44,45). For type 2 diabetes, intensive glucose-lowering therapy prevents microvascular complications, and postrandomization follow-up data from several RCTs suggest there

may be long-term cardiovascular benefits as well (46–48).

There are now several classes of medications approved for the treatment of diabetes (Table 1). Most oral therapies have similar average effects on hemoglobin A_{1c} (HbA$_{1c}$), but they differ in their contraindications and side effects (49,50). There is surprisingly little information about the comparative benefits and harms for different drugs (51), and treatment guidelines for type 2 diabetes (52) permit the use of most approved drug classes as second-line therapy after metformin, which is the recommended first-line therapy for most patients because of its good safety profile and potential cardiovascular benefits (53,54). There is also substantial interindividual variability in drug response (55), and many patients eventually fail to achieve recommended levels of glycemic control with their initial therapy (56,57). For example, in the U.K. General Practice Research Database, only half of patients who initiated therapy with metformin or a sulfonylurea achieved an HbA$_{1c}$ level of <7% (58). The factors that account for this variation are not well understood (59). Because of the wide range of side effects from different therapies and because of the person-to-person variability in treatment response and adverse effects, pharmacogenomic testing for genetic variants that define subgroups of patients who are most likely to benefit from or least likely to be harmed by specific drugs is an attractive potential application of genomics in diabetes.

Pharmacogenomic studies have typically focused on candidate genes involved in pharmacokinetics (absorption, distribution, metabolism, and elimination) or pharmacodynamics (the biologic effect of a drug on its target) (60). The pharmacogenomics of oral diabetes therapies has been reviewed in detail elsewhere (61–63); selected findings for the most extensively studied drugs, sulfonylureas and metformin, are listed in Table 2. Sulfonylureas undergo metabolism by cytochrome P450 (CYP) enzyme 2C9, and loss-of-function variants in the *CYP2C9* gene have been associated with greater glucose-lowering effects and an increased risk of hypoglycemia (64,65). The genes encoding the sulfonylurea receptor, *KCNJ11* and *ABCC8*, have also been associated with increased sulfonylurea response in some studies (66,67) but not others (68,69), and in one study the association was in the opposite direction (70). Unlike sulfonylureas, metformin does not undergo metabolism by CYP enzymes; it is excreted intact by the kidneys (71). Genes encoding several transporters that facilitate the movement of metformin into the bloodstream, into target tissues, and into renal tubular cells have been associated with effects on serum levels of metformin, glucose-lowering effect, and drug intolerance (72,73).

Candidate gene studies of sulfonylureas and metformin have not typically accounted for false positives from multiple comparisons, and most findings from these studies have failed to replicate

Table 1—Classes of medications commonly used to treat diabetes

Drug classes	Oral	Average HbA$_{1c}$ reduction	Other benefits	Adverse effects	Cost
Metformin	Yes	~1.0–1.5	Weight loss, possible cardiovascular benefit	Lactic acidosis (rare), gastrointestinal side effects	Low
Sulfonylureas	Yes	~1.0–1.5		Hypoglycemia, weight gain, potential cardiovascular risk	Low
Meglitinides	Yes	~1.0		Hypoglycemia, weight gain	Moderate
Thiazolidinediones	Yes	~1.0		Heart failure, myocardial infarction (rosiglitazone), bone loss and fractures	Moderate
α-Glucosidase inhibitors	Yes	~0.8		Flatulence, diarrhea	Moderate
Amylin analog	No	~0.6		Hypoglycemia, nausea	High
DPP-4 inhibitors	Yes	~0.6–0.8		Potential heart failure (saxagliptin)	High
GLP-1 receptor agonists	No	~1.0	Weight loss	Nausea, vomiting, diarrhea	High
SGLT2 inhibitors	Yes	~0.6–0.8	Possible cardiovascular benefit	Genitourinary infections, ketoacidosis (rare)	High
Insulin	No	Unlimited	Most potent treatment	Hypoglycemia, weight gain	Low-high

Adapted from refs. 49,50. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; SGLT2, sodium–glucose cotransporter 2.

Table 2—Selected pharmacogenomic findings for sulfonylureas and metformin

Drug	Locus	Phenotype	N	Effect**	Refs.
Sulfonylureas					
Pharmacokinetic	*CYP2C9*	HbA$_{1c}$ response	1,073	0.5% absolute greater reduction in HbA$_{1c}$ (homozygous for variant alleles)	64
		FBG response	475	No association	75
		Hypoglycemia	357	OR 5.2 for hypoglycemia (homozygous for variant alleles)	65
Pharmacodynamic	*KCNJ11/ABCC8**	HbA$_{1c}$ and FBG response	1,268	3.5% relative greater reduction in HbA$_{1c}$ and 7.7% relative greater reduction in FBG (homozygous for variant alleles)	66
		HbA$_{1c}$ response	101	0.2% absolute greater reduction in HbA$_{1c}$ (per variant allele)	67
		Insulin treatment	525	No association	68
		FBG response	228	No association	69
		HbA$_{1c}$ response	97	Less reduction in HbA$_{1c}$	70
	TCF7L2	On treatment HbA$_{1c}$ <7%	901	OR 1.9 for treatment failure (homozygous for variant allele)	164
		On treatment HbA$_{1c}$ <7%	189	OR 1.6 for treatment failure (per variant allele)	165
Metformin					
Pharmacokinetic	*SLC22A1*	HbA$_{1c}$ response	102	0.3% absolute lower reduction in HbA$_{1c}$ (per variant allele)	166
		HbA$_{1c}$ response	371	1.1% absolute lower reduction in HbA$_{1c}$ (per variant allele)	77
		On treatment HbA$_{1c}$ <7%	1,531	No association	76
		Drug intolerance	2,166	OR 2.4 for discontinuation (homozygous for variant alleles)	73
	SLC47A1	HbA$_{1c}$ response	116	0.3% absolute lower reduction in HbA$_{1c}$ (per variant allele)	167
		HbA$_{1c}$ response	371	No association	77
		Risk of type 2 diabetes	2,994	Less reduction in diabetes risk	
	SLC47A2	HbA$_{1c}$ response	253	0.1% absolute lower reduction in HbA$_{1c}$ (any variant allele)	168
		HbA$_{1c}$ response	371	No association	77
GWA studies	*ATM*	HbA$_{1c}$ response, on treatment HbA$_{1c}$ <7%	2,896	0.1% absolute greater reduction in HbA$_{1c}$ and OR 1.4 for treatment success (per variant allele)	80
		HbA$_{1c}$ response, on treatment HbA$_{1c}$ <7%	1,366	No association with HbA$_{1c}$ response, OR 1.2 for treatment success (per variant allele)	81

FBG, fasting blood glucose. *Loss-of-function variants rs757110 in *ABCC8* and rs5219 in *KCNJ11* are in near-complete linkage disequilibrium. **Effect listed only if reported as statistically significant in cited article.

