Defining Heterogeneity Among Women With Gestational Diabetes Mellitus

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Attention to precision medicine in type 2 diabetes (T2D) has provided two favored approaches to subclassifying affected individuals and parsing heterogeneity apparent in this condition: phenotype-based and genotype-based. Gestational diabetes mellitus (GDM) shares phenotypic characteristics with T2D. However, unlike T2D, GDM emerges in the setting of profound pregnancy-related physiologic changes in glucose metabolism. T2D and GDM also share common genetic architecture, but there are likely to be unique genetic influences on pregnancy glycemic regulation that contribute to GDM. In this Perspective, we describe efforts to decipher heterogeneity in T2D and detail how we and others are applying approaches developed for T2D to the study of heterogeneity in GDM. Emerging results reveal the potential of phenotype- and genotype-based subclassification of GDM to deliver the promise of precision medicine to the obstetric population.

Gestational diabetes mellitus (GDM), maternal hyperglycemia identified during pregnancy, is associated with adverse perinatal outcomes and a high risk of future maternal type 2 diabetes (T2D) (1–4). The current approach to GDM treats all diagnosed women similarly. Recommended treatment during pregnancy is burdensome and includes monitoring capillary glucose at least 4 times per day, making trial-and-error dietary modifications based on glucose readings, and pharmacologic therapy when dietary modification does not achieve strict glycemic control (3,4). The use of oral medications for treatment of GDM has been called into question, based on data suggesting adverse short- and long-term outcomes associated with these therapies; thus, insulin is considered the first-line pharmacologic treatment (3,4). After delivery, because

women with a history of GDM are at high risk for T2D, it is recommended that they undergo postpartum screening for glucose intolerance, with repeated screening every 1–3 years thereafter (3,4). Yet, the number of women with a history of GDM who are screened appropriately or who receive evidence-based therapy for T2D prevention is quite low (1,5–8).

Despite the one-size-fits-all approach to GDM in current clinical practice, heterogeneity among women with GDM has been recognized (9–12). Similarly, heterogeneity of effects of maternal GDM on the fetus are readily apparent to clinicians that treat mothers with GDM and their offspring. Inspired by ongoing work in T2D, these observations have led us to hypothesize that subtyping women with GDM may provide the opportunity for more personalized risk assessment, therapy selection, and T2D prevention among women with this condition. In this Perspective, we describe recent approaches to deciphering heterogeneity in nonpregnant people with T2D and how these approaches are being applied to women with GDM.

Approaches to Defining Heterogeneity in T2D
Phenotype-Based Approaches
Patients with T2D demonstrate considerable heterogeneity in their clinical characteristics (13), and it is well appreciated that development of T2D involves defects in both β-cell function (insulin deficiency) and insulin action (insulin resistance) (14). It is appealing clinically to subgroup patients with T2D based on observed phenotypic characteristics, and recent efforts have proposed phenotype-based approaches that take advantage of modern computational capabilities. These approaches have the potential to highlight underlying disease pathophysiology, enhance prognostication, and refine treatment selection.

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DIABETES SYMPOSIUM

With the goal of identifying subgroups of patients that differ based on well-established diabetes-related parameters, including insulin deficiency and resistance, Ahlqvist et al. (15) studied six metrics (glutamic acid decarboxylase [GAD] antibody, age, BMI, hemoglobin A_{1c} [HbA$_{1c}$], homeostatic model assessments of β-cell function [HOMA2-B] and insulin resistance [HOMA2-IR]), assessed at the time of diagnosis, in Scandinavian adults with any form of new-onset diabetes. Using k-means and hierarchical clustering algorithms, they identified five reproducible subgroups of patients: a severe autoimmune form (capturing type 1 diabetes and latent autoimmune diabetes of adults), a severe insulin-deficient form, a severe insulin-resistant form, a mild obesity-related form, and a mild age-related form. They further investigated whether the groups differed with regard to escalation of therapy or diabetes-related complications; indeed, there were significant intergroup differences, including reduced time to sustained insulin use in the severe autoimmune and severe insulin-deficient groups, and increased risk of chronic kidney disease in the severe insulin-resistant group (15).

Several groups have replicated the findings of Ahlqvist et al., including in more ethnically diverse populations (16–18). Zaharia et al. (18) examined the Ahlqvist clusters in the German Diabetes Study, in which detailed physiologic measurements were performed on adults with new-onset diabetes. They found that insulin sensitivity, as measured by euglycemic clamps, was reduced in individuals with severe insulin-resistant diabetes; this group also had higher hepatocellular lipid content, which appeared to translate into more hepatic fibrosis at 5-year follow-up. In addition, individuals with severe insulin-deficient diabetes had a greater prevalence of diabetic neuropathy.

