A Simple Model for Predicting Two-Year Risk of Diabetes Development in Individuals with Prediabetes

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ABSTRACT

Context: Given the dramatic rise in the incidence of type 2 diabetes mellitus (T2DM) in recent decades, identifying individuals at increased risk of T2DM and validating methods to reduce their risk of disease progression is important. With more than one-third of US adults having prediabetes, a more precise stratification of absolute risk of T2DM incidence would help in prioritizing prevention efforts.

Objective: To develop a simple and clinically useful schema to stratify short-term (2-year) absolute risk of T2DM.

Design: Observational study of more than 77,000 adult members (age 18-75 years) from 3 Regions of the Kaiser Foundation Health Plan with prediabetes (hemoglobin A_{1C} [HbA_{1C}] = 5.7%-6.4%).

Main Outcome Measures: The 2-year probability for development of diabetes as a function of baseline HbA_{1C} and body mass index (BMI).

Results: The 2-year risk of diabetes diagnosis varied widely by HbA_{1C} and BMI. A small subset (5.2%) had a very high risk of T2DM developing within 2 years. Another 13.3% had a moderate 2-year risk of T2DM, whereas most (81.5%) of the population was at much lower risk. Thus, most Kaiser Foundation Health Plan members with prediabetes have only modest risk of progression to T2DM within 2 years.

Conclusion: Using HbA_{1C} and BMI, we created a simple stratification scheme to more precisely estimate risk of T2DM incidence. This will enable more efficient assignment of prevention interventions and clinical and laboratory follow-up to the small subset at highest risk, while minimizing the potentially negative effects of overdiagnosis among the majority with prediabetes who are not at high short-term risk of T2DM.

INTRODUCTION

In recent decades we have seen a dramatic increase in worldwide incidence and prevalence of type 2 diabetes mellitus (T2DM), particularly in low- and middle-income countries.[1] Diabetes currently affects 29 million people in the US—about 9% of the population—with a predicted increase to 30% by 2050,[2] although more recent data suggest that the growth in incidence has been slowing since 2009.[3] In 2010, diabetes was the seventh leading cause of death in the US, and in 2012 estimated diabetes costs in the US were $245 billion: $176 billion for direct medical costs and another $69 billion for indirect costs related to disability, work loss, and premature death.[4]

In response to these trends, much work has been conducted to identify individuals at increased risk of development of T2DM, and to intervene to prevent or delay this progression. This has led to the recognition of a dysglycemic state ("prediabetes") between normal glucose tolerance and T2DM. The Centers for Disease Control and Prevention[4] estimates that 37% of US adults aged 20 years and older with prediabetes are at increased risk of diabetes development. Prediabetes may be identified as a hemoglobin A_{1C} (HbA_{1C}) of 5.7% to 6.4%, a fasting plasma glucose level of 100 mg/dL to 125 mg/dL (impaired fasting glucose), or a plasma glucose level of 140 mg/dL to 199 mg/dL 2 hours after an oral glucose challenge (impaired glucose tolerance).[5] The HbA_{1C} test is increasingly being used to screen for the presence of T2DM or increased risk of T2DM because of improved standardization of the HbA_{1C} test, the increasing availability of rapid point-of-care testing, and the convenience of a nonfasting blood test.[6]

Fortunately, studies have shown that for many individuals with prediabetes, progression to T2DM may be prevented or delayed through improved diet, increased physical activity, and modest weight loss.[7-9] The lifestyle program tested in the Diabetes Prevention Program (DPP) study prevented or delayed almost 60% of new cases of T2DM in adults with prediabetes.[9] Recently published long-term outcomes of the DPP confirm a sustained effect of improved diet and physical activity to reduce progression to T2DM over 15 years.[10] Medication (metformin) can also reduce the incidence of T2DM (by 31% in the DPP study) and may be an attractive option for some patients.[11]

The sheer size of the at-risk population, however, is daunting—as many as 86 million people in the US have prediabetes.[12] Although several studies have indicated that diabetes prevention efforts such as those tested in the DPP are cost-effective,[13] the benefits of interventions are maximized when those efforts are targeted at the highest risk subset of the total prediabetes population.[14-17] In the prediabetic group, there is likely to be a spectrum of risk. Indeed, a recent article in the *British Medical Journal*[18] raised concerns about diagnosis creep, suggesting that we may be overdiagnosing prediabetes, and supporting differential

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intensity of prevention efforts focused on the subset at highest risk. A simple algorithm for stratifying the risk of progression to diabetes would allow for more efficient allocation of limited prevention resources, with individuals at highest risk receiving more intensive outreach and follow-up than those at lower risk.

