Precision Medicine, Diabetes, and the U.S. Food and Drug Administration

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Diabetes Care 2016;39:1874–1878 | DOI: 10.2337/dc16-1762

The U.S. Food and Drug Administration (FDA) has long sought to achieve the broader use of personalized medicine, which is better targeting of FDA-approved therapies through incorporating precise knowledge of a patient's underlying condition to therapies optimally chosen to match those needs. While some strides have been made in precision medicine—particularly in oncology and rare genetic diseases—most of the standard general medicine indications have yet to realize the benefits of precision-guided therapies. This includes those for diabetes mellitus (DM), both type 1 and type 2. Although the scientific and regulatory considerations needed to move to a more "precise" future of DM prevention and treatment differ between the two disease subsets, scientific advances in both must occur before the FDA can incorporate precision medicine into its oversight of DM drug development and approval. This article provides an overview of the regulatory expectations and challenges in realizing a future where the therapeutics for DM are informed by precise knowledge of a patient's genetics and specific phenotype.

The U.S. Food and Drug Administration (FDA) has long sought to promote the widespread adoption of personalized medicine, which the immediate past commissioner of the FDA characterized as "the tailoring of medical treatment to the individual characteristics, needs and preferences of each patient" (1). This definition certainly reflects the best goals for rational therapeutics but in actuality represents a concept broader than "precision medicine," as the FDA's definition also includes considering information such as individual patient preferences and social situation in optimally meeting a specific patient's therapeutic needs. Precision medicine is rather a narrower concept, though one encompassed by personalized medicine, being better captured by the National Institutes of Health definition: "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle" (2). The National Institutes of Health vision of precision medicine incorporates information from genomics/genetics and systems biology (and other ". . .omics") coupled with effective analyses of large data sets to more precisely segment diseases and patient population. Therefore, the goal of precision medicine is to inform specific targeted therapeutics through the precise use of integrated, complex scientific information in each patient.

In this article, the promise of precision medicine as it relates to diabetes mellitus (DM) is considered from the regulatory perspective. As such, the discussion focuses on DM itself as a primary disease state rather than the protean secondary complications of DM, as that becomes a much more complex and lengthy undertaking. Nonetheless, while significant advances have been made in the understanding of the pathogenesis and mechanisms of both type 1 (T1DM) and type 2 diabetes (T2DM), to date these advances have not yet translated into preventive or

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Received 15 August 2016 and accepted 23 August 2016.

See accompanying articles, pp. 1854, 1858, 1870, 1879, 1889, 1896, 1902, 1909, and 1915.

treatment paradigms that incorporate precisely targeted interventions in either of the disease subsets. The discussion of the regulatory consideration regarding precision medicine as it relates to the prevention and/or treatment of DM is therefore necessarily forward looking. In keeping with the differences between T1DM and T2DM, these will be separately addressed, as these differences inform how precision medicine may be relevant in the development and regulatory approval of targeted interventions.

T1DM

The mainstay of treatment for fully established T1DM is now, and likely will remain for the foreseeable future, insulin therapy. Personalized approaches to the dosing of insulins have long been an important part of effectively treating T1DM patients. Achieving reasonable glycemic control while avoiding excessive hypoglycemic episodes necessitates a thorough consideration of a patient's pharmacodynamic response to insulin, taking into account their overall health status, their body habitus, the level of pretherapy glycemic control, diet, and their expected levels of exercise/exertion and daily routines. Significant therapeutic advances have taken place for control of blood glucose in T1DM in recent years, as novel insulins and insulin analogs with differing pharmacokinetics and pharmacodynamics have been introduced, from ultrashort-acting to long-acting basal agents allowing for better tailoring of daily insulin regimens. These advances, however important, do not meet the definition of precision medicine, as they are broadly applicable to the entirety of T1DM patients, with the tailoring of choices of agents and doses/schedules based on clinical and lifestyle considerations, not underlying mechanisms of disease pathology or genetics. Since the final common pathway to T1DM is loss of pancreatic β-cell function with resultant failure of endocrine function, insulin repletion is likely to remain the intervention of choice without much relevance from precision medicine approaches.