(68,74–77). Unfortunately, this low replication rate is consistent with the rate in other candidate gene studies, which may be as low as 1–3% (78,79). The potential reasons include small sample sizes, heterogeneity of genetic architecture across different populations, and publication bias. In contrast, large GWA studies that use rigorous, prespecified statistical methods have produced more valid and reproducible results. For example, the only GWA study of treatment response to a diabetes therapy, conducted in a Scottish observational cohort with nearly 3,000 participants, identified a locus for glucose-lowering response to metformin near the *ATM* gene that met a stringent threshold for statistical significance (80), and this finding has replicated in other populations (81). Well-powered pharmacogenomic studies that use rigorous statistical methods may identify genetic variants that result in greater glucose-lowering effects or fewer adverse effects from other diabetes therapies.

GWA studies rely on information about the nonrandom association of alleles (linkage disequilibrium) to "tag" common and low-frequency variation throughout the genome in a subset of directly genotyped variants. Because these studies have identified only a small portion of the known heritability of most complex traits (82) and because theory predicts that rare variants are more likely to be damaging to gene function than common variants (83,84), there has been growing interest in studying rare variants. Advances in technology and informatics have made possible the high-throughput sequencing of whole exomes and whole genomes, which provide a complete assessment of both common and rare variation (85). A recent study that sequenced 202 genes encoding drug targets in 14,000 individuals identified on average one rare variant per 17 base pairs, and 90% of these variants were newly discovered (86). Another exome-sequencing study of 12 *CYP* genes, which are responsible for about 75% of all known oxidative drug metabolism, identified 1,006 variants in these genes and found that 73% were rare, a third were predicted to affect protein structure, and 9% of individuals had at least one newly discovered functional variant (87). Whether this abundance of rare

variation explains some of the interindividual variability in drug response is unknown at this time, but the topic merits further evaluation.

CHALLENGES IN CONDUCTING GENOMIC RESEARCH

Study Power and Sample Size

One major barrier to genomic discovery in diabetes research has been the limited power to detect associations, which is a function of the frequency of the genetic variant, the magnitude of the effect to be detected, and the sample size (88). Large GWA studies with study populations of tens of thousands or more have helped to unravel the biology underlying many complex diseases, but most genetic loci identified by these studies have small effects. For example, the largest GWA study of type 2 diabetes, which included nearly 35,000 case and 115,000 control subjects, identified 65 genetic loci; all but the *TCF7L2* locus had ORs of 1.2 or lower per copy of the variant allele (15).

In pharmacogenomic studies, restriction to users of a particular drug further limits the available study population (89). Rare immune-mediated adverse drug reactions (ADRs) such as drug-induced liver injury or severe skin reactions may be caused by pathogenic variants with ORs of 100 or greater, and these associations can be detected with fewer than 50 cases (90–92). For diabetes therapies, rare adverse effects such as metformin-associated lactic acidosis or ketoacidosis related to sodium–glucose cotransporter 2 inhibitors may be amenable to pharmacogenomic discovery in similarly small studies.

It has been more difficult to identify pharmacogenomic associations with complex phenotypes such as myocardial infarction or stroke (93) or with quantitative traits such as QT interval prolongation or cholesterol lowering. For example, a large GWA study with over 30,000 participants from 10 observational cohorts evaluated QT interval prolongation from various drugs and failed to identify any pharmacogenomic loci at genome-wide levels of significance (94), and a GWA study with over 40,000 statin-using participants discovered and replicated two new loci for LDL cholesterol lowering, but each variant allele resulted in a relative change in LDL lowering effect of less than 2%

(95). While these sorts of findings may reveal new information about human population biology, these effect sizes, which cannot be distinguished from intraindividual variation or measurement error in individual patients, are so small that the effort to genotype these variants can be safely omitted from clinical practice. As pharmacogenomic efforts move to whole-exome and whole-genome sequencing, even larger sample sizes may be required to identify associations with rare variants.

Individual pharmacogenomic variants often have small effects or fail to reach stringent thresholds of statistical significance, but they can be combined within a gene or within a pathway of several genes to identify clinically important effects. As an example, Dujic et al. (73) evaluated the relationship between metformin intolerance and four reduced-function variants in the gene *SLC22A1*, which transports metformin into the intestine and may mediate some of the gastrointestinal side effects from this drug. They found that the presence of any two reduced-function alleles increased the risk of metformin discontinuation by 2.4-fold (73).

To assess associations with the large number of variants identified by whole-exome and whole-genome sequencing, more innovative approaches are necessary. Annotation tools have been used to restrict analyses to variants that are likely to be functional, on the basis of expected protein structure, associations with gene expression levels (96,97), and information from the Encyclopedia of DNA Elements (ENCODE) project, which has systematically mapped nonprotein coding regulatory function—including transcription factor binding sites, chromatin structure, and histone modifications—throughout the genome (98). Various statistical methods have been developed that aggregate rare functional variants for gene-based association tests, which can improve the power to detect an association if there are multiple damaging variants within a gene (99,100). Data from whole-exome and whole-genome sequencing have not yet been systematically evaluated in pharmacogenomic studies, but for some complex traits these methods have been used to identify rare variants with large effects, both in new and previously unidentified loci (101).

The studies of statin response and drug-induced QT prolongation described in the preceding paragraphs represent one model for conducting genomic research in large populations: local analysis of deeply phenotyped cohorts followed by a meta-analysis of summary results in large research consortia (15,102). The increasing availability of electronic health data and a recognition of the large sample sizes required for genomic discovery research have led to the emergence of another model: biobank studies that genotype tens or hundreds of thousands of individuals and link these genetic data with participants' electronic health data to create large data repositories. Some of these studies include a baseline visit for physical measurements, the collection of specimens, and imaging tests (103,104), similar to the traditional cohort studies, and they all rely on electronic health databases for longitudinal information on health care encounters, laboratory tests, vital status, and medication use. Two of the largest biobank studies, the Million Veteran Program (105) and the UK Biobank (104), have recruited close to 500,000 individuals each.

