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External Validation of Health Economic Models for Complex Chronic Diseases: Lessons From a Population Model for Diabetic Retinopathy

William L. Herring, Deidre M. Mladsi

RTI Health Solutions, Research Triangle Park