

Personalized Management of Hyperglycemia in Type 2 Diabetes

Reflections from a *Diabetes Care* Editors' Expert Forum

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In June 2012, 13 thought leaders convened in a *Diabetes Care* Editors' Expert Forum to discuss the concept of personalized medicine in the wake of a recently published American Diabetes Association/European Association for the Study of Diabetes position statement calling for a patient-centered approach to hyperglycemia management in type 2 diabetes. This article, an outgrowth of that forum, offers a clinical translation of the underlying issues that need to be considered for effectively personalizing diabetes care. The medical management of type 2 diabetes has become increasingly complex, and its complications remain a great burden to individual patients and the larger society. The burgeoning armamentarium of pharmacological agents for hyperglycemia management should aid clinicians in providing early treatment to delay or prevent these complications. However, trial evidence is limited for the optimal use of these agents, especially in dual or triple combinations. In the distant future, genotyping and testing for metabolomic markers may help us to better phenotype patients and predict their responses to antihyperglycemic drugs. For now, a personalized ("n of 1") approach in which drugs are tested in a trial-and-error manner in each patient may be the most practical strategy for achieving therapeutic targets. Patient-centered care and standardized algorithmic management are conflicting approaches, but they can be made more compatible by recognizing instances in which personalized A1C targets are warranted and clinical circumstances that may call for comanagement by primary care and specialty clinicians.

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In April 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) published a joint position statement titled "Management of Hyperglycemia in Type 2 Diabetes: A Patient-

Centered Approach" (1). It was an important update to earlier guidelines (2–8), providing a thorough examination of the ever-more-complex therapeutic options for glycemic management, the benefits and risks of tight glycemic control, the

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efficacy and safety evidence for new drug classes, and the data supporting withdrawals of or restrictions on other agents. Furthermore, it placed great emphasis on patient-centered and personalized care.

These recommendations captured the attention of the *Diabetes Care* editorial team. On the one hand, the recommendations call for a more personalized approach, which, in theory, should be liberating for all health care providers (HCPs) involved in diabetes care. On the other hand, their "less prescriptive" nature has been viewed as providing insufficient guidance to some HCPs who may feel overwhelmed when trying to match the nuances of differences among the increasing number of antihyperglycemic medications to the nuances of each patient's preferences and medical characteristics.

To explore these issues, we convened a *Diabetes Care* Editors' Expert Forum in June 2012. Thirteen thought leaders from around the world convened and discussed approaches to personalized medicine, the rationale behind personalization in diabetes care, the tools necessary to implement such a strategy, and the current perceptions of personalized medicine. This narrative provides our view and clinical translation of the underlying issues that need to be considered for personalizing care and offers suggestions to stimulate future research in this area. Table 1 summarizes the main points discussed below.

PRACTICAL APPROACHES TO PERSONALIZED MEDICINE

From intervention trials to personalized targets

There can be little more than semantic differences among the terms "personalized medicine," "patient-centered care," and "clinical judgment." Factors such as patients' preferences, life expectancy, disease duration, comorbid conditions, socioeconomic status, and cognitive abilities have long played a role in the selection of optimal therapeutic options and,

more recently, in the selection of therapeutic targets.

In 1998, the UK Prospective Diabetes Study (UKPDS) showed that treating patients with recently diagnosed type 2 diabetes reduced the risk of microvascular, but not macrovascular, complications (9). Of the three subsequent randomized controlled trials (RCTs) on glucose lowering and cardiovascular outcomes, two—ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) and VADT (Veterans Affairs Diabetes Trial)—showed no statistically significant reduction in cardiovascular outcomes, while the glycemic intervention of the third—ACCORD (Action to Control Cardiovascular Risk in Diabetes)—was

ended early because of increased mortality in participants randomized to intensive glycemic control (10–12). However, meta-analyses of the four intervention trials (UKPDS, ACCORD, ADVANCE, and VADT) have shown modest but statistically significant benefit of intensive glucose control on the risk for myocardial infarction, but not mortality (13).