In other analyses, Dennis et al. (16) noted that clinical differences between subtypes described by Ahlqvist et al. could be better captured by a model using simple continuous clinical characteristics (e.g., age, sex, BMI, renal function, HbA$_{1c}$). These investigators confirmed, using data from a randomized trial, that patients with certain Ahlqvist diabetes subtypes had greater HbA$_{1c}$ response to certain therapies; however, a model based on simple continuous clinical characteristics performed similarly or better in predicting progression, complications, and therapy response. For example, compared with the Ahlqvist subtype-based model, a model using only age at diagnosis equally explained glycemic progression and baseline estimated glomerular filtration rate was a better predictor of time to chronic kidney disease. Similarly, a model incorporating sex, age at diagnosis, baseline BMI, and baseline HbA$_{1c}$ was more predictive of treatment response than the Ahlqvist approach. These findings raise the question of whether patients with T2D are best approached clinically by binning into discrete subtypes or by modeling each clinical question directly using available phenotypic data.

Genotype-Based Approaches

Unlike phenotypic characteristics, which can vary over time and disease course, genotype is set prior to birth and is fixed over a lifetime. Thus, genotype-based approaches to T2D subclassification have the potential to reveal underlying biologic pathways leading to disease and delineate stable subtypes that could be used in clinical decision-making.

The wealth of genetic data generated in genome-wide association studies (GWAS) of T2D, with more than 400 distinct T2D-associated genetic signals now identified, offers an opportunity to unravel mechanistic pathways with therapeutic potential (19). The traditional approach to determine the mechanism of action for a given genetic locus identified in GWAS has been laboratory based, but this has been met with variable success. As an alternative complementary strategy, we and others pursued clustering approaches to identify mechanistic pathways using T2D-associated genetic loci by examining their associations with additional disease-related phenotypic traits. The underlying concept is that loci acting along a shared pathway are expected to have similar association profiles across multiple traits. To group traits and variants, we and others have applied a "soft" clustering approach, in which variants and traits can belong to one or more cluster (20,21). Unlike several prior attempts using unsupervised hierarchical "hard" clustering, the clusters resulting from this approach have been reproducible and interpretable (22). This approach appears to be well suited for modeling the pleiotropy of complex disease biology, as it allows a given locus to impact one or more genes, which in turn may alter one or more disease pathways.

Our 2018 analysis (Udler et al. [20]) involved clustering of 94 T2D variants and their associations with 47 metabolic traits using Bayesian nonnegative matrix factorization (bNMF). The resulting five clusters were readily interpretable, with two representing pathways of insulin deficiency and three representing pathways of insulin resistance (Table 1) (20). The two insulin deficiency clusters contained variant alleles that were associated with increased T2D risk and reduced fasting insulin levels; they differed from each other in terms of associations with high versus low proinsulin levels, which likely represent defective insulin processing versus defective insulin synthesis, respectively. The three other clusters, representing mechanisms of insulin resistance, contained variant alleles associated with T2D and increased fasting insulin, in addition to other defining phenotypes: obesity-mediated (increased BMI and waist circumference), lipodystrophy-like (reduced BMI, adiponectin, and HDL cholesterol and increased triglycerides), and disrupted liver-lipid metabolism (reduced serum triglycerides). The clusters were enriched for active regulatory elements in tissues that were consistent with suspected pathways. For example, the defective insulin processing cluster was most strongly enriched for regulatory elements in pancreatic islets, and the disrupted

Table 1—Cluster-based partitioned polygenic scores capturing heterogeneity in T2D (22)

| | | Cluster name | | |
| | | Udler et al. 2018 (20) | Mahajan et al. 2018a (21) | |
Physiologic impact	Phenotypic features	Udler et al. 2018 (20)	Mahajan et al. 2018a (21)	Examples of T2D loci
Insulin deficiency				
High proinsulin	Low fasting insulin (+ high proinsulin)	Beta cell	Insulin secretion 1	*ABO, ADCY5, HNF1A, HNF1B, MTNR1B, SLC30A8, TCF7L2*
Low proinsulin	Low fasting insulin (+ low proinsulin)	Proinsulin	Insulin secretion 2	*IGF2BP2, CENTD2/ARAP1, CCND2*
Insulin resistance				
Mediation via fat distribution	High fasting insulin + low BMI + low WC + high TG	Lipodystrophy	Insulin action	*MACF1, GRB14, IRS1, PPARG, ANKRD55, KLF14, LPL, CMIP*
Mediation via obesity	High fasting insulin + high BMI + high WC	Obesity	Adiposity	*NRXN3, FTO, MC4R*
Mediation via lipid metabolism	Low TG	Liver/lipid	Dyslipidemia	*GCKR, TM6SF2*
Undetermined	No striking phenotype association	No assignment	Mixed features	*BCL11A, TLE1, PLEKHA1, HMGA2, MTMR3*

Table modified from Udler et al. (22). Comparison of variant-trait clusters identified by Udler et al. (20) and Mahajan et al. (21). TG, triglycerides; WC, waist circumference.

liver-lipid metabolism cluster was significantly enriched for elements in liver tissue.