We also know that not all people identified with prediabetes progress to T2DM. The long-term DPP outcomes data show that approximately 50% of subjects in the control group remained free of diabetes after 15 years. This is likely to be more common for those currently identified with prediabetes using the expanded range of HbA_{1C} of 5.7% to 6.4% vs 6.0% to 6.4%, because the DPP used a more stringent criterion to identify diabetes risk.

Nevertheless, substantial anxiety and increased utilization of medical resources may follow the identification of prediabetes. Although increased relative risk of diabetes incidence is typically reported, *absolute risk of diabetes development* may be more useful and actionable information for patients as well as for medical professionals.

We describe the development and validation of a simple algorithm for classification of absolute risk of progression to T2DM among individuals with prediabetes who were members of a large managed care organization in three different geographic regions of the US.

METHODS

This work was initially carried out as part of ongoing quality improvement efforts and was subsequently expanded under the Health Insurance Portability and Accountability Act (HIPAA) preparatory to research work for a research grant application. We subsequently applied for and received approval from the Kaiser Permanente (KP) Northwest (KPNW) institutional review board to publish these findings. Patient-level data were anonymized and deidentified before analysis.

Setting and Study Population

We carried out our study in 3 Regions of the KP Medical Care Program: KPNW, Hawaii (KPHI), and Georgia (KPGA). KP is a federally qualified, prepaid group-model integrated Health Plan. Currently, KPNW provides medical care to approximately 545,000 primarily white members in northwest Oregon and southwest Washington. The KPHI membership includes approximately 248,000 individuals: About 27% whites, 33% Asians, 12% native Hawaiians or Pacific Islanders, 24% of mixed heritage, about 1% combined American Indian/Alaska Native and Black or African American, and 3% unknown or not reported. Finally, KPGA provides care to approximately 295,000 members in the metropolitan Atlanta area. The membership is racially and socioeconomically similar to the surrounding geographic region: approximately 50% white, 45% African American, 4% Hispanic, and 1% other races and ethnicities.

Our analysis focused on KP members with HbA_{1C} levels between 5.7% and 6.4%. We focused solely on HbA_{1C} because, as noted earlier, it is becoming a commonly accepted test for classifying prediabetes and is likely to be more acceptable to patients as part of a large-scale screening program. A scheme based on use of HbA_{1C} would allow for immediate risk stratification without the need for patients to return for testing in a fasting state.

Development of Risk Index

Our risk classification system was originally developed as part of ongoing disease management efforts in KPNW. We selected patients with any HbA_{1C} measurement in 2011 that fell between 5.7% and 6.4%, using the first such value if multiple values were available as the index date. To ensure these patients did not already have a diagnosis of diabetes, we required 1 year of pre-index date eligibility with no indication of diabetes (diagnosis in the electronic medical record [EMR], use of an antihyperglycemic drug, or a laboratory value above diagnostic thresholds). Body mass index (BMI) was calculated using the mean of all height and weight values recorded in 2011. We assessed risk of development of diabetes for 1 year after the index HbA_{1C} value.

Validation of Risk Index

The initial risk index was refined and validated as part of the development of a diabetes prevention research proposal involving KPHI and KPGA as well as KPNW. We assessed the initial risk classification described earlier using data from all three KP Regions to determine the consistency of the risk strata, and then used this expanded dataset to develop final classification rules and corresponding risk levels associated with them.