Post hoc analyses seeking explanations for these results set the stage for today's new emphasis on personalized care. Suggestions that adverse effects of individual therapeutic agents or severe hypoglycemia were directly implicated in causing cardiovascular events were not supported by these analyses but cannot be ruled out because efforts to capture hypoglycemic events were probably inadequate, especially in individuals with hypoglycemia unawareness (13). However, individuals assigned to intensive therapy who failed to improve control to A1C levels <7.0% (<53 mmol/mol) in ACCORD fared poorly and had more severe hypoglycemia, and severe hypoglycemia was noted to be a risk marker for a wide range of medical conditions in ADVANCE (14,15). It was also suggested that individuals with long-standing type 2 diabetes, existing cardiovascular disease (CVD), and other comorbidities were unable to achieve cardiovascular benefit from better glucose lowering within the timeframe of these studies (16).

Accordingly, these trials and their subsequent analyses raised important questions about rigid, algorithm-based, "glucentric" approaches to therapy. One message, then, is that "one size does not fit all" for glucose targets, choice of therapy, or number of therapies used in combination. However, some questions pertinent to personalization remain unanswered. What were the characteristics of the small group of individuals in ACCORD who failed to respond to further glucose-lowering therapy but who contributed much of the excess case fatality (12)? Similarly, what can these studies teach us about patients who benefitted most from the interventions? Gaining insight into the pathophysiological, genetic, lifestyle, adherence, comorbidity, or other factors responsible for these disparate responses could improve our ability to effectively personalize therapy.

The 2012 ADA/EASD position statement still recommends an A1C goal of <7.0% (<53 mmol/mol) for most individuals with type 2 diabetes if it can

be achieved safely in low-risk individuals with early diabetes or a relatively long life expectancy; it suggests an acceptance of higher A1C targets for individuals with a history of severe hypoglycemia, limited life expectancy, long-standing diabetes, or advanced micro- and macrovascular complications (1). Prior guidelines from multiple organizations (3–8) included recommendations about setting personalized glycemic targets based on phenotype and empirically matching "the right drugs to the right patients," but without hard evidence to substantiate such an approach. Personalized treatment was articulated more vigorously in the new position statement (1).

The challenges of personalized care

Patient-centered personalized therapy, although appealing, may be difficult to implement without a good understanding of the ever-changing glucose-lowering armamentarium. β -Cell dysfunction is progressive in type 2 diabetes (9), and thus monotherapy, or even combinations of oral agents, is not likely to control hyperglycemia indefinitely (17), although the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial demonstrated sustained normoglycemia with basal insulin glargine plus metformin and near-normoglycemia even with standard therapy using metformin plus a sulfonylurea over a 6–7 year period in early type 2 diabetes (18). At this time, the processes of assessing β -cell function and providing reliable clinical decisions based on this factor are less than optimal. Furthermore, so-called evidence-based guidelines may be limited in their ability to be more prescriptive given the lack of clinical trial evidence from properly conducted long-term RCTs comparing the effects of various agents on clinically important outcomes. Clinical inertia is also a problem, and most clinicians do not alter their patients' glucose-lowering regimens until A1C is significantly elevated (19). Developing and implementing personalized care plans may be especially daunting for those HCPs whose practice extends beyond diabetes alone and who must address these issues in the context of limited time and resources.

The need for translational tools

The task now at hand is clear: We should develop and make available tools that will enable effective translation of existing guidelines on targets and therapeutic options into practical clinical applications.

Table 1—Summary of the main points from the Diabetes Care Editors' Expert Forum

- The complexity of management of type 2 diabetes is underappreciated.
- Its complications, once established, remain a largely intractable burden.
- The number of available antihyperglycemic agents has increased markedly during the past 2 decades, but trial evidence for their optimal use—especially in dual or triple combinations—is limited and unlikely to ever be complete.
- The availability of multiple pharmacological options should be instrumental to early, appropriate treatment to target, which is the only recognized strategy for the prevention of complications.
- In the more distant future, genotyping and testing for metabolomic markers may help to phenotype patients and predict their responses to antihyperglycemic drugs.
- At present, a personalized ("n of 1") approach may aid in achieving therapeutic targets.
- Patient-centered care and standardized, algorithmic management are conflicting approaches, but they can be made more compatible by recognizing instances in which personalized A1C targets are warranted and clinical circumstances that may call for primary care and specialty comanagement.
- Failure to achieve glycemic targets, failure to respond to therapy, recurrent hypoglycemia, drug intolerances/contraindications, the development of complications, hyperglycemia during hospitalization, pregnancy, and suspicion of unusual variants such as MODY, LADA, heavy proteinuria with short disease duration in the absence of other microvascular complications, or secondary diabetes all may serve as triggers for comanagement.