Precision medicine will, however, likely impact the development of preventatives or early, ameliorating treatments aimed at preserving β-cell function. Important strides have taken place in identifying genetic predictors for the propensity to develop T1DM. Almost 50% of the risk of T1DM is genetic, with one-half of the risk residing in the HLA region on chromosome 6 (e.g., HLA DR/DQ) (3) and the remaining genetic risk residing in over 40 non-HLA loci (4). While important, the positive predictive value of genetics is dependent on the prevalence of disease, which for T1DM is relatively low—2.0 per 1,000 in non-Hispanic whites and even lower in other populations (5). However, when paired with an individual's family history of T1DM and the presence of certain biomarkers of early islet disease (i.e., one or more subtypes of anti–islet cell autoantibodies or other autoantibodies to insulin [AIAAs], glutamic acid decarboxylase, and/or zinc transporter ZnT8), the risk for proximate development of T1DM rises substantially. Understanding the interplay of genetics with these autoantibodies in predicting the risk of T1DM has led to a proposal to define a new class of patients, those with "presymptomatic T1DM." This classification schema, endorsed by JDRF, the Endocrine Society, and the American Diabetes Association (developed with support from the Helmsley Charitable Trust), is intended to inform the development of preventive and/or ameliorative strategies (6). Although the FDA and other regulatory bodies are likely aware of such proposals, to date no official adoption of this proposed staging has been achieved with any major regulatory body. Nonetheless, the FDA has itself long accepted the need for effective approaches to forestall the development of frank T1DM (7). In fact, the FDA has provided general development guidance on the subject as a part of its 2008 draft guidance titled *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (8). Although it significantly predates the proposed staging outlined above, the FDA draft guidance refers to assessment of the presence of AIAAs, as well as the desirability of genotypic identification of individuals at significant risk, for the purposes of designing and conducting T1DM prevention trials.

In considering "preventive" strategies in T1DM, two distinctions need to be considered. The first might be referred to as true primary prevention aimed at genetically susceptible but still unaffected individuals (i.e., prior to any disease onset including pathological damage to the exocrine pancreas). The second can be called secondary prevention or amelioration and incorporates interventions once AIAAs have already developed. With the latter, individuals likely have some level of islet damage by the time they are identified with multiple predictive autoantibodies, even if they do not show clinical evidence of dysglycemia (9).

The challenge for developing precision medicine–based strategies for prevention of T1DM (e.g., a preventive vaccine) prior to any disease state is that many people who carry the most predictive, identified genetic markers for the development of T1DM (HLA-DRB1 and HLA-DBQ1) do not go on to develop the disease. While genetics are important in T1DM, the positive predictive value of a genetic test depends in part on the frequency of disease, which for T1DM is low in Caucasians (approximately 4 per 1,000) and even lower in non-Caucasians. Without the subsequent development of additional predictive biomarkers that can readily identify subjects at very high risk prior to any disease, diabetes researchers are left with two quandaries that impact regulatory oversight of development and approval. The first is that developing large-scale preventive interventions, including vaccines, entails exposing a large number of individuals to an experimental intervention. However, most of these exposed individuals will never develop the disease even though they carry the genetic markers and may have a relevant family history. As in any prevention trial, those individuals who would never develop disease are exposed to risks from the intervention without individual benefit, and currently for T1DM there is no way to refine our prediction for who might be in that category. Further complicating this consideration is that any such early prevention strategy will likely need to be targeted at children, raising the general ethical hurdles in pediatric research regarding unknown risks, unproven efficacy (even accepting the serious nature of the disease—the FDA's diabetes guidance [8] cites its regulation 21 CFR 56.111(a)(1)(i) in making this point), and infeasibility of direct patient informed consent. From a regulatory perspective, short of new science allowing for a much better refinement of the target population, the safety and tolerability of a primary prevention approach

in T1DM will be paramount and an overarching consideration. Regulators will have little tolerance for experimental prevention approaches that carry anything but the smallest of potential or known risks, given the predictive nature of the susceptibility biomarkers/genetics to date. The second quandary is that conducting prevention trials in large populations where the risk of disease in the enrolled population is not high requires very large studies, likely event-driven in design, to obtain the necessary power to show efficacy. Further complexities of such trials include how to feasibly screen a population for genetic characteristics, given that these genetic markers are not a part of routine clinical care. Given these challenges reflecting the current state of the art, producing a primary prevention intervention for T1DM necessitates advances in precision medicine that better refine the true "at-risk" population and/or novel intervention strategies that are highly safe and broadly applicable (or quite possibly both).

More promising in the near term are T1DM prevention strategies that are aimed at secondary or ameliorative prevention, i.e., interventions targeting a very high-risk population (those with first-degree relatives, predisposing HLA genotypes, and one or more AIAAs or other predictive autoantibodies) whose disease state is yet subclinical. These approaches entail developing interventions aimed at stage 1 prediabetes (patients without evident dysglycemia) and/or stage 2 prediabetes (patients with some level of dysglycemia) with the intent of preventing the development of frank T1DM or at least to meaningfully delay its development. Because the distinguishing characteristics of these patients include having islet autoantibodies, intervention strategies are likely to involve addressing the immune derangements themselves with a goal of halting further islet cell destruction while preserving residual endocrine function in terms of insulin response as well as glucagon counterregulatory function. A precision medicine refinement to such an approach would be to define whether certain attributes of the at-risk population predict a higher responsiveness to a particular immune-targeted intervention. For instance, it is possible that certain patients might respond better to an immunosuppressive agent to achieve these goals versus others who might respond better to an oral insulin desensitization strategy. These are speculative examples, and clearly more specific information on the factors that incite and sustain the AIAAs is needed before this kind of refinement to secondary preventive strategies could be entertained. In any case, the regulatory acceptance of risk in the situation of stage 2 prediabetes will be higher than for primary prevention. With that said, since currently available immunomodulatory agents carry significant known risks, the acceptance of such approaches by regulators remains to be seen.