Unlike the initial development work, which focused on 1-year diabetes risk, we calculated 2-year diabetes incidence and used this to estimate the 2-year risk (probability) of diabetes developing. This was done to be consistent with the proposed outcome of a study assessing the impact of diabetes prevention interventions. We also took a more pragmatic approach to defining the base population that reflected the screening guidelines we proposed to use for that study. Specifically, we classified an individual's prediabetes status using his or her most recent HbA_{1C} measurement in the previous 3 years, and we relied solely on a diabetes diagnosis code in the EMR to rule out diabetes in defining the at-risk cohort and in determining subsequent incidence of new diabetes. A single diagnosis code for diabetes can yield a positive predictive value of 86% to 95%.[19,20] Furthermore, we believe this is a realistic paradigm for how screening and risk classification might be done in the real world, and hence believe this gives added validity to our findings. Finally, whereas the initial development work looked at individuals aged 10 to 75 years, our validation work focused on adults, using a lower age limit of 18 years.

Statistical Methods

We calculated prospective risk from two perspectives, and for each perspective calculated two-year risk as defined here.

For what we term the *cross-sectional perspective*, we defined an at-risk population as of a given point in time and then followed individuals forward for 2 years to determine diabetes incidence. To evaluate 2-year incidence, we defined our starting population as KP members without diabetes as of January 1, 2012, and looked back 3 years from this date (2009-2011) to find the most recent HbA_{1C} measurement and BMI for purposes of

risk classification. We then followed each person forward in time from January 1, 2012, for up to 24 months. We defined length of follow-up as minimum of time to first diagnosis of diabetes or time to loss of Health Plan coverage, then computed the incidence rate as 100 × (total number of new cases of diabetes) ÷ (total person-years of follow-up). This is equivalent to the number of new cases per 100 person-years of follow-up. We then doubled the latter figure to estimate the number of new cases per 100 persons per 2 years of follow-up (ie, the cumulative 2-year incidence).

For what we term the *longitudinal perspective*, we defined our population not on the basis of a single fixed time point, but rather on the date of individuals' most recent HbA_{1C} measurement or BMI, and then followed individuals forward in time accordingly. That is, we still classified individuals on the basis of their most recent HbA_{1C} and BMI levels in the 3 years from 2009 to 2011, but we measured their 24-month follow-up from the date of the most recent HbA_{1C} level.

Finally, for each of these 2 approaches we estimated the absolute risk (ie, 2-year probability) of development of diabetes as $1 - e^{-H(2)}$, where H(2) is the cumulative 2-year incidence calculated as just described. Because not everyone had complete follow-up, the risks estimated in this manner tend to be somewhat larger than the observed proportions of individuals in whom diabetes actually developed over these same time frames.

RESULTS

Table 1 shows the results of the initial development work for the risk index. A total of 45,620 individuals aged 10 to 75 years with HbA_{1C} between 5.7% and 6.4% were cross-classified by BMI, and 1-year T2DM incidence probabilities were calculated. On the basis of these data, 3 risk strata (low, moderate, and high) were proposed. The BMI could not be calculated for a small proportion of members, usually because of absence of a measured weight in the EMR.

Table 2 shows the corresponding 2-year validation data for each of the 3 participating KP Regions separately and overall using the longitudinal perspective. The

Table 1. One-year probability (%) of diabetes developing, from initial development work[a]

	Body mass index, kg/m²				
Hemoglobin A_{1C}	Missing	< 25	25-30	30-35	≥ 36
5.7-5.8	0	0.1	0.1	0.1	0.4
5.9-6.0	0.5	0.4	0.4	0.9	1.4
6.1-6.2	1.8	0.8	1.9	3.2	4.3
6.3-6.4	6.4	6.7	12.6	12.5	15.7

[a] Estimates are based on data from 45,620 Kaiser Permanente Northwest members aged 10 to 75 years. No shading = low risk; gray shading = moderate risk; black shading = high risk.