It is one thing to assess the efficacy of an intervention within the context of a structured clinical trial setting, but entirely different to evaluate that intervention in ordinary clinical practices with resource variations, variable patient adherence, and sociodemographic and cultural differences. Thus, the translation of results from RCTs to real-world situations is not an exact science. Until more hard evidence becomes available, clinicians need well-structured and user-friendly evidence summaries that outline safe and effective processes for therapeutic intensification, while still allowing for the personalization of care.

Although such an undertaking is beyond the scope of this discussion, we are providing a starting point that may guide the development of such tools to aid HCPs in personalizing both targets and therapeutic regimens. For target-setting, suggestions have been made in the past (20,21). Another possible starting place might be the decision-making scale developed by Ismail-Beigi et al. (22) and adapted for inclusion in the ADA/EASD position statement (1). That scale includes seven parameters to consider when determining glycemic targets. Expanding it or providing some means of rating each parameter for individual patients could help clinicians to better weigh factors such as life expectancy, duration of diabetes, risk from hypoglycemia, comorbidities, and availability of support systems. Such a tool could assist clinicians in choosing targets and help to involve patients in the decision-making process in an easily understood manner.

Tools are also needed to help HCPs in selecting appropriate agents and intensifying therapy. The ADA/EASD position statement leaves treatment-goal decisions to clinicians and patients (1). However, some believe that because of the vast and expanding array of available drugs, there should be a systematic way to prioritize the selection of drugs in relation to their efficacy, safety, and cost. It is most important to emphasize that the percentage of patients who show sufficient clinical response to any of these drugs varies widely. Nonadherence to treatment regimens may be as high as 50% in patients with chronic diseases such as diabetes (23), often because of the patients' lack of symptoms, negative emotions, and poor knowledge of their disease (24). Side effects are another cause of stopping or limiting treatment. Thus, patients must

be adequately monitored, especially after changes to their treatment regimen, to evaluate whether they have reached targets and to ensure that there are no major side effects or adherence issues. This information is crucial to make informed decisions regarding whether to continue, change, or add to the therapy regimen.

STATE OF THE ART FOR PERSONALIZING MEDICINE

Personalized medicine can be defined in many ways. A shared decision-making approach that takes patient preferences and values into account in developing a management plan is widely endorsed. Another definition involves identifying a particular set of phenotypic and genotypic markers that would define ideal and nonideal therapies for individuals based, to whatever extent possible, on evidence rather than on clinical impressions. Perhaps the most relevant question is whether current science is at a stage where specific patient characteristics—genetic, pathophysiological, or phenotypic—might effectively guide us in more general diabetes practice.

Contributions from genetics: a distant hope

The field of genetics is not yet ready to contribute in these broader areas. Despite recent identification of monogenic forms of diabetes for which specific treatments seem to give benefit (25), for more typical type 2 diabetes, genetic information does not contribute greatly in guiding treatment choices. Recently, pharmacogenetic analysis has begun providing insights, finding possible links, for example, to poor responses to metformin (26,27) and glucagon-like peptide-1 (GLP-1) receptor agonists (28–30). Such research holds promise for eventually helping to identify individuals who are likely to be classified as “responders” or “nonresponders” to specific agents.

Human genome sequencing also offers some hope, but again, in the distant future (31). Because the development of diabetes, patients' responses to available therapies, and the risks for complications are all multifactorial and probably involve numerous genes, the chances are small that specific mutations will turn out to be powerful markers of diabetes risk or of variable treatment responses. Even assuming a significant increase in pharmacogenetics research and decreases in the costs associated with genome sequencing, for the

foreseeable future these efforts will not significantly improve our ability to predict, prevent, or diagnose diabetes or illuminate definitive pathways for selecting drug therapies for specific individuals.