Phenotyping With Electronic Health Data

Electronic health data have been immensely useful for research, but they have important limitations. Results from laboratory tests that are measured in the course of clinical care, such as HbA$_{1c}$ or cholesterol levels, are likely to be recorded accurately and completely, but they may be related to the clinical indications for the tests and lack standardization across sites. Diagnosis codes associated with health care encounters, an important source of information about disease status, are assigned for clinical and billing rather than research purposes; geographic location (106), changes in reimbursement (107,108), and other factors can influence the assignment of these codes. For a given study design, different databases can produce different estimates of association between a drug exposure and a health outcome, sometimes in opposite directions (109). Nonetheless, diagnosis code–based algorithms have been used to identify some acute diabetes complications, such as hypoglycemia (110,111) and myocardial infarction

(112,113), with a reasonably high degree of accuracy (positive predictive value [PPV] 80–90%).

For other diabetes complications, such as heart failure, the accuracy of a diagnostic algorithm may vary substantially by the diagnosis code used and even the position of the code (primary vs. secondary) (114,115). The use of low-PPV algorithms can attenuate estimate of associations toward the null (116), sometimes dramatically. When a new diagnosis code was introduced for rhabdomyolysis, a severe ADR related to statin use, we evaluated the accuracy of this code in a large health care system by reviewing electronic medical records to validate potential cases, and we estimated the risk of rhabdomyolysis associated with the 80-mg dose of simvastatin, which was known to be high from a recent RCT (117). The PPV of the rhabdomyolysis code for the statin-related ADR was only 8%. Moreover, the relative risk for rhabdomyolysis associated with high-dose versus low-dose simvastatin was 12.2 when validated cases were evaluated, replicating the RCT estimate, but only 1.8 when the diagnosis code was used without validation (118). This marked attenuation of a genuine association is not an isolated finding; the quality (119) and severity (120) of disease phenotypes have also been shown to impact the magnitude of pharmacogenomic associations. For studies that evaluate genetic associations with disease outcomes, including ADRs, it may sometimes be necessary to conduct validation studies to assess the accuracy of claims-based data (121). Despite these limitations, the linkage of genomic data with electronic health data in large study populations holds promise as a powerful tool for research.

FRAMEWORK FOR EVALUATING A GENOMIC TEST

For the regulatory approval of new therapies directed at specific genetic defects, such as ivacaftor for the treatment of cystic fibrosis caused by a specific *CFTR* mutation (122), the U.S. Food and Drug Administration (FDA) requires the same standard used to evaluate all new drugs: substantial evidence of efficacy and safety from well-controlled studies, typically rigorously conducted RCTs. For therapies already in use that have demonstrated efficacy and safety in non-genetically determined populations, the evidence standard for using genomic information to select the best drug or dose is less certain. The FDA currently includes pharmacogenomic information in the prescribing information for over 160 drugs (123), but its oversight of laboratory-developed genetic tests is concerned primarily with analytic validity (i.e., ability to reliably measure a genetic variant or a biomarker) (124), which is inadequate to guide treatment decisions. A recent study of pharmacogenomic information in drug labels found convincing evidence of clinical validity (i.e., how accurately and consistently genetic variation predicts a phenotype) for only 36% of these drugs, and evidence of clinical utility (i.e., ability to improve outcomes for patients) for only 15% (125). The Centers for Disease Control and Prevention Office of Public Health Genomics has developed a more comprehensive framework for the evaluation of a genetic test that includes questions about analytic validity, clinical validity, and clinical utility, as well as ethical, legal, and social implications (ACCE), which are summarized in Table 3 (126,127). These standards are important to protect the health of the public.

As described earlier, most reported pharmacogenomic findings fail to replicate and therefore lack clinical validity. Similarly, rare variants identified by sequencing and initially identified as "pathogenic" are often downgraded to "uncertain significance" or "benign" after further study (128,129). For example, in the FHS and the Jackson Heart Study (JHS), seven genes responsible for MODY were sequenced and rare variants were identified that had previously been identified as causal for MODY or were predicted to be damaging to protein function by using annotation tools. These variants, present among 2% of persons in these population-based cohorts, were not associated with the risk of diabetes, and only one variant carrier out of 68 met the criteria for MODY (130).

Of the genomic findings for diabetes that have clinical validity, most have effects on disease outcomes or surrogate end points that are uncertain or too small to be clinically meaningful. Genetic risk panels for the prediction of type 2 diabetes are one example (131). Another example is the *ATM* locus for metformin treatment response, the most widely replicated diabetes pharmacogenomic finding; each copy of the variant allele was associated with only a 0.1% greater reduction in HbA_{1c} (81). Even if patients had whole-genome sequence data already available in their medical records, this treatment effect is still too small to be clinically useful. For MODY, which often has a clear genetic cause, most cases appear to be undiagnosed, in part because of uncertainty from clinicians about the clinical benefits of genetic testing (132). Making treatment decisions based on genetic tests that lack clinical validity, clinical utility, or both can have unintended consequences, including withholding beneficial treatments, an unnecessary increase in costs, or the use of drugs with harmful effects.

For examples of actionable genetic tests that meet the criteria for clinical validity and clinical utility, areas of medicine other than diabetes are instructive. Abacavir is a first-line treatment for HIV that is effective and well tolerated in most people, but about 5% of persons exposed to this drug develop a serious hypersensitivity reaction characterized by rash, fever, and damage to multiple organ systems (133). Initial studies of men of mostly European ancestry identified the cause of this ADR to be the *HLA-B*57:01* variant (91,134), with an OR of well over 100 (119), and this finding was later extended to other populations (135). A double-blind RCT demonstrated that genetic testing for the *HLA-B*57:01* variant prevented all cases of abacavir-induced hypersensitivity (136), and genetic testing is now routinely conducted before initiating treatment with this drug.