Table 2. Two-year probability (%) of diabetes developing, longitudinal perspective[a]

		Body mass index,[b] kg/m²				
KP Region	HbA_{1C}	Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	0.8	0.6	0.5	0.9	2.0
	5.9-6.0	1.3	0.6	1.4	2.5	4.2
	6.1-6.2	7.6	2.4	3.4	6.9	9.3
	6.3-6.4	19.9	11.5	13.8	18.5	24.1
Hawaii (n = 31,906)	5.7-5.8	0.4	0.2	0.4	1.0	1.7
	5.9-6.0	1.1	0.8	1.0	1.5	3.1
	6.1-6.2	2.4	2.3	3.9	4.2	7.8
	6.3-6.4	8.6	4.9	7.9	11.5	15.5
Georgia (n = 8286)	5.7-5.8	3.0	1.2	0.3	2.4	3.4
	5.9-6.0	4.1	2.3	3.4	4.3	6.1
	6.1-6.2	9.3	4.8	4.5	9.3	8.9
	6.3-6.4	16.0	16.3	13.2	17.2	19.1
Total (N = 77,107)	5.7-5.8	1.2	0.4	0.5	1.1	2.1
	5.9-6.0	2.0	0.8	1.4	2.3	4.1
	6.1-6.2	5.8	2.5	3.8	6.3	8.8
	6.3-6.4	12.7	7.9	10.8	15.6	20.7

[a] Two-year probability was estimated as $1 - e^{-H(2)}$, where H(2) is the cumulative 2-year incidence. Data are based on percentage of members with prediabetes aged 18 to 75 years. For corresponding numbers of members, see Table 3. No shading = low risk; gray shading = moderate risk; black shading = high risk.
[b] Body mass index was rounded to the nearest whole number.
HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

Table 3. Cell sizes for corresponding data in Table 2

		Body mass index,[a] kg/m²				
KP Region	HbA_{1C}	Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	312	2685	5964	3675	3515
	5.9-6.0	204	1539	3987	2921	3005
	6.1-6.2	125	605	1937	1659	1840
	6.3-6.4	49	218	843	754	1078
Hawaii (n = 31,906)	5.7-5.8	642	3458	4896	2107	1604
	5.9-6.0	508	2411	3806	1836	1510
	6.1-6.2	273	1192	2268	1215	1118
	6.3-6.4	185	462	1101	657	657
Georgia (n = 8286)	5.7-5.8	379	456	984	714	675
	5.9-6.0	293	240	780	522	647
	6.1-6.2	185	138	459	455	409
	6.3-6.4	109	63	266	219	293
Total (N= 77,107)	5.7-5.8	1333	6599	11844	6496	5794
	5.9-6.0	1005	4190	8573	5279	5162
	6.1-6.2	583	1935	4664	3329	3367
	6.3-6.4	343	743	2210	1630	2028

[a] Body mass index was rounded to nearest whole number.
HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

corresponding number of subjects in each cell is shown in Table 3. The overall data are also shown in Figure 1. Corresponding data based on the cross-sectional perspective are included in Table 4. Collectively, Table 2 and Figure 1 represent data on more than 77,000 individuals. The risk strata suggested by each Region's data were more similar than dissimilar, although absolute levels of risk varied modestly from Region to Region. With a single exception, individuals whose HbA_{1C} value was 6.0% or less, as well as those with HbA_{1C} levels of 6.1% to 6.2% and BMI below 30 kg/m^2, consistently defined a low-risk category; those with HbA_{1C} of 6.1% to 6.2% and BMI of 30 kg/m^2 or higher were consistently classified as moderate risk; and those with HbA_{1C} of 6.3% to 6.4% and BMI of 30 kg/m^2 or higher were consistently classified as high risk. The remaining cells were generally classified as either moderate or high risk.

Table 5 shows, using the risk strata defined for the pooled sample at the bottom of Table 2, the proportion of individuals falling into each risk stratum and the associated 2-year risk of developing diabetes. Under this schema, 5.2% of the pooled sample is defined to be at high risk, with an estimated 2-year probability of diabetes development of 18.0%; 13.3% of the sample is defined to be at moderate risk, with a 2-year probability of development of diabetes of 8.2%; and 81.5% of the sample is defined to be at low risk, with a 2-year probability of diabetes development of just 1.6%.