The second recent use of a soft clustering approach by Mahajan et al. involved a set of 94 T2D association signals partly overlapping with those used in Udler et al. and 10 T2D-related traits (21). They applied a different soft clustering approach and identified six clusters (21). Five of the clusters broadly mapped to the clusters from Udler et al. described above (Table 1). Thus, these two independent applications of soft clustering to T2D variant-trait associations resulted in similar robust findings (22).

As a first step toward applying these results to clinical care, we derived polygenic scores based on the Udler clusters. Traditional T2D polygenic scores estimate a given individual's genetic risk of T2D by aggregating together all of his or her T2D-increasing alleles; individuals with the top 2.5–5% polygenic scores from the UK Biobank study population are at approximately threefold-increased risk of developing T2D compared with the mean of the rest of the sample (19,23). In contrast, cluster-based "partitioned" polygenic scores are comprised only of the genetic variants belonging to a given cluster. Among 17,365 individuals with T2D across four cohorts, we found that individuals uniquely in the top 10th percentile of the partitioned polygenic score for each of the Udler et al. clusters had clinical phenotypes that distinguished them from all others with T2D (20). Thus, using genetic information alone, employed through cluster-based partitioned polygenic scores, could help deconstruct the phenotypic heterogeneity of patients with T2D.
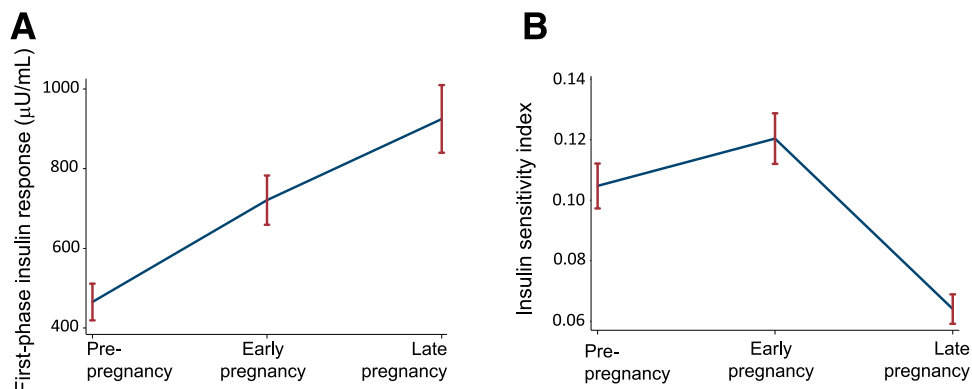

Figure 1—Longitudinal changes in insulin secretion and sensitivity across pregnancy (28). Reproduced with permission from Powe et al. (28). Insulin secretory response (by intravenous glucose tolerance test) and insulin sensitivity (by euglycemic clamp) were assessed in 34 women prior to pregnancy, in early pregnancy (12–14 weeks' gestation), and in late pregnancy (34–36 weeks' gestation). Depicted are the mean first-phase insulin response (*A*) and insulin sensitivity index (*B*) at the three study time points. Error bars denote SEM for each time point.

Phenotypic Characteristics of GDM

GDM shares phenotypic characteristics and risk factors with T2D. However, unlike T2D, GDM emerges in the setting of profound pregnancy-related physiologic changes in glucose metabolism. In pregnant women, by late gestation, insulin sensitivity has declined by 40–60% (12,24–26). This gestational insulin resistance, which begins in the second half of pregnancy (Fig. 1) and resolves immediately upon delivery, has been attributed to circulating hormones released by the placenta (25,27–29). By late gestation, the profound insulin resistance is matched by a dramatic augmentation of β-cell insulin secretion (12,24,26). The augmentation of β-cell function is not entirely attributable to compensation for insulin resistance, as it begins prior to and independent of the decline in insulin sensitivity (28) (Fig. 1). This physiologic observation in humans is corroborated by laboratory work, which suggests that the transcriptional program resulting in enhanced β-cell function in pregnant rodents is distinct from that which is stimulated by high-fat diet (30); the hormonal mediators of this gestational adaptation in humans remain unelucidated (28).

The aforementioned physiologic changes result in dynamic alterations in glycemia across gestation. Pregnant women develop progressive elevations of postprandial glucose, likely attributable to escalating insulin resistance (11,31,32). In contrast, fasting glucose levels are generally lower than in nonpregnant women; proposed mechanisms to account for this phenomenon include glucose uptake by the fetus/placenta (33), enhanced β-cell function discussed above, and perhaps others, yet undiscovered. At 24–30 weeks' gestation, obstetric providers typically perform universal screening for GDM using oral glucose tolerance test–based methods (3,34). If either the fasting or postload glucose levels exceed diagnostic thresholds, GDM is diagnosed. The exact glycemic thresholds that should lead to a diagnosis of GDM are controversial, but all accepted thresholds are lower than those used to diagnose diabetes outside of pregnancy, based on well-established associations of mild hyperglycemia with pregnancy complications (1,3,34).