For another severe immune-mediated ADR, the translation of genetic testing into practice followed a different course. Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) related to carbamazepine use was found to be strongly associated with the *HLA* variant *HLA-B*15:02* in several Asian populations (92,137), and screening for this variant can effectively prevent the ADR (137). In 2008, Hong Kong instituted a policy of routine genetic screening before initiating carbamazepine treatment, but providers simply avoided prescribing this medication and instead prescribed other antiepileptic drugs that can also cause

Table 3—ACCE criteria for the implementation of a genetic test

	Key questions	Example applications to diabetes
Analytic validity	How often does the genetic test fail to give a useable result?	For a GRS for type 2 diabetes risk, how often does the test result in a genotype at each locus?
	What is the sensitivity and specificity of the test for a genetic variant?	For the rare *HNF1A* missense variant associated with diabetes risk, how often does the test detect the variant when it is present and how often does the test result in a false positive when the variant is not present?
	What is the within- and between-laboratory precision?	Are standardized methods used in different laboratories? How does the accuracy of the test vary from laboratory to laboratory?
	Is confirmatory testing required?	When a pathogenic variant in a MODY gene is identified from high-throughput sequencing, is confirmatory genotyping by another method required?
Clinical validity	What is the quality of the disease phenotype or treatment response measurement? What is the quality of the study designs used to evaluate these outcomes?	For a GRS that discriminates type 1 from type 2 diabetes, are standardized definitions of diabetes type used? Was the study design cross-sectional or longitudinal?
	What is the prevalence of the phenotype or the distribution of treatment response in the studied populations?	For a pharmacogenomic test for metformin treatment response, how is treatment failure/success defined and what is the rate of treatment failure/success in the studied population?
	What is the sensitivity and specificity of the test for the disease phenotype or treatment response? What is the magnitude and precision of the genotype-phenotype relationship?	What is the relative change in HbA$_{1c}$ lowering associated with the *ATM* locus for metformin treatment response?
	What are the genetic or environmental modifiers of the genotype-phenotype relationship?	Do diabetes severity, obesity, the use of additional drug therapies, or other factors modify the pharmacogenomic associations for metformin treatment response?
	Has the test been adequately validated on all populations in which it may be offered?	For a GRS for type 2 diabetes risk, has the test been validated among obese individuals and among persons from different racial/ethnic populations?
Clinical utility	What is the impact of a positive or negative test on patient care in terms of health outcomes?	What is the absolute change in HbA$_{1c}$ lowering associated with the *ATM* locus for metformin treatment response? Does this pharmacogenomic test result in projected or tangible health benefits in terms of clinical complications, such as a reduced risk of blindness or cardiovascular disease?
	What are the financial costs associated with testing and the economic benefits associated with actions resulting from testing?	What is the cost to test for the common *TCF7L2* variant for type 2 diabetes risk, including laboratory, reporting, educational, and counseling costs? What is the cost per case of diabetes predicted? Does this test result in cost-effective screening or prevention of diabetes later in life?
	What educational materials for patients have been developed and validated?	Do educational materials clearly explain the magnitude of the increased risk of type 2 diabetes associated with the common *TCF7L2* variant in relation to other known risk factors?
Ethical, legal, and social implications	What is known about how this test could lead to stigmatization, discrimination, privacy/confidentiality, and personal/family social issues?	Does the identification of a pathogenic variant responsible for a hereditary form of early-onset diabetes have implications for family planning?
	Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, disclosure, or reporting requirements?	Are physicians providing sufficient information about the potential risks and benefits from genetic testing so that patients can make informed decisions?
	What safeguards have been described and are these safeguards effective?	

Adapted from refs. 126,127.

severe skin reactions. As a result, the overall rate of SJS/TEN in Hong Kong did not change (138). This unintended result of a policy decision on a genetic test with clinical validity and clinical utility demonstrates that other concerns, such as convenience or cost, may influence the harms or benefits for a population.

Even for well-replicated pharmacogenomic findings with large effects, there can be disagreement about what constitutes clinical utility. Warfarin is an anticoagulant drug that is notoriously difficult to dose because of wide interindividual variability in the anticoagulant effect, much of which is explained

by variation in the pharmacokinetic genes *CYP2C9* and *VKORC1*. The benefits of testing for variants in these genes have even been evaluated in three large well-designed RCTs, two of which demonstrated that genetic testing resulted in a shorter time to therapeutic effect but no reduction in thrombotic or

bleeding complications (139–141). Opinions differ about whether pharmacogenomic testing has a role in warfarin treatment (142–144), and there has been a broader debate about whether RCTs are required to demonstrate the utility of a genetic test (79,145,146). Nonetheless, genetic testing for warfarin treatment has been minimal in practice. In the absence of consistent recommendations about when to use genetic information in prescribing and other treatment decisions, health care providers, patients, and also payers and health care systems will have an important voice in this discussion.

ADDITIONAL BARRIERS TO THE IMPLEMENTATION OF GENOMICS

The implementation of genomics in practice has generally involved a decision about whether to order a genetic test before starting a new treatment. For patients who have already undergone preemptive genotyping or sequencing, which is not yet common but likely to increase in the future (147–149), the decision may be about whether to use a patient's existing genetic information to guide treatment. With either approach, the main barrier to the implementation of genomics for diabetes care at this time is a robust lack of actionable findings in the areas of diabetes and cardiovascular medicine. There are also practical issues that must be addressed, which include the storage and integration of complex genomic data into the electronic health record, the interpretation of these data in an accessible format, and the creation of clinical decision support (CDS) tools that aid health care providers in using this information to make treatment decisions at the point of care (150). Various groups have made important contributions in developing model systems that address these problems (147,148,151,152).

CDS tools, which have been in use for many years for diabetes management, provide automated testing or treatment recommendations based on information in the electronic health record (153). The CDS tools for genomics that are under development rely on externally curated data resources, such as PharmGKB (154) and ClinVar (155), to determine which potentially actionable variants to incorporate and how to translate genotypes into expected phenotypes. PharmGKB currently includes information about pharmacogenomic associations for metformin and sulfonylureas; however, none of the associations meet the criteria for the highest level of evidence, and there is no recommendation for pharmacogenomic testing for these drugs (156). In drug-specific evidence summaries and guidelines, the Clinical Pharmacogenetics Implementation Consortium has begun to provide standardized terms, sample text for electronic health record documentation and point of care alerts, and clinical implementation workflows, which will be a valuable resource as the role of pharmacogenomics expands in clinical practice (157,158).

The increasing availability of CDS tools and online databases with information on actionable genomic findings will facilitate the use of genomic testing for diabetes by clinicians. However, because most clinicians are not yet comfortable using genomic information to make clinical decisions (159,160), improved education for both trainees and practicing clinicians is needed, and opportunities for both are improving (161,162). Professional societies and specialty boards will play an important role in the integration of genomics in physician training and continuing medical education; credentialing requirements for ordering genomic tests could help to ensure that such tests are used appropriately (163). If the use of genomic information ultimately proves useful in the care of patients with diabetes, even with adequate educational and training opportunities for clinicians, financial incentives may be required to spur widespread implementation, as was the case with the increased adoption of electronic health records after legislation was passed that provided reimbursements to hospitals and providers for this purpose (9–11).