Table 4. Two-year probability of diabetes developing, cross-sectional perspective[a]

KP Region	HbA_{1C}	Body mass index,[b] kg/m^2 (%)				
		Missing	< 25	25-30	31-35	≥ 36
Northwest (n = 36,915)	5.7-5.8	0.5	0.6	0.5	0.9	1.9
	5.9-6.0	1.5	0.7	1.3	2.4	4.2
	6.1-6.2	8.4	2.3	3.2	7.2	9.7
	6.3-6.4	16.7	12.3	14.4	18.9	25.1
Hawaii (n = 31,906)	5.7-5.8	0.5	0.2	0.4	0.9	1.7
	5.9-6.0	1.3	0.8	0.9	1.5	3.3
	6.1-6.2	1.7	1.9	3.8	4.2	8.0
	6.3-6.4	5.6	4.9	7.9	11.4	15.8
Georgia (n = 8286)	5.7-5.8	2.4	1.2	0.4	2.3	3.7
	5.9-6.0	4.7	2.5	3.6	4.5	6.0
	6.1-6.2	9.7	5.1	4.5	9.0	8.8
	6.3-6.4	12.9	15.7	14.0	17.2	20.9
Total (N = 77,107)	5.7-5.8	1.0	0.4	0.5	1.1	2.0
	5.9-6.0	2.3	0.8	1.3	2.3	4.2
	6.1-6.2	5.8	2.3	3.6	6.4	9.0
	6.3-6.4	9.6	8.1	11.2	15.7	21.6

[a] Two-year probability estimated as $1\text{-}e^{-H(2)}$, where H(2) is the cumulative 2-year incidence. Data are based on percentage of members with prediabetes aged 18 to 75 years. No shading = low risk; gray shading = moderate risk; and black shading = high risk.

[b] Body mass index was rounded to the nearest whole number.

HbA_{1C} = hemoglobin A_{1C}; KP = Kaiser Permanente.

DISCUSSION

The dramatic worldwide rise in incidence and prevalence of T2DM in recent decades has resulted in increased attention to prevention. Several studies have demonstrated the ability of lifestyle or medication interventions to prevent or delay the development of diabetes. Although cost-effective, such interventions are resource intensive and have limited effectiveness, which has led some to decry widespread population-level T2DM prevention efforts.[18] Diagnosing as many as one-third of the population as having prediabetes may not be useful if the resources to manage their diabetes risk are not available. Our results, summarized in Figure 1 and Table 5, indicate that in the category of prediabetes, there is a wide range of short-term risk of progression to incident T2DM, highlighting the importance of being able to more precisely estimate absolute risk of diabetes onset, and allowing for simple identification of the subset of patients at the greatest risk of progression.

Risk of T2DM is related to numerous clinical, historical, biochemical, genomic, metabolomic, and lifestyle factors.[21] Several predictive models have been proposed, but, to our knowledge, none are currently used in clinical practice. This may be because model performance when applied to alternative populations is poor.[22] The Framingham Offspring Study developed a relatively simple clinical model using only age, sex, parental history of diabetes, BMI, and levels of high-density lipoprotein cholesterol, triglycerides, and fasting plasma glucose to produce an area under the receiver operating characteristic curve of 0.852,[23] a model that was subsequently validated in KPNW (area under the curve = 0.824).[24] However, that model predated the use of HbA_{1C} as a diagnostic test and hence requires for its use fasting laboratory values that may not be available at the point of care. This, in turn, limits the model's utility for day-to-day clinical use. Patients, physicians, health plans, and public health agencies seeking more readily available and simpler ways of placing individuals with prediabetes along the spectrum of risk of diabetes onset may find our results useful.

Table 5. Two-year probability of diabetes developing, by risk strata, for individuals with prediabetes aged 18 to 75 years[a]

Risk stratum	No. (% of sample)	Probability of diabetes developing, %
Low	62,874 (81.5)	1.6
Moderate	10,232 (13.3)	8.2
High	4001 (5.2)	18.0
Total	77,107 (100.0)	

[a] The categorization shown in Table 5 matches that from Table 2. No shading = low risk; gray shading = moderate risk; black shading = high risk.