From a regulatory standpoint, end points that the FDA would consider informative for the evaluation of efficacy with secondary prevention strategies are mentioned in their draft guidance (8) and include preservation of C-peptide levels (fasting and stimulated), maintenance of euglycemia (achieving or maintaining normal fasting and postprandial glucose levels; HbA_{1c}), and/or the clinical need for instituting insulin therapy. It could be argued that early "proof-of-concept" might be provided by assessments of a strategy's impact on more proximate markers of efficacy, such as diminishing or abolishing AIAAs; however, these autoantibodies are not fully predictive biomarkers, so their acceptance as primary end points for demonstrating "substantial evidence of effectiveness" by the FDA (or other regulators) is unlikely. Some information to inform choices of immunomodulators could potentially be gleaned by the analysis of large databases for "real world evidence," another aspect of precision medicine. For instance, examination of electronic health records for patients who are otherwise identified as high risk for T1DM and are on immunomodulatory therapeutics for other reasons (e.g., at-risk individuals who are receiving immunosuppressive therapy for previous nonpancreatic organ transplantation) could provide some supportive evidence to undergird the choice of a specific preventive approach, were these data to show a protective association. However, identifying such "high-risk" patients itself could prove challenging at the current time, given the limitations of current electronic health records (such as infrequently containing genomic information). A summary of the regulatory considerations for precision medicine applied to T1DM are shown in Table 1.

T2DM

In contrast to that for T1DM, the near-term application of precision medicine

Table 1—Regulatory considerations for advancing precision medicine in T1DM

Stage of Disease	Scientific Gap	Implications
Primary Prevention	Identifying very high-risk individuals beyond current genetics Identifying effective preventive interventions with sufficient safety to study broadly	With low disease prevalence, feasible prevention trials would benefit from precision medicine–guided enrichment (and would also inform targeted preventive use clinically) Broad vaccination programs require interventions that are highly protective and very safe/well tolerated
Secondary Prevention	Practical means to identify individuals with subclinical disease Full understanding of the immune mediators and propagators of β-cell damage	Immune-based interventions carry safety/toxicity risks requiring targeting of use both in clinical trials and subsequent clinical deployment Better understanding of the inciting and sustaining immune mechanisms would allow for better targeting of intervention vs. broad immunosuppressive approaches
Treatment	No apparent "precision" considerations in choice of insulin therapy/approach	Insulin therapy likely to remain more "personalized" than "precise," absent new science

for T2DM is more likely to consist of optimizing therapies for declared disease rather than prevention. Clearly, for patients at risk for T2DM (e.g., those with elevated BMIs, family histories, etc.), prevention strategies related to diet and exercise are already advisable and effective when adhered to. From a regulatory perspective, such nonpharmacological approaches are preferable as they do not entail pharmacologically imposed risks. The FDA reflects this in its labeling of medications for T2DM, with all T2DM agents containing the following wording in their labels: "[product X] is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." This is an implicit endorsement by the FDA of diet and exercise as the first means of preventing and managing T2DM.

While there is a large and diverse array of agents approved for T2DM, current guidelines make recommendations based on general disease characteristics of patients, rather than genetics of the disease or pharmacologic response. For instance, the latest American Diabetes Association guidelines on pharmacological treatment of T2DM refer to "a patient-centered approach" based on level of disease, patient preferences, and economic considerations (10). Although they are important and informative, existing guidelines do not incorporate what could be considered to be information relevant to precision medicine, such as genotyping or incorporation of specific biomarkers. This lack of incorporation of precision medicine into guidelines reflects the scientific reality that there is a paucity of data to undergird approaches to matching specific therapeutic choice to an individual's underlying pathophysiological characteristics. While T2DM exhibits greater heritability than T1DM, the extent of genetic risk known to account for T2DM risk (~10%) is much less than for T1DM (~90%), with practically no overlap in the identified genes between the two. Further, data that links certain genotypes in T2DM to therapeutic response are neither so strongly predictive nor sufficiently mature (11) as to provide a basis for regulators to include them in product labeling, let alone for these associations to inform guidelines. Despite the large number of choices in T2DM therapeutics with differing mechanisms of action, there remains very little "precise" information to move the choice of agents beyond clinical judgement. A sobering reminder of this is that the only current inclusion of genetic information in FDA-approved labeling for any T2DM medication is related to pharmacogenomics—specifically, the need to consider G6PD status of patients given certain sulfonylureas (12). A review of the current FDA listing shows that T2DM drug labels account for only 4 of the current 164 drug labels that contain any pharmacogenomics information. There remains a great need to further develop the scientific understanding of pharmacological interventions in T2DM to inform the better targeting of therapies to specific patients in order to enhance the likelihood of effectiveness, to minimize risks, or both.