CONCLUSIONS

At this time, there are few if any actionable genomic findings for diabetes that are ready for implementation. However, the increasing availability of genomic data in large populations linked with electronic health data may become a powerful resource for genomic discovery, and examples from other areas of medicine offer lessons about the limitations of these data that can help guide the direction of future research. Whether genomic information should be used in clinical practice requires a framework for evaluating the validity and clinical utility of this approach, an improved integration of genomic data into electronic health records, and the clinical decision support and educational resources for clinicians to use these data. Efforts to identify optimal approaches in all of these domains are creating a growing body of evidence that may help to bring diabetes into the era of genomic medicine.

References
1. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 2005;37:161–165
2. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264–1272
3. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372:1489–1499
4. Sabatine MS, Giugliano RP, Wiviott SD, et al.; Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1500–1509
5. McLeod HL. Cancer pharmacogenomics: early promise, but concerted effort needed. Science 2013;339:1563–1566
6. Chapman PB, Hauschild A, Robert C, et al.; BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–2516
7. Jameson JL, Longo DL. Precision medicine—personalized, problematic, and promising. N Engl J Med 2015;372:2229–2234
8. Hayden EC. Technology: The $1,000 genome. Nature 2014;507:294–295
9. Adler-Milstein J, Furukawa MF, King J, Jha AK. Early results from the hospital Electronic Health Record Incentive Programs. Am J Manag Care 2013;19:e273–e284
10. Xierali IM, Hsiao CJ, Puffer JC, et al. The rise of electronic health record adoption among

family physicians. Ann Fam Med 2013;11:
14–19

11. Lehmann CU, O'Connor KG, Shorte VA, Johnson TD. Use of electronic health record systems by office-based pediatricians. Pediatrics 2015;135:e7–e15

12. McCarthy MI. Genomic medicine at the heart of diabetes management. Diabetologia 2015;58:1725–1729

13. Geiss LS, Wang J, Cheng YJ, et al. Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980-2012. JAMA 2014;312:1218–1226

14. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2014*. National Center for Chronic Disease Prevention and Health Promotion, Atlanta, GA, 2014

15. Morris AP, Voight BF, Teslovich TM, et al.; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981–990

16. Scott RA, Lagou V, Welch RP, et al. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet 2012;44:991–1005

17. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Mexican American Type 2 Diabetes (MAT2D) Consortium; Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples (T2D-GENES) Consortium. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 2014;46:234–244

18. Sladek R, Prokopenko I. Genome-Wide Association Studies of Type 2 Diabetes. In *The Genetics of Type 2 Diabetes and Related Traits*. Florez JC, Ed. Springer International Publishing, 2016, p. 13–61

19. Zeggini E, Scott LJ, Saxena R, et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645

20. Estrada K, Aukrust I, Bjorkhaug L, et al. Association of a low-frequency variant in HNF1A with type 2 diabetes in a Latino population. JAMA 2014;311:2305–2314

21. Moltke I, Grarup N, Jorgensen ME, et al. A common Greenlandic TBC1D4 variant confers muscle insulin resistance and type 2 diabetes. Nature 2014;512:190–193

22. Fuchsberger C, Flannick J, Teslovich TM, et al. The genetic architecture of type 2 diabetes. Nature 2016;536:41–47

23. Meigs JB, Shrader P, Sullivan LM, et al. Genotype score in addition to common risk factors for prediction of type 2 diabetes. N Engl J Med 2008;359:2208–2219

24. Vassy JL, Hivert MF, Porneala B, et al. Polygenic type 2 diabetes prediction at the limit of common variant detection. Diabetes 2014;63:2172–2182

25. Pepe MS, Janes H, Longton G, Leisenring W, Newcomb P. Limitations of the odds ratio in gauging the performance of a diagnostic, prognostic, or screening marker. Am J Epidemiol 2004;159:882–890

26. Lyssenko V, Laakso M. Genetic screening for the risk of type 2 diabetes: worthless or valuable? Diabetes Care 2013;36(Suppl. 2):S120–S126

27. Yuan W, Xia Y, Bell CG, et al. An integrated epigenomic analysis for type 2 diabetes susceptibility loci in monozygotic twins. Nat Commun 2014;5:5719

28. Chambers JC, Loh M, Lehne B, et al. Epigenome-wide association of DNA methylation markers in peripheral blood from Indian Asians and Europeans with incident type 2 diabetes: a nested case-control study. Lancet Diabetes Endocrinol 2015;3:526–534

29. Wang TJ, Larson MG, Vasan RS, et al. Metabolite profiles and the risk of developing diabetes. Nat Med 2011;17:448–453

30. Walford GA, Porneala BC, Dauriz M, et al. Metabolite traits and genetic risk provide complementary information for the prediction of future type 2 diabetes. Diabetes Care 2014;37:2508–2514

31. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403

32. Florez JC, Jablonski KA, Bayley N, et al.; Diabetes Prevention Program Research Group. TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. N Engl J Med 2006;355:241–250

33. Hivert MF, Jablonski KA, Perreault L, et al.; DIAGRAM Consortium; Diabetes Prevention Program Research Group. Updated genetic score based on 34 confirmed type 2 diabetes Loci is associated with diabetes incidence and regression to normoglycemia in the diabetes prevention program. Diabetes 2011;60:1340–1348

34. Hollands GJ, French DP, Griffin SJ, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. BMJ 2016;352:i1102

35. Grant RW, O'Brien KE, Waxler JL, et al. Personalized genetic risk counseling to motivate diabetes prevention: a randomized trial. Diabetes Care 2013;36:13–19

36. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA 2014;311:806–814

37. Farmer A, Fox R. Diagnosis, classification, and treatment of diabetes. BMJ 2011;342:d3319

38. Oram RA, Patel K, Hill A, et al. A type 1 diabetes genetic risk score can aid discrimination between type 1 and type 2 diabetes in young adults. Diabetes Care 2016;39:337–344

39. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003;362:1275–1281

40. Pearson ER, Flechtner I, Njolstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006;355:467–477

41. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011;34:1878–1884

42. Vaxillaire M, Froguel P. Monogenic diabetes in the young, pharmacogenetics and relevance to multifactorial forms of type 2 diabetes. Endocr Rev 2008;29:254–264

43. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523

44. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977–986

45. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology ofDiabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653

46. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406

47. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589

48. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;372:2197–2206

49. Nathan DM. Diabetes: advances in diagnosis and treatment. JAMA 2015;314:1052–1062

50. Lipska KJ, Krumholz H, Soones T, Lee SJ. Polypharmacy in the aging patient: a review of glycemic control in older adults with type 2 diabetes. JAMA 2016;315:1034–1045

51. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet 2014;383:2008–2017

52. American Diabetes Association. Summary of Revisions. In Standards of Medical Care in Diabetes—2016. Diabetes Care 2016;39(Suppl. 1):S4–S5

53. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–865

54. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013;36:1304–1311

55. Walford GA, Colomo N, Todd JN, et al. The study to understand the genetics of the acute response to metformin and glipizide in humans (SUGAR-MGH): design of a pharmacogenetic resource for type 2 diabetes. PLoS One 2015;10:e0121553

56. Zeitler P, Hirst K, Pyle L, et al. A clinical trial to maintain glycemic control in youth with

type 2 diabetes. N Engl J Med 2012;366:2247–2256

57. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443

58. Cook MN, Girman CJ, Stein PP, Alexander CM. Initial monotherapy with either metformin or sulphonylureas often fails to achieve or maintain current glycaemic goals in patients with type 2 diabetes in UK primary care. Diabet Med 2007;24:350–358

59. Donnelly LA, Doney AS, Hattersley AT, Morris AD, Pearson ER. The effect of obesity on glycaemic response to metformin or sulphonylureas in type 2 diabetes. Diabet Med 2006;23:128–133

60. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. Annu Rev Genomics Hum Genet 2014;15:349–370

61. Manolopoulos VG, Ragia G, Tavridou A. Pharmacogenomics of oral antidiabetic medications: current data and pharmacoepigenomic perspective. Pharmacogenomics 2011;12:1161–1191

62. Becker ML, Pearson ER, Tkac I. Pharmacogenetics of oral antidiabetic drugs. Int J Endocrinol 2013;2013:686315

63. Pollastro C, Ziviello C, Costa V, Ciccodicola A. Pharmacogenomics of drug response in type 2 diabetes: toward the definition of tailored therapies? PPAR Res 2015;2015:415149

64. Zhou K, Donnelly L, Burch L, et al. Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study. Clin Pharmacol Ther 2010;87:52–56

65. Holstein A, Plaschke A, Ptak M, et al. Association between CYP2C9 slow metabolizer genotypes and severe hypoglycaemia on medication with sulphonylurea hypoglycaemic agents. Br J Clin Pharmacol 2005;60:103–106

66. Feng Y, Mao G, Ren X, et al. Ser1369Ala variant in sulfonylurea receptor gene ABCC8 is associated with antidiabetic efficacy of gliclazide in Chinese type 2 diabetic patients. Diabetes Care 2008;31:1939–1944

67. Javorsky M, Klimcakova L, Schroner Z, et al. KCNJ11 gene E23K variant and therapeutic response to sulfonylureas. Eur J Intern Med 2012;23:245–249

68. Sesti G, Laratta E, Cardellini M, et al. The E23K variant of KCNJ11 encoding the pancreatic beta-cell adenosine 5′-triphosphate-sensitive potassium channel subunit Kir6.2 is associated with an increased risk of secondary failure to sulfonylurea in patients with type 2 diabetes. J Clin Endocrinol Metab 2006;91:2334–2339

69. Nikolac N, Simundic AM, Katalinic D, Topic E, Cipak A, Zjacic Rotkvic V. Metabolic control in type 2 diabetes is associated with sulfonylurea receptor-1 (SUR-1) but not with KCNJ11 polymorphisms. Arch Med Res 2009;40:387–392

70. Holstein A, Hahn M, Stumvoll M, Kovacs P. The E23K variant of KCNJ11 and the risk for severe sulfonylurea-induced hypoglycemia in patients with type 2 diabetes. Horm Metab Res 2009;41:387–390

71. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet 2011;50:81–98

72. Pawlyk AC, Giacomini KM, McKeon C, Shuldiner AR, Florez JC. Metformin pharmacogenomics: current status and future directions. Diabetes 2014;63:2590–2599

73. Dujic T, Zhou K, Donnelly LA, Tavendale R, Palmer CN, Pearson ER. Association of organic cation transporter 1 with intolerance to metformin in type 2 diabetes: a GoDARTS study. Diabetes 2015;64:1786–1793

74. Cho HJ, Lee SY, Kim YG, et al. Effect of genetic polymorphisms on the pharmacokinetics and efficacy of glimepiride in a Korean population. Clin Chim Acta 2011;412:1831–1834

75. Becker ML, Visser LE, Trienekens PH, Hofman A, van Schaik RH, Stricker BH. Cytochrome P450 2C9 *2 and *3 polymorphisms and the dose and effect of sulfonylurea in type II diabetes mellitus. Clin Pharmacol Ther 2008;83:288–292

76. Zhou K, Donnelly LA, Kimber CH, et al. Reduced-function SLC22A1 polymorphisms encoding organic cation transporter 1 and glycemic response to metformin: a GoDARTS study. Diabetes 2009;58:1434–1439

77. Christensen MM, Brasch-Andersen C, Green H, et al. The pharmacogenetics of metformin and its impact on plasma metformin steady-state levels and glycosylated hemoglobin A1c. Pharmacogenet Genomics 2011;21:837–850

78. Ioannidis JP, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. Epidemiology 2011;22:450–456

79. Aslibekyan S, Claas SA, Arnett DK. To replicate or not to replicate: the case of pharmacogenetic studies: Establishing validity of pharmacogenomic findings: from replication to triangulation. Circ Cardiovasc Genet 2013;6:409–412; discussion 412

80. GoDARTS and UKPDS Diabetes Pharmacogenetics Study Group, Wellcome Trust Case Control Consortium, Zhou K, et al. Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes. Nat Genet 2011;43:117–120

81. van Leeuwen N, Nijpels G, Becker ML, et al. A gene variant near ATM is significantly associated with metformin treatment response in type 2 diabetes: a replication and meta-analysis of five cohorts. Diabetologia 2012;55:1971–1977

82. Manolio TA, Collins FS, Cox NJ, et al. Finding the missing heritability of complex diseases. Nature 2009;461:747–753

83. Kryukov GV, Pennacchio LA, Sunyaev SR. Most rare missense alleles are deleterious in humans: implications for complex disease and association studies. Am J Hum Genet 2007;80:727–739

84. Pritchard JK, Cox NJ. The allelic architecture of human disease genes: common disease-common variant...or not? Hum Mol Genet 2002;11:2417–2423

85. Tucker T, Marra M, Friedman JM. Massively parallel sequencing: the next big thing in genetic medicine. Am J Hum Genet 2009;85:142–154