What can we learn from pathophysiology?

Insulin resistance in the liver and muscle and islet β -cell failure represent the core pathophysiological defects in type 2 diabetes (32,33). Insulin resistance can often be demonstrated long before the onset of β -cell failure, but as long as the β -cells secrete sufficient amounts of insulin to offset the insulin resistance, glucose tolerance remains normal (32–36). With time, however, there is progressive β -cell failure, which leads to the development of impaired glucose tolerance and/or impaired fasting glucose and eventually type 2 diabetes (32–36). As the plasma insulin response declines, insulin resistance in the liver becomes manifest as an overproduction of glucose by the liver and the development of fasting hyperglycemia, while insulin resistance in muscle results in diminished glucose uptake and postprandial hyperglycemia (32,33).

Although the relative contributions of β -cell failure (possibly more severe in Asian populations) and insulin resistance (more severe in Westernized societies with a high prevalence of obesity) may vary among different ethnic groups (37), virtually all adults with type 2 diabetes have some combination of the two. Thus, antihyperglycemic agents that improve β -cell function and enhance hepatic and muscle insulin sensitivity may have a more durable effect in reducing A1C (38–45).

The importance of other pathophysiological disturbances in the development of type 2 diabetes is well recognized (32,33). These disturbances include

- Adipocyte insulin resistance, which leads to increased lipolysis, increased plasma free fatty acids, and eventual β -cell failure and muscle and hepatic insulin resistance (46)
- Excess glucagon secretion by α -cells and enhanced hepatic sensitivity to glucagon, leading to increased basal hepatic glucose production and impaired suppression of hepatic glucose production after meals (47,48)
- Dysfunction related to incretin hormones (GLP-1 and glucose-dependent insulinotropic peptide) (49), which are

responsible for ~50% of the insulin secreted in response to meals

- Possible renal adaptive mechanisms to hyperglycemia, which result in enhanced glucose reuptake leading to decreased urinary glucose clearance and the maintenance of established hyperglycemia (50)
- Central nervous system insensitivity to the anorectic effect of insulin and multiple neurotransmitter synaptic abnormalities resulting in excessive energy intake and obesity (33)

No single antihyperglycemic agent can correct all of these pathophysiological abnormalities. Thus, many patients may require multiple agents with different mechanisms of action to achieve their individualized A1C goal (33). Patients with type 2 diabetes who have a high initial A1C, in particular, may require two or more antihyperglycemic agents to achieve their A1C goal (1,4,7,8,33,51,52).

The precise choice of pharmacological agents to use remains a topic for debate, in part because of safety concerns involving several drug classes (53–55). But the basic point remains: To achieve durability of glycemic control, optimal regimens will likely need to address both insulin resistance and β -cell failure.

Does phenotype allow for personalized treatment?

The main characteristics that might influence approaches to treatment can be divided into two categories: patient features and disease features. Among the patient features are race/ethnicity, sex, age of onset or diagnosis, duration of diabetes, body weight, frailty/comorbidities, complications, propensity for side effects/drug tolerance, personality and aspirations, and psychosocial-economic context. Among the disease features are the balance between insulin deficiency and insulin insensitivity, fasting versus postprandial hyperglycemia, short versus long disease duration, and special circumstances such as maturity-onset diabetes of the young (MODY) or latent autoimmune diabetes in adulthood (LADA).

However, we are faced with a paucity of data on how patients with certain characteristics respond to specific therapies (56). We know that most glucose-lowering drugs for type 2 diabetes work in most patients. But we also know that there are nonresponders to any drug. Numerous post hoc studies have revealed some predictors of better responses, but

the data are inconclusive (57–60). Furthermore, those response differences tend to be small, and the strongest predictor remains baseline A1C, with the patients with higher A1C levels responding with greater reductions although not necessarily attaining target levels (58,61).