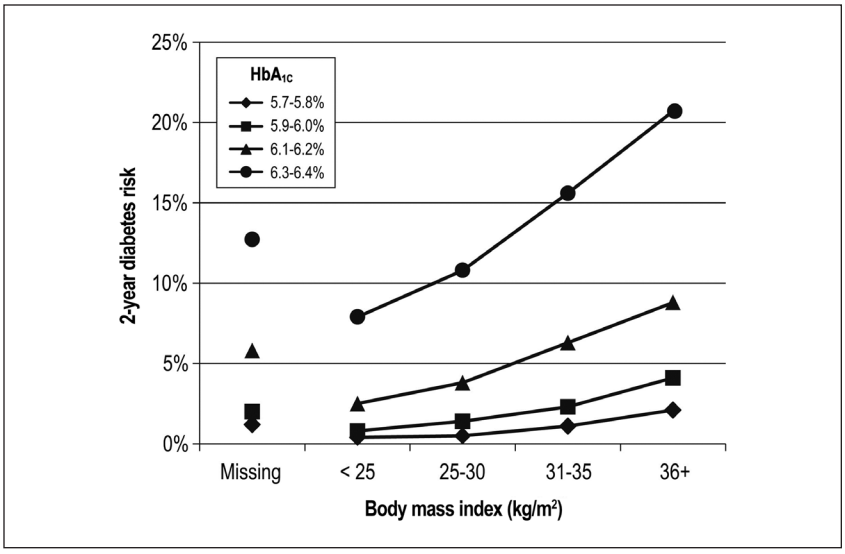

Figure 1. Two-year probability for progression from prediabetes to type 2 diabetes on the basis of hemoglobin A_{1C} (HbA_{1C}) and body mass index for 77,107 members, aged 18 to 75 years, of Kaiser Permanente Northwest, Hawaii, and Georgia.

CONCLUSION

With the increasingly widespread use of the HbA_{1C} test in the US to screen for T2DM,[6] a growing number of people are being recognized as having prediabetes (HbA_{1C} level = 5.7%-6.4%). Obesity, as assessed by BMI, is an additional readily available and important predictor of risk of incident T2DM. Using observational data from 3 demographically different Regions of KP, we have combined HbA_{1C} and BMI into a simple risk model to more precisely classify 2-year absolute risk of progression to T2DM that ranges from less than 0.5% for those with an HbA_{1C} of 5.7% to 5.8% who are not obese, to more than 20% in those with an HbA_{1C} of 6.3% to 6.4% who are obese. On the basis of this categorization of patients representing all age, sex, and race/ethnicities, only about 5% of individuals with prediabetes are at greater than 10% risk of diabetes developing in the next 2 years, whereas more than 80% are at much lower risk of T2DM (< 2%).

With a lifetime risk of occurrence of 40% in the US,[25] diabetes mellitus is a major public health problem that directly or indirectly affects the lives of nearly all Americans, as well as increasing numbers of people in low- and middle-income countries.[1] Lifestyle interventions can successfully delay or prevent onset of T2DM, but the cost-effectiveness of such programs is likely to depend on risk stratification that directs limited resources to the patients at greatest immediate risk.[16] The case has been made for use of HbA_{1C} as a diagnostic tool and risk stratifier.[26,27] Our additional use of BMI provides an enhanced estimator of short-term diabetes risk that is easy to implement and can intelligently inform targeted diabetes prevention efforts. Use of these prediction tables would be analogous to use of the FRAX (Fracture Risk Assessment Tool) model[28] to assess 10-year risk of osteoporotic fracture, or use of tools such as the Framingham Risk Score or the American Heart Association calculator to assess risk of cardiovascular events.[29] When a patient and his/her clinician have an idea of the absolute risk of the clinical event, in this case progressing from the prediabetic to the diabetic states, shared decision making regarding benefits, risks, cost, and indications for interventions is helped.

This simple approach of using readily available clinical (BMI) and laboratory (HbA_{1C}) measures to stratify risk of progression from prediabetes to diabetes mellitus could reduce anxiety as well as the intensity of interventions and follow-up laboratory testing for most individuals with prediabetes (ie, those in our low-risk group). At the same time, this approach could allow increased intensity of lifestyle change interventions and medication use and frequency of HbA_{1C} monitoring for the much smaller number of individuals in the high-risk group. Given the wide variation in diabetes incident rates among age, sex, and race/ethnicity categories,[6] refinements of this approach by studying the impact of these characteristics would be valuable, as would be longer-term and confirmatory studies in a range of populations. ❖

Disclosure Statement

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Die Young Late

Clearly, if disease is man-made, then it can be man prevented.
It should be the function of medicine to help people die young as late in life as possible.

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