86. Nelson MR, Wegmann D, Ehm MG, et al. An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. Science 2012;337:100–104

87. Gordon AS, Tabor HK, Johnson AD, et al. Quantifying rare, deleterious variation in 12 human cytochrome P450 drug-metabolism genes in a large-scale exome dataset. Hum Mol Genet 2014;23:1957–1963

88. Burton PR, Hansell AL, Fortier I, et al. Size matters: just how big is BIG?: Quantifying realistic sample size requirements for human genome epidemiology. Int J Epidemiol 2009;38:263–273

89. Motsinger-Reif AA, Jorgenson E, Relling MV, et al. Genome-wide association studies in pharmacogenomics: successes and lessons. Pharmacogenet Genomics 2013;23:383–394

90. Daly AK, Donaldson PT, Bhatnagar P, et al. HLA-B*5701 genotype is a major determinant of drug-induced liver injury due to flucloxacillin. Nat Genet 2009;41:816–819

91. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet 2002;359:727–732

92. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486

93. Bis JC, Sitlani C, Irvin R, et al. Drug-gene interactions of antihypertensive medications and risk of incident cardiovascular disease: a pharmacogenomics study from the CHARGE Consortium. PLoS One 2015;10:e0140496

94. Avery CL, Sitlani CM, Arking DE, et al. Drug-gene interactions and the search for missing heritability: a cross-sectional pharmacogenomics study of the QT interval. Pharmacogenomics J 2014;14:6–13

95. Postmus I, Trompet S, Deshmukh HA, et al. Pharmacogenetic meta-analysis of genome-wide association studies of LDL cholesterol response to statins. Nat Commun 2014;5:5068

96. Lonsdale J, Thomas J, Salvatore M, et al. The Genotype-Tissue Expression (GTEx) project. Nat Genet 2013;45:580–585

97. Koester SE, Insel TR. Understanding how noncoding genomic polymorphisms affect gene expression. Mol Psychiatry 2016;21:448–449

98. The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature 2012;489:57–74

99. Asimit J, Zeggini E. Rare variant association analysis methods for complex traits. Annu Rev Genet 2010;44:293–308

100. Liu DJ, Peloso GM, Zhan X, et al. Meta-analysis of gene-level tests for rare variant association. Nat Genet 2014;46:200–204

101. Lange LA, Hu Y, Zhang H, et al. Whole-exome sequencing identifies rare and low-frequency coding variants associated with LDL cholesterol. Am J Hum Genet 2014;94:233–245

102. Psaty BM, O'Donnell CJ, Gudnason V, et al.; CHARGE Consortium. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet 2009;2:73–80

103. The German National Cohort. Aims, study design and organization. Eur J Epidemiol 2014;29:371–382

104. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779

105. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. J Clin Epidemiol 2016;70:214–223

106. Song Y, Skinner J, Bynum J, Sutherland J, Wennberg JE, Fisher ES. Regional variations in diagnostic practices. N Engl J Med 2010;363:45–53

107. Lindenauer PK, Lagu T, Shieh MS, Pekow PS, Rothberg MB. Association of diagnostic coding with trends in hospitalizations and mortality of patients with pneumonia, 2003-2009. JAMA 2012;307:1405–1413

108. Psaty BM, Boineau R, Kuller LH, Luepker RV. The potential costs of upcoding for heart failure in the United States. Am J Cardiol 1999; 84:108–109, A9

109. Madigan D, Ryan PB, Schuemie M, et al. Evaluating the impact of database heterogeneity on observational study results. Am J Epidemiol 2013;178:645–651

110. Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC Endocr Disord 2008;8:4

111. Schelleman H, Bilker WB, Brensinger CM, Wan F, Hennessy S. Anti-infectives and the risk of severe hypoglycemia in users of glipizide or glyburide. Clin Pharmacol Ther 2010;88:214–222

112. Cutrona SL, Toh S, Iyer A, et al. Validation of acute myocardial infarction in the Food and Drug Administration's Mini-Sentinel program. Pharmacoepidemiol Drug Saf 2013;22:40–54

113. Floyd JS, Blondon M, Moore KP, Boyko EJ, Smith NL. Validation of methods for assessing cardiovascular disease using electronic health data in a cohort of Veterans with diabetes. Pharmacoepidemiol Drug Saf 2016;25:467–471

114. Psaty BM, Delaney JA, Arnold AM, et al. Study of cardiovascular health outcomes in the era of claims data: the Cardiovascular Health Study. Circulation 2016;133:156–164

115. Agarwal SK, Wruck L, Quibrera M, et al. Temporal trends in hospitalization for acute decompensated heart failure in the United States, 1998-2011. Am J Epidemiol 2016;183:462–470

116. Chubak J, Pocobelli G, Weiss NS. Tradeoffs between accuracy measures for electronic health care data algorithms. J Clin Epidemiol 2012;65:343–349.e2

117. Link E, Parish S, Armitage J, et al. SLCO1B1 variants and statin-induced myopathy–a genome-wide study. N Engl J Med 2008;359:789–799

118. Floyd JS, Heckbert SR, Weiss NS, Carrell DS, Psaty BM. Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. JAMA 2012;307:1580–1582

119. Sousa-Pinto B, Pinto-Ramos J, Correia C, et al. Pharmacogenetics of abacavir hypersensitivity: a systematic review and meta-analysis of the association with HLA-B*57:01. J Allergy Clin Immunol 2015;136:1092–1094.e3

120. Carr DF, O'Meara H, Jorgensen AL, et al. SLCO1B1 genetic variant associated with statin-induced myopathy: a proof-of-concept study using the clinical practice research datalink. Clin Pharmacol Ther 2013;94:695–701

121. Manuel DG, Rosella LC, Stukel TA. Importance of accurately identifying disease in studies using electronic health records. BMJ 2010;341:c4226

122. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011;365:1663–1672

123. U.S. Food and Drug Administration. Table of pharmacogenomic biomarkers in drug labeling [Internet]. Available from http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. Accessed 15 August 2016

124. Sharfstein J. FDA regulation of laboratory-developed diagnostic tests: protect the public, advance the science. JAMA 2015;313:667–668

125. Wang B, Canestaro WJ, Choudhry NK. Clinical evidence supporting pharmacogenomic biomarker testing provided in US Food and Drug Administration drug labels. JAMA Intern Med 2014;174:1938–1944