Although the hyperglycemia in GDM is typically mild, women with GDM and their infants are at risk for a host of adverse perinatal outcomes that include preeclampsia, preterm delivery, fetal overgrowth, shoulder dystocia, birth injury, cesarean section, neonatal hypoglycemia, neonatal hyperbilirubinemia, neonatal respiratory distress, and neonatal intensive care unit admission (1,6,7). Glucose-lowering treatment reduces these risks in women with GDM (6,7). Recommended GDM management includes four times daily capillary blood glucose measurements, dietary modification (often with extensive food logging and trial and error), and pharmacologic agents (insulin preferred) if necessary to meet strict glycemic targets (<95 mg/dL fasting and <120 mg/dL 2 h after eating) (3,4). Currently, all women with GDM are treated in a similar manner, without regard to any heterogeneity present within this condition.

The population of women with GDM likely includes a cross-section of hyperglycemia in women of childbearing age including undiagnosed prediabetes, type 1 diabetes, T2D, and monogenic diabetes, as well as pregnancy-related hyperglycemia (35,36). It is unclear how many women with GDM, if any, have glucose intolerance that is strictly limited to pregnancy, but the GDM recurrence rate of ~50% is less than one would expect if it solely represented a chronic maternal condition (37). There is a known increased risk of GDM in twin pregnancies, implicating the fetal-placental unit in GDM development (38). Congruent with this, some epidemiologic studies have identified paternal factors that increase the risk of GDM, presumably through the effects of placental biology on maternal physiology (39). Characterization of women who do and do not develop diabetes after pregnancy and women who do and do not experience GDM recurrence could shed more light on these potential sources of heterogeneity.

Genetic Architecture of GDM

Few pregnancy cohorts with available DNA have been large enough to conduct GWAS on the scale required for genetic discovery of disease-contributing common variants. Common variants generally have small effect sizes, but in aggregate they can influence physiology in a clinically significant manner. Because of limited sample sizes of available pregnancy cohorts, much less is known about the genetic architecture of GDM as compared with what is known about the genetic architecture of T2D.

Known T2D-Associated Loci and GDM

Thus far, most genetic investigations of GDM have highlighted variants that are already known to increase risk of T2D (40,41), underscoring the overlap in the genetic architecture of the two conditions. Most studies have investigated known T2D-associated loci using GDM case-control studies in populations of various ethnic backgrounds including European, African American, Chinese, and Hispanic (42–46). The T2D-associated loci that have been most robustly associated with GDM are *IRS1, IGF2BP2, CDKAL1, GCK, TCF7L2, MTNR1B, KCNJ11,* and *KCNQ1* (40). Some studies have also evaluated how polygenic scores, built using known T2D-associated loci, are able to predict GDM in pregnancy (46,47).

GWAS of GDM

Kwak et al. reported results from a GWAS of GDM in a Korean population using a two-stage approach: in the first stage, they conducted a standard agnostic GWAS (2.19 million single nucleotide polymorphisms) in 468 women with GDM and 1,242 control subjects (48). In the second stage, they selected 11 loci to be genotyped in a follow-up population including 931 women with GDM and 783 control subjects. In both stages, women included in the control group were >50–60 years old with euglycemia (based on both fasting glucose and HbA$_{1c}$) and had no family history of T2D. The choice of this control group, which may have increased the differences between groups (and therefore

statistical power), may also have increased the chances that this study would identify loci involved in both GDM and T2D pathogenesis (rather than GDM alone). After combining data from both stages, Kwak et al. identified two loci that reached genome-wide significance: *CDKAL1* and *MTNR1B* (both known to be associated with T2D) (48). Recently, one other study attempted to perform GWAS for GDM, but none of the findings reached genome-wide significance, likely due to limited sample size (49). Just as in T2D and many other complex diseases, it is likely that GWAS will require much larger sample sizes to reveal novel loci specifically associated with GDM.