With regard to prevention strategies in T2DM, the role for early use of hypoglycemic treatments prior to the frank development of T2DM remains a matter of some regulatory controversy. While there have been clinical trials that have demonstrated success in preventing patients with prediabetes from converting to frank T2DM with hypolglycemic drugs (13), the FDA has not approved any drugs for this use (irrespective of precision medicine). A primary reason for this is that, per its guidance, the FDA remains concerned that the diagnosis of T2DM is based on a biochemical definition (e.g., HbA_{1c} ≥6.5%) and that any drug that durably lowers blood glucose will, by definition, impact the likelihood of meeting that biochemically defined threshold of disease. In the FDA's view, simply forestalling meeting the definition of T2DM may have no salutary effect on the patient or their underlying pathophysiology and/or secondary complications (8). This also partly reflects a regulatory challenge with HbA_{1c} itself as a primary end point for DM medications. HbA_{1c} is used widely clinically to guide therapy as it integrates glucose control over time. It has face validity to practitioners as an assessment of the clinical status of a T2DM patient and in that regard can be considered a "direct" regulatory end point for approval purposes. However, beyond ameliorating any signs and symptoms of poor glycemic control (e.g., polyuria, polydipsia, or impaired eyesight), an aim of therapy in T2DM is to forestall the development of long-term complications, as elevated levels of HbA_{1c} have been linked to macrovascular and microvascular complications. In that regard, HbA_{1c} also serves as a surrogate end point, albeit one under considerable scrutiny and regulatory controversy (14). In treating prediabetes, the use of HbA_{1c} is even more clearly a surrogate end point, and the FDA insists on a demonstration of a lasting effect on glycemic control beyond treatment and/or a demonstrated effect on morbidity/mortality in this setting, since all therapeutics have risks (known and unknown). An impact on secondary complications has been challenging to show in the setting of frank T2DM. Such a demonstration is even more daunting in the setting of treating subjects at risk for T2DM. The development of predictive biomarkers of future secondary complications, for example, would be invaluable in informing therapeutic development of preventives and for informing optimal therapeutics once disease develops. Perhaps even more so than preventive

Table 2—Regulatory considerations for advancing precision medicine in T2DM

Stage of Disease	Scientific Gap	Implications
Prevention	Identification of specific mechanisms leading to disease (beyond clinical risks of obesity, diet, sedentary lifestyle)	Prevention likely to remain diet and exercise in at-risk individuals particularly showing early signs of dysglycemia ± nontargeted use of hypoglycemic agents
Treatment	Lack of data to inform matching of specific underlying disease characteristics in a given patient to optimal therapeutic approach Predictive biomarkers for secondary complications (micro/macrovascular)	Therapy will remain guided by expert guidelines and empiric treatment Would allow for tailoring of therapies not just to achieve a glycemic goal but to more precisely mitigate risks of long-term complications

strategies in T1DM, precision medicine approaches to prevention of T2DM will necessitate a large set of scientific advances to achieve tangible clinical advances and therefore impart regulatory ramifications. A summary of the regulatory considerations for precision medicine applied to T2DM are shown in Table 2.

CONCLUSIONS

While the scientific underpinnings necessary to advance precision medicine in diabetes are robust and exciting, drug regulation by the FDA and other agencies requires both maturity of evidence and demonstrable results to inform that regulation. Though there is much promise in incorporating precision medicine into the prevention and therapy of both T1DM and T2DM, the current realities are that it is still a hope for the future and much more basic research informing clinical and developmental science will be required to realize that hope. Regulators are committed to helping advance precision medicine but also require strong science and a robust evidence base to put it into regulatory practice.

Acknowledgments. The author would like to thank the reviewers for helpful advice and insights.
Duality of Interest. R.J.M. is a past senior leader at the FDA and participated in the initial development of the FDA draft guidance referred to in this article. R.J.M. has equity interest in Merck (through his retirement accounts), Johnson & Johnson, and Pfizer and sits on the Board of Directors of Cardiome Pharma. R.J.M. has been a regulatory and drug development consultant through his university with a number of relevant pharmaceutical companies (companies involved in diabetes drug research, but the role of R.J.M. was not necessarily related to diabetes drug development) including Merck, Johnson & Johnson, AstraZeneca, Intarcia, and EMD Serono. No other potential conflicts of interest relevant to this article were reported.

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