126. Centers for Disease Control and Prevention. ACCE model process for evaluating genetic tests [Internet]. Available from http://www.cdc.gov/genomics/gtesting/ACCE/. Acessed 26 March 2016

127. Teutsch SM, Bradley LA, Palomaki GE, et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. Genet Med 2009;11:3–14

128. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405–424

129. Manrai AK, Ioannidis JP, Kohane IS. Clinical genomics: from pathogenicity claims to quantitative risk estimates. JAMA 2016;315:1233–1234

130. Flannick J, Beer NL, Bick AG, et al. Assessing the phenotypic effects in the general population of rare variants in genes for a dominant Mendelian form of diabetes. Nat Genet 2013; 45:1380–1385

131. Palomaki GE, Melillo S, Marrone M, Douglas MP. Use of genomic panels to determine risk of developing type 2 diabetes in the general population: a targeted evidence-based review. Genet Med 2013;15:600–611

132. van der Zwaag AM, Weinreich SS, Bosma AR, et al. Current and best practices of genetic testing for maturity onset diabetes of the young: views of professional experts. Public Health Genomics 2015;18:52–59

133. Gunthard HF, Aberg JA, Eron JJ, et al.; International Antiviral Society-USA Panel. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA 2014;312:410–425

134. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet 2002;359:1121–1122

135. Saag M, Balu R, Phillips E, et al.; Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation Study Team. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis 2008;46:1111–1118

136. Mallal S, Phillips E, Carosi G, et al.; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568–579

137. Chen P, Lin JJ, Lu CS, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126–1133

138. Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology 2014;83:2077–2084

139. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. N Engl J Med 2013;369:2283–2293

140. Pirmohamed M, Burnside G, Eriksson N, et al. Group E-P: A randomized trial of genotype-guided dosing of warfarin. N Engl J Med 2013;369:2294–2303

141. Verhoef TI, Ragia G, de Boer A, et al.; EU-PACT Group. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. N Engl J Med 2013;369:2304–2312

142. Furie B. Do pharmacogenetics have a role in the dosing of vitamin K antagonists? N Engl J Med 2013;369:2345–2346

143. Pirmohamed M, Kamali F, Daly AK, Wadelius M. Oral anticoagulation: a critique of recent advances and controversies. Trends Pharmacol Sci 2015;36:153–163

144. Cavallari LH, Nutescu EA. Warfarin pharmacogenetics: to genotype or not to genotype, that is the question. Clin Pharmacol Ther 2014; 96:22–24

145. Ioannidis JP, Khoury MJ. Are randomized trials obsolete or more important than ever in the genomic era? Genome Med 2013;5:32

146. Gillis NK, Innocenti F. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. Clin Pharmacol Ther 2014;96:655–657

147. Gottesman O, Scott SA, Ellis SB, et al. The CLIPMERGE PGx Program: clinical implementation of personalized medicine through electronic health records and genomics-pharmacogenomics. Clin Pharmacol Ther 2013; 94:214–217

148. Bielinski SJ, Olson JE, Pathak J, et al. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. Mayo Clin Proc 2014;89:25–33

149. Rasmussen-Torvik LJ, Stallings SC, Gordon AS, et al. Design and anticipated outcomes of the eMERGE-PGx project: a multicenter pilot for preemptive pharmacogenomics in electronic health record systems. Clin Pharmacol Ther 2014;96:482–489

150. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature 2015;526:343–350

151. Gottesman O, Kuivaniemi H, Tromp G, et al. The Electronic Medical Records and Genomics (eMERGE) Network: past, present, and future. Genet Med 2013;15:761–771

152. Weitzel KW, Alexander M, Bernhardt BA, et al. The IGNITE network: a model for genomic medicine implementation and research. BMC Med Genomics 2016;9:1

153. Jeffery R, Iserman E, Haynes RB; CDSS Systematic Review Team. Can computerized clinical decision support systems improve diabetes management? A systematic review and meta-analysis. Diabet Med 2013;30:739–745

154. Thorn CF, Klein TE, Altman RB. Pharmacogenomics and bioinformatics: PharmGKB. Pharmacogenomics 2010;11:501–505

155. Rehm HL, Berg JS, Brooks LD, et al.; ClinGen. ClinGen–the Clinical Genome Resource. N Engl J Med 2015;372:2235–2242

156. PharmGKB. Available from https://www.pharmgkb.org. Accessed 12 July 2016

157. Martin MA, Hoffman JM, Freimuth RR, et al.; Clinical Pharmacogenetics Implementation Consortium. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing: 2014 update. Clin Pharmacol Ther 2014;95:499–500

158. Ramsey LB, Johnson SG, Caudle KE, et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther 2014;96:423–428

159. Haga SB, Burke W, Ginsburg GS, Mills R, Agans R. Primary care physicians' knowledge of and experience with pharmacogenetic testing. Clin Genet 2012;82:388–394

160. Overby CL, Erwin AL, Abul-Husn NS, et al. Physician attitudes toward adopting genome-guided prescribing through clinical decision support. J Pers Med 2014;4:35–49

161. Gerhard GS, Paynton B, Popoff SN. Integrating cadaver exome sequencing into a first-year medical student curriculum. JAMA 2016;315:555–556

162. Manolio TA, Green ED. Leading the way to genomic medicine. Am J Med Genet C Semin Med Genet 2014;166C:1–7

163. Manolio TA, Murray MF; Inter-Society Coordinating Committee for Practitioner Education in Genomics. The growing role of professional societies in educating clinicians in genomics. Genet Med 2014;16:571–572

164. Pearson ER, Donnelly LA, Kimber C, et al. Variation in TCF7L2 influences therapeutic response to sulfonylureas: a GoDARTs study. Diabetes 2007;56:2178–2182

165. Holstein A, Hahn M, Korner A, Stumvoll M, Kovacs P. TCF7L2 and therapeutic response to sulfonylureas in patients with type 2 diabetes. BMC Med Genet 2011;12:30

166. Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the organic cation transporter 1 is associated with metformin response in patients with diabetes mellitus. Pharmacogenomics J 2009;9:242–247

167. Becker ML, Visser LE, van Schaik RH, Hofman A, Uitterlinden AG, Stricker BH. Genetic variation in the multidrug and toxin extrusion 1 transporter protein influences the glucose-lowering effect of metformin in patients with diabetes: a preliminary study. Diabetes 2009;58:745–749

168. Choi JH, Yee SW, Ramirez AH, et al. A common 5′-UTR variant in MATE2-K is associated with poor response to metformin. Clin Pharmacol Ther 2011;90:674–684