Indeed, the most fruitful phenotypic considerations for personalizing care today may be patients' propensity for side effects and tolerance of various medicines. There may be practical value to using a trial-and-error, or "n of 1," approach (62) based on the anticipation of a drug's efficacy (for example, "Pioglitazone will be highly effective in this very insulin-resistant patient"), a patient's need for certain added benefits ("A GLP-1 receptor agonist will help control hyperglycemia and may encourage weight loss in this obese patient"), and concerns about adverse events ("I will not prescribe a sulfonylurea for this elderly patient who lives alone and had a severe hypoglycemic episode a few years ago"). This is becoming standard clinical procedure for diabetes, just as it is for hypertension and numerous other chronic diseases.

The challenge is how to proceed in more complex situations. How, for example, would one select an appropriate pharmacological regimen for a 68-year-old man with diabetes of 14 years' duration who has coronary disease, obstructive sleep apnea, prostate cancer, and a history of possible pancreatitis; who is obese and has edema but no heart failure; who smokes and has a family history of bladder cancer; who has high fasting blood glucose and A1C levels; and who has some renal dysfunction and poorly controlled lipids? With so many competing comorbidities, what are this individual's targets and treatment options?

Table 2—Classes of antihyperglycemic agents

1. Insulins
2. Sulfonylureas
3. Metformin
4. α -Glucosidase inhibitors
5. Glinides
6. Pioglitazone
7. Pramlintide
8. GLP-1 receptor agonists
9. Dipeptidyl peptidase-4 inhibitors
10. Colesevelam
11. Bromocriptine
12. SGLT-2 inhibitors

Ultimately, clinicians must develop highly personalized care regimens, and, in the absence of other conclusive evidence, "n of 1" trials may prove to be the best approach, providing strong evidence of therapy effectiveness and safety at the individual level and incorporating shared decision making with patients.

ARE ADEQUATE THERAPEUTIC TOOLS AVAILABLE NOW FOR PERSONALIZED DIABETES CARE?

Multiple glucose-lowering medication classes: freedom or confusion?

We now have numerous classes of antihyperglycemic therapies (Table 2) and more are expected to be licensed. Does this extensive arsenal provide us with more flexibility in designing personalized diabetes regimens, or does it make the task more difficult by multiplying the options? For specialists, the answer is no doubt the former. But for many primary care providers who must simultaneously stay abreast of developments in numerous fields of medicine, the expanding array of choices may, at times, seem intimidating.

Recent meta-analyses have shown that there is not much difference among available therapies in glycemic control (e.g., A1C reduction and likelihood of achieving targets when adding an agent to metformin). However, when one considers other benefits, such as the risk of hypoglycemia and effects on body weight (63,64), there appears to be separation among the agents. In addition to these agents' relative glycemic efficacy and effects on body weight and hypoglycemia, HCPs immersed in diabetes care must balance the potential benefits of each agent against concerns that have been raised regarding possible associations between various agents and the risk of developing other diseases (65–67).

Difficulties in making benefit-risk judgments are further amplified by the fact that marketing may seek to create demand for drugs that is out of proportion to their efficacy. In addition, there remains a general lack of adequate comparative and exploratory controlled trials between the medications available, not to mention a lack of research into phenotype- and pathophysiology-based regimens.

Developing a straightforward algorithm that narrows the field of viable options will clearly require more evidence

than is currently available. Without such evidence, we can offer only opinion, albeit opinion based on an understanding of pathophysiology, epidemiology, pharmacodynamics, toxicology, and costs. Unfortunately, the studies needed to make evidence-based treatment decisions—those that involve comparisons among multiple agents and are adequately powered for important, long-term clinical outcomes—have, for the most part, not been performed.

The upcoming GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) trial will address some of these points (68). In addition, studies on how best to combine the various agents, as well as the optimal timing (early combination therapy vs. the traditional step-wise approach), are urgently needed.

Furthermore, even the most carefully considered set of guidelines is based on averages—average A1C-lowering effect, average efficacy, average risk of adverse effects—without adequate consideration of the confidence intervals around those averages. Averages fail to identify subpopulations that respond better and have better tolerance to specific agents, and without these data, evidence-based personalized advice cannot be provided. For now, all HCPs, whether in specialty or primary care settings, should test the efficacy and weigh the safety risks of any given drug in each patient, ideally trying options over a period of months to see how well they work at the individual level.