GWAS of Glycemic Traits in Pregnancy
In a collaborative effort (Hayes et al. [50]) led by investigators of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, we participated in investigations that identified two genetic variants that influence continuous glycemic traits specifically in pregnancy. In meta-analyses that included multiple ethnic groups from HAPO, plus two other pregnancy cohorts (up to $N = 7,463$), these studies revealed that rs4746822 at *HKDC1* was associated with glucose level 2 h after an oral 75-g glucose load (2-h glucose) and that rs6517656 at *BACE2* was associated with fasting C-peptide levels (50). These loci appear to be specific to glycemic regulation in pregnancy: for example, a prior large GWAS meta-analysis of glycemic traits in nonpregnant individuals reported only a modest association at *HKDC1* ($P = 1.24 \times 10^{-4}$) with 2-h glucose in 42,854 Europeans (51). Hayes et al. also confirmed that certain loci identified in GWAS for glycemic traits outside of pregnancy (*GCKR*, *G6PC2*, *PCSK1*, *PPP1R3B*, and *MTNR1B*) regulate glycemia in pregnancy (all reaching genome-wide significance for at least one glycemic trait) (50). In a recent study, Moen et al. (52) conducted GWAS of multiple glycemic traits in pregnancy (at two time points: 14–16 weeks and 30–32 weeks of gestation) in 529 women of European ancestry. They did not robustly identify novel loci that influence glycemic traits in pregnancy, likely due to lack of power.

Known Glycemic Trait–Associated Loci and Glycemic Traits in Pregnancy
Using data from two prospective cohorts of pregnant women with European ancestry (Genetics of Glucose Regulation in Gestation and Growth [Gen3G]: $N = 551$; HAPO: $N = 1,380$) with continuous measures of glycemic traits, we have investigated various polygenic scores derived from previous GWAS in nonpregnant individuals to capture genetic determinants of fasting insulin, insulin secretion, insulin sensitivity, fasting glucose, and T2D risk (53). Our findings showed that a fasting glucose polygenic score (made up of 38 variants known to determine fasting glucose outside of pregnancy) was strongly associated with fasting glucose in pregnancy (explaining about 7% of variance in each cohort). Moreover, we showed that an insulin secretion polygenic score (24 variants that result in reduced insulin

secretory response outside of pregnancy) was associated with the Stumvoll first-phase insulin secretion estimate (1.3% variance explained) and that an insulin sensitivity polygenic score (14 variants that lead to reduced insulin sensitivity outside of pregnancy) was associated with the Matsuda insulin sensitivity index (0.6% variance explained) in pregnancy. In contrast, associations of a fasting insulin polygenic score with fasting insulin or C-peptide in pregnancy were inconsistent. Finally, we demonstrated that each of these polygenic scores (including a T2D polygenic with 85 loci) was significantly associated with risk of GDM in the HAPO cohort ($n = 207$ cases), with consistent associations in Gen3G (43 cases) (53).

Similarly, Moen et al. (52) compared polygenic scores for fasting glucose and 2-h glucose built using loci identified in nonpregnant individuals of European descent and found good concordance in variance explained in fasting glucose (explaining 4% to 5% in pregnancy, similar to nonpregnant individuals). In contrast, there was no association between a 2-h glucose polygenic score derived outside of pregnancy and 2-h glucose in pregnancy, suggesting that pregnancy-specific factors may affect regulation of glucose in the postprandial state during gestation (52).

Defining Heterogeneity in GDM
In most instances, all women with GDM are considered to have the same disease. However, as discussed above, GDM is likely to represent a number of diverse pathways leading to hyperglycemia in women of childbearing age. The focus of research in GDM over the past four decades has largely been to describe characteristics of the average woman with GDM rather than to examine the differences among women with this condition, with a few exceptions. We recently examined heterogeneity in GDM using a maternal physiology-based approach that has now been replicated in other cohorts and is being tested in clinical trials for GDM management. Subsequent work will borrow genetic approaches pioneered outside of pregnancy to perform genetically informed GDM subclassification. Heterogeneity in the fetal response to maternal GDM is an underexplored area of investigation.

Maternal Phenotype-Based Approaches to Heterogeneity in GDM
Heterogeneity among women with GDM has been recognized for some time. Small studies conducted over 30 years ago classified women with GDM as "lean" or "obese" and reported differences between these subgroups (9,11,12). For example, in 1985, Cheney et al. (9) studied glycemic and insulin response to a mixed meal in 23 women with GDM whose prepregnancy BMI was ≤ 27 kg/m^2 and 12 women with GDM with prepregnancy BMI >27 kg/m^2. The higher-BMI group was more hyperglycemic and hyperinsulinemic after a mixed meal compared with lean women with GDM. The women with GDM and prepregnancy BMI ≤ 27 kg/m^2 were more hyperglycemic but also

hypoinsulinemic relative to lean women without GDM. The women with GDM who had prepregnancy BMI >27 kg/m^2 had larger infants who were more likely to have hypoglycemia compared with the women with GDM with prepregnancy BMI ≤27 kg/m^2 (9).