How will new and emerging therapies enhance our ability to personalize care?

To complicate future decision making, there are many new therapies in the research and development pipeline, including newer and longer-acting injectable incretin-based drugs, newer basal insulins, oral sodium-glucose cotransporter-2 (SGLT-2) inhibitors, agents targeting the various peroxisome proliferator-activated receptors, and free fatty acid receptor agonists.

It is hoped that pharmaceutical companies developing new glucose-lowering agents will focus on providing some added value beyond what is already available by addressing unmet clinical needs such as the effects leading to a reduction in CVD risk factors and meaningful cardiovascular and other outcomes. Arguably, we lack what we seek most in a diabetes treatment: definitive demonstration

that an agent can safely lower A1C in a sustained and durable manner by definitively modifying disease progression, does so with minimal side effects (e.g., hypoglycemia), favorably improves CVD risk factors (e.g., weight, lipids, and blood pressure), and reduces cardiovascular and other morbidity and mortality.

As new drugs continue to be developed and submitted to regulatory agencies for approval, we should also consider the limitations of RCTs for informing a personalized approach to diabetes care (69,70). RCTs, at least as currently carried out, focus on selected populations and have restricted inclusion and exclusion criteria. They are generally of short duration, making it impossible to assess durability. They do not test individual responder rates and are not designed to identify responders who have a low safety risk. These trials are conducted in artificial environments, which pose problems for realistically measuring adherence. Finally, RCTs are not powered to assess subpopulations prospectively. Thus, efforts to personalize therapy are hindered by our reliance on trials that may be neither generalizable to the larger population nor individualized to specific patients.

Moving forward, there may be other informative data from these trials, not from the average results, but rather from outliers—the results from subjects who respond very well or not at all.

REGIONAL PERSPECTIVES ON PERSONALIZED MEDICINE

—The questions, concerns, and practical considerations discussed here pose difficult challenges for diabetes HCPs throughout the world. Because diabetes is a burgeoning pandemic, it behooves us to understand the issues from an international perspective.

The viewpoint that personalized diabetes care may be too complex to be implemented in many care settings is common in Europe, as it is in the United States and elsewhere. In Italy, for example, the Renal Insufficiency And Cardiovascular Events (RIACE) multicenter study, which included 15,773 patients with type 2 diabetes attending hospital-based diabetes clinics, showed that 40% of patients were taking metformin, 15% were managed through diet only, 24% were on insulin, 18% were taking sulfonylureas, and 3% were taking thiazolidinediones (71). Strikingly, this pattern did not change with age or with renal function,

duration of disease, or other stratifying criteria.

The story is much the same in other parts of the world, although patient characteristics differ. In China, key issues include rapid nutritional and lifestyle transitions, large patient populations, young age of onset, and heterogeneous phenotypes characterized by β -cell dysfunction, insulin resistance, and visceral obesity (72,73). High rates of kidney disease and diabetes-related cancer complicate diabetes care (72,74,75). All of these problems are compounded by a relative scarcity of research, low levels of awareness, an insufficient number of trained HCPs, and less-organized health care and financing systems.

Given the large population and finite resources, one may argue for using risk algorithms and biomarkers, including genetic variants, to identify high-risk subjects for early or intensified intervention, although the cost-effectiveness of such an approach will need to be formally tested. As elsewhere, patients with insulin-resistant features such as fatty liver, high triglycerides, and low HDL cholesterol may benefit from initial treatment with metformin, pioglitazone, and GLP-1 receptor agonists, whereas patients who are lean and face a long disease duration may benefit from dipeptidyl peptidase-4 (DPP-4) inhibitors or sulfonylureas with the early use of insulin. Other drugs such as α -glucosidase inhibitors and SGLT-2 inhibitors may help to lower A1C with a low risk of hypoglycemia and weight gain.

Although these phenotype-based therapies have a theoretical basis, clinical practice studies are needed to confirm their cost-effectiveness. There is also a need to empower medical and nonmedical personnel (diabetes educators) in clinics to collect patient data on demographics, risk factors, complications, social habits, emotional needs, self-care behaviors, compliance, expectations, and values to enable HCPs to personalize treatment goals, self-management strategies, and therapy regimens (76). These personnel should monitor patients' adherence to treatment, as well as their achievement of treatment goals.

In the United States, attempts to implement a concept as expansive as personalized care quickly run up against two opposing traditions that permeate not only the field of medicine, but indeed the entire U.S. culture. The first, rooted in American industrialism, is standardization, exemplified by the processes of production

line efficiency and continuous quality improvement. One recognizes this tradition in the vision of industrialist Henry J. Kaiser, who founded the prototype non-profit health system Kaiser Permanente (77). The second tradition, embodied by the image of artist Norman Rockwell's humble country doctor, is personalization. This is apparent in the teachings of Dr. Francis W. Peabody, whose seminal dissertation on patient care concluded, "The secret of care of the patient is caring for the patient," (78) and in the work of Dr. Elliott P. Joslin, who wrote that "... unless the physician takes care, he will fall into schematic ways and forget that it is the patient who comes for treatment and not the diabetes. Each is a case unto itself" (79).

Recent guidelines for diabetes care in the United States have fallen somewhere along a continuum between these traditions. The ADA Standards of Care (80) have sought to straddle the line, whereas the algorithm-based 2009 ADA/EASD consensus statement (2) leaned more toward standardization, and the 2012 ADA/EASD position statement (1) evolved more toward personalized care.

ENHANCING PERSONALIZED CARE THROUGH COMANAGEMENT—Research has yielded strong evidence in favor of fairly standardized treatment goals and an algorithmic initial therapy pathway involving lifestyle modification, metformin, and the eventual addition of other oral agents

(sulfonylureas and basal insulin, in most cases). This approach allows many newly diagnosed patients to attain a reasonable blood glucose range and to maintain it for some period of time.

However, there will always be patients for whom the standard A1C target is not appropriate (Fig. 1). Likewise, patients' clinical circumstances often become more complicated over time, at which point the core treatment algorithm must give way to a more personalized approach. In such situations, the ideal course of action would be a patient-centered comanagement approach involving primary and specialty care providers as well as diabetes educators, dietitians, psychologists, and other HCPs as warranted by individual patient needs. Figure 2 depicts such an approach, which could be invoked by specific triggers such as failure to respond to treatment (14,81), failure to attain A1C targets, drug intolerances or contraindications, severe hypoglycemia, hyperglycemia during hospitalization, pregnancy, suspicion of unusual variants such as LADA, MODY, or secondary diabetes, heavy proteinuria with short disease duration in the absence of other microvascular complications, or other complicating circumstances.

Regardless of the final form such a process takes, it seems clear that personalizing diabetes care will require improved cooperation and comanagement of patients among HCPs in various disciplines. In such a paradigm, algorithmic care would

be both a useful starting place for most patients with type 2 diabetes and a framework on which to build more personalized therapy as needed.

CONCLUSIONS—Publication of the latest ADA/EASD position statement on type 2 diabetes management has generated strong interest in the concept of a personalized medical approach for individuals with diabetes (1). However, there are a multitude of pharmacological antihyperglycemic therapies now available, often with incomplete evidence concerning their long-term efficacy, effectiveness, tolerability, and safety. Accordingly, questions remain regarding the best ways to implement the recommendations of the position statement in the care of patients.

Emerging research in genetics, pathophysiology, metabolomics, and human behavior, as well as longer-term, randomized comparative trials could eventually yield new information to inform the personalization of care. In the meantime, we must develop tools to translate existing guidelines into practical clinical applications, and, more importantly, to develop processes that encourage the organized comanagement of patients by primary care providers, specialists, educators, dietitians, and other diabetes HCPs as patients' unique needs and risks require. Another consideration is how well the tools we develop can be implemented around the globe given the differences in pathophysiology among ethnic