Unlike previous studies that used adiposity measures to subclassify GDM, we described physiologic subtypes of GDM based on the underlying physiologic mechanisms leading to hyperglycemia (10). Among 809 pregnant women participating the Gen3G cohort, we demonstrated heterogeneity in the contribution of insulin resistance and insulin deficiency to GDM, using a hypothesis-based approach. We used validated indices of insulin sensitivity and secretory response measured during a 75-g oral glucose tolerance test (Fig. 2) to define insulin resistance and deficiency based on having insulin sensitivity or insulin secretory response that was below the 25th percentile in pregnant women with normal glucose tolerance (10,54). Women with insulin-resistant GDM (51% of cases) had a greater BMI, hypertriglyceridemia, and marked hyperinsulinemia compared with women with normal glucose tolerance (Table 2) (10,55). Women with insulin-resistant GDM had an increased risk of fetal overgrowth and a composite hyperglycemia-associated adverse outcome (large for gestational age birth weight, cesarean section, neonatal hypoglycemia) compared with women with normal glucose tolerance. In contrast, neither women with insulin-deficient GDM (30% of cases) nor those with both insulin resistance and deficiency (mixed defect, 20% of cases) had an elevated risk of fetal overgrowth or the composite adverse outcome (10). Following our study, investigations in independent cohorts have confirmed our findings, suggesting that women with

GDM who have excess insulin resistance (defined using various indices and cut points) are at greater risk for perinatal complications (56–58).

The reason for the greater perinatal risk among women with insulin resistance has not been fully elucidated, but there are several plausible biologic explanations. First, obesity is a common cause of insulin resistance and has previously been linked to adverse pregnancy outcomes independent of hyperglycemia (59). Yet, adjustment for adiposity, as measured by BMI, did not attenuate the observed association between GDM with excess insulin resistance and adverse outcomes in our own study (10) or that of Benhalima et al. (56). Second, insulin resistance is usually accompanied by a variety of metabolic changes, including elevations in insulin levels and circulating lipids. Elevated insulin levels in early pregnancy have been linked to increased placental size and alterations in placental gene expression (60,61). Elevations in plasma triglycerides have been linked to newborn adiposity (62). Third, it is unclear whether women with GDM spend more time hyperglycemic than other subtypes. While postload glycemia was similarly elevated in all three GDM subtypes, the women with insulin resistance tended to have higher fasting glucose. Since nocturnal (fasting) hyperglycemia has been linked to an increased risk of large for gestational age birth weight, it is possible that fetuses born to mothers with GDM due to excess insulin resistance have greater exposure to hyperglycemia, accounting for the observed fetal overgrowth (63). However, Benhalima et al. (56) found that adjusting for fasting glucose did not attenuate the significantly increased risk of adverse perinatal outcomes in insulin-resistant women with GDM. To our
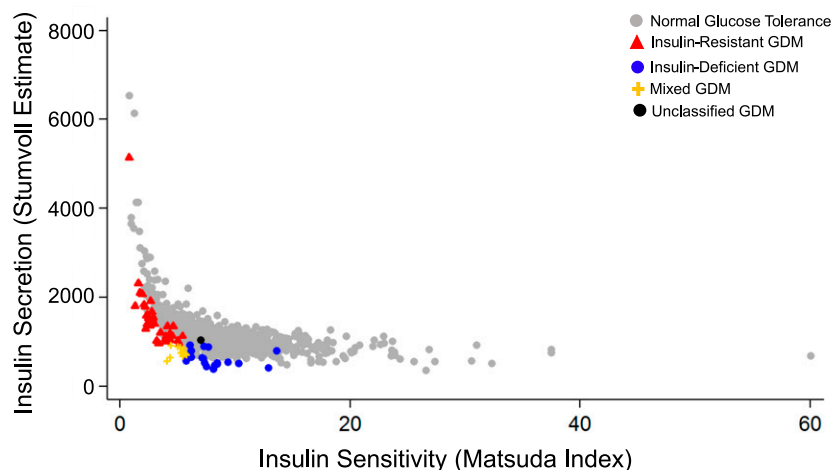

Figure 2—Insulin secretion and sensitivity in women with normal glucose tolerance and GDM physiologic subtypes (10). Figure reproduced from the online supplement of Powe et al. (10). In the Gen3G cohort (N = 809), there were 67 women (8.3%) with GDM. The gray circles represent women with normal glucose tolerance. Based on insulin sensitivity or secretion defects (Matsuda index or Stumvoll first-phase estimate <25th percentile in women with normal glucose tolerance), we classified women with GDM into physiologic subtypes: insulin-resistant GDM (N = 34, 51% of GDM) (red triangles), insulin-deficient GDM (N = 20, 30% of GDM) (blue circles), and mixed GDM (N = 12, 18% of GDM) (gold plus signs). One participant could not be classified because she had neither excess insulin resistance nor evidence of insulin deficiency (N = 1, 1.5% of GDM) (black circle).