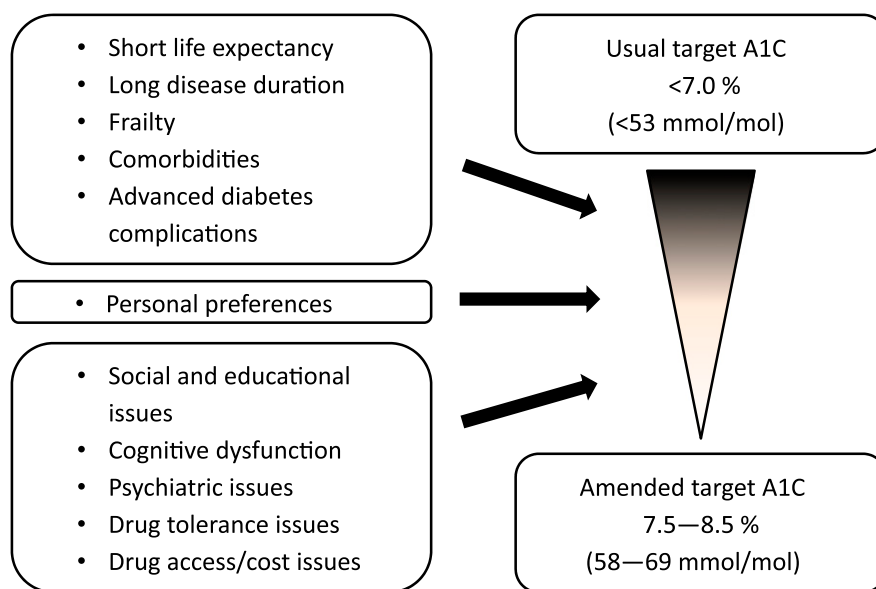


Figure 1—Personalizing A1C targets for individuals with type 2 diabetes.

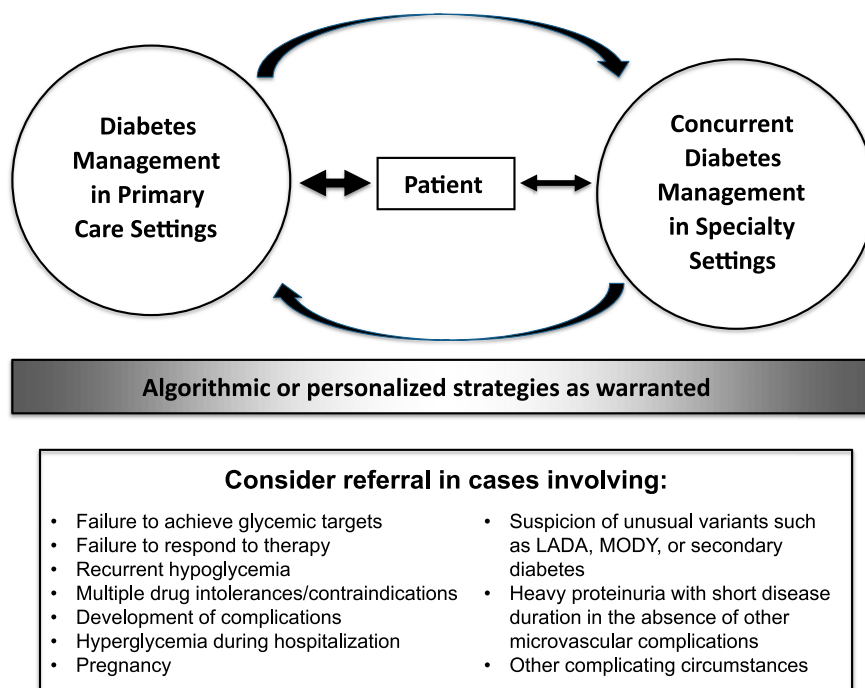


Figure 2—A comanagement approach to personalized therapy for type 2 diabetes. The majority of patient care occurs in primary care settings with concurrent comanagement in specialty settings as warranted for individual patients. In such a model, the patient remains at the center of care, comanaging HCPs all provide algorithmic or personalized care as warranted, and communication occurs among all parties.

groups, country-specific resources and medical care infrastructure, training level of providers, and knowledge of patients.

We hope these reflections have provided a broad overview of the evidence deficits and procedural challenges that will need to be overcome to ensure success in our efforts to implement effective, personalized therapy regimens for patients with type 2 diabetes.

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