Table 2—Summary of selected characteristics by GDM physiologic subtype (compared with women with normal glucose tolerance) (10,55)

	Insulin-deficient GDM	Insulin-resistant GDM	Mixed GDM	Normal glucose tolerance
Insulin sensitivity	↔	↓↓	↓	Reference
Insulin secretion	↓↓	↑	↓	Reference
Disposition index	↓	↓	↓	Reference
Fasting glucose	↔	↑	↑	Reference
Postload glucose	↑	↑	↑	Reference
BMI	↔	↑	↔	Reference
Triglycerides	↔	↑	↔	Reference
Adiponectin	↔	↓	↔	Reference
Leptin	↔	↑	↔	Reference
Infant birth weight	↔	↑	↔	Reference

Modified from the online supplement of Powe et al. (10).

knowledge, no study has examined postdiagnosis glycemic control in women with different physiologic subtypes of GDM, but in both Gen3G and Benhalima et al., there was no difference in the portion of women with each type of GDM requiring insulin (10,56). Finally, it is possible that differences among the subtypes in placental function or fetal characteristics explain the differences in physiology and perinatal risk observed. Our recent study of placental epigenetics suggests that DNA methylation changes related to imprinted genes in the placenta causally influence maternal physiology (64). In future studies, examining each physiologic subtype separately may provide greater insight into the pathophysiologic mechanisms that lead to GDM and associated perinatal complications.

It remains to be seen whether GDM management should differ between GDM physiologic subtypes; however, a past study provides the scientific premise for this hypothesis: in a seminal trial of treatment for mild GDM, investigators found that the effects of glucose-lowering treatment on birth weight and neonatal fat mass differed among women according to maternal BMI (65). There are at least two ongoing clinical trials testing physiologic subtype–specific approaches to GDM management using diet (NCT04187521) or pharmacologic agents (NCT03029702).

Maternal Genotype-Based Approaches to Heterogeneity in GDM

We have begun preliminary efforts to determine whether maternal genetics could provide insight into heterogeneity among women with GDM. In the Gen3G cohort, we examined polygenic scores for T2D, fasting insulin, and insulin secretion among women with different physiologic subtypes of GDM (66). When compared with pregnant women with normal glucose tolerance, women with insulin-resistant GDM had a higher polygenic score for increased fasting insulin (mean [SD]: 21.5 [2.0] vs. 20.2 [2.7], $P = 0.01$), consistent with their phenotype. Women with insulin-deficient GDM appeared to carry a larger burden of genetic variants associated with reduced insulin
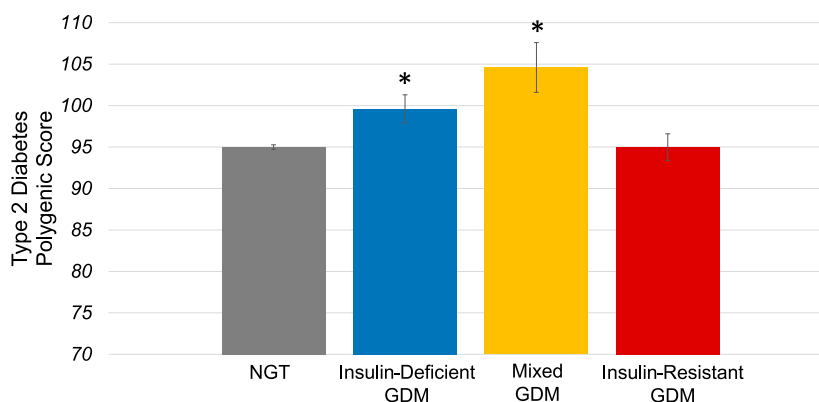
Figure 3—Differences in T2D-associated genetic variant burden across GDM physiologic subtypes (66). In Gen3G cohort participants with genetic information ($N = 501$), a polygenic score for T2D risk was constructed by aggregating the T2D risk–increasing alleles at 85 loci discovered in previous GWAS (53). Scores were compared across GDM physiologic subtypes (66). The T2D polygenic score was significantly higher in women with insulin-deficient GDM and mixed GDM. The graph depicts mean scores and SD in each group. *Indicates significantly different from women with normal glucose tolerance (NGT).

secretion, though this did not reach statistical significance (insulin secretion polygenic score 24.1 [2.0] vs. 22.4 [3.1] in normal glucose tolerance, $P = 0.10$). Women with GDM and mixed insulin resistance and deficiency had a larger burden of genetic variants associated with reduced insulin secretion (polygenic score 27.4 [4.1] vs. 22.4 [3.1], $P = 0.01$) compared with women with normal glucose tolerance. Notably, the women with insulin-resistant GDM, those at the greatest risk of perinatal complications, had no increased burden of T2D-associated genetic variants (polygenic score 95.0 [7.9] vs. 95.0 [6.1] in normal glucose tolerance, $P > 0.99$ [Fig. 3]). In contrast, both insulin-deficient GDM and mixed insulin-resistant and insulin-deficient GDM carried a greater burden of T2D-associated risk alleles compared with women with normal glucose tolerance (95.0 [6.1] in normal glucose tolerance vs. 99.6 [6.1], $P = 0.04$ in insulin deficiency and 104.6 [7.4], $P = 0.01$ in mixed GDM), despite no demonstrated increase in perinatal risk (Fig. 3).

In the Gen3G cohort, we have also applied the bNMF soft clustering methods used in Udler et al. to cluster genetic variants according to their relationship with physiologic traits measured in the late 2nd trimester of pregnancy (67). We described five variant-trait clusters that appear to represent different physiologic pathways that influence gestational glucose metabolism. Studies testing polygenic scores based on these clusters and those derived for T2D in Udler et al. for association with GDM are underway. However, both of these approaches rely on genetic variants identified from prior GWAS in nonpregnant individuals, most of whom had European ancestry. Until sample sizes in available pregnancy cohorts with genetic information grow substantially, our collective ability to classify women with GDM via genetic approaches will be limited by our ignorance around genetic variants that influence glycemic physiology and diabetes risk in pregnancy. In addition, continued lack of ethnic diversity in genetic studies will limit the generalizability of such approaches to racial and ethnic minority women who are most likely to benefit, given the higher prevalence of GDM in Asian, Native American, and Latina women (68–71).

Heterogeneity of Fetal Response to GDM
Among clinicians caring for women with diabetes in pregnancy it is well recognized that fetuses differ substantially in their response to maternal hyperglycemia, with some appearing to be much more sensitive to maternal glucose than others, developing overgrowth and neonatal hypoglycemia with lesser degrees of maternal hyperglycemia. While differences in maternal metabolic physiology (for example, lipid metabolism) could contribute to this phenomenon, it is likely that fetal characteristics play a role.

Many of effects of maternal hyperglycemia on the fetus are thought to be driven by fetal hyperinsulinemia, which is a result of maternal hyperglycemia. Studies of mothers and fetuses carrying autosomal dominant genetic variants in the pancreatic β-cell enzyme glucokinase (*GCK*), leading to maturity-onset diabetes of youth (MODY), prove that fetal genetics influencing insulin release can modulate the effects of maternal hyperglycemia on fetal growth (72–75). In *GCK* MODY, insulin secretion is regulated to a higher glycemic set point, causing mild lifelong hyperglycemia due to less insulin secretion for a given glucose level (76). In pregnant women with *GCK* MODY, the fetal genotype influences birth weight: fetuses who inherit the maternal genotype (and therefore are relatively hypoinsulinemic) are protected from maternal hyperglycemia-induced overgrowth (72–75). While *GCK* MODY is a rare disease, common fetal genetic variation also influences birth weight and may operate through similar mechanisms. A recent study in HAPO demonstrated that these common genetic determinants of birth weight (in aggregate) and maternal hyperglycemia have additive effects on infant birth weight (77). Some birth weight–associated variants overlap with those known to be associated with T2D, suggesting that they influence birth weight through fetal insulin physiology, similar to the variants that lead to *GCK* MODY (78).

With the recognition of the heterogeneity in the fetal response to maternal hyperglycemia, randomized trials conducted 15–25 years ago examined modification of glycemic targets or criteria for insulin initiation in GDM based on fetal growth parameters measured on ultrasound (79–81). At the time, the glycemic targets and thresholds for insulin initiation were higher than in current practice. Together, the results of these studies suggest that a fetal growth–based strategy for glycemic targets and insulin initiation has potential to improve fetal growth outcomes, with more infants born appropriate for gestational age birth weight as compared with glycemia only–based targets (79–82). Limitations of these studies include their small sample size and unclear translation to current clinical practice, as glycemic targets have changed. Still, these data raise the possibility that incorporating either genetic and/or phenotypic characteristics of fetuses into treatment algorithms will enable an effective precision medicine approach for GDM.

Conclusions and Future Directions
Like T2D, which shares common phenotypic characteristics and genetic architecture, there is strong evidence of clinical heterogeneity among women with GDM. Both phenotype- and genotype-based approaches have shown early success in parsing heterogeneity in T2D. We and others have applied similar approaches to describe heterogeneity in GDM. Phenotype-based subclassification of GDM has identified a group of women who are at higher risk for adverse perinatal outcomes on the basis of insulin resistance. Initial work in genotype-based approaches to heterogeneity in GDM has suggested that genetic data provides both information that overlaps with phenotypic data as well as distinct information pointing to underlying

disease mechanisms and informing future T2D risk. Ongoing studies will test the ability of novel subtype-based approaches to GDM management to deliver the promise of diabetes precision medicine to the obstetric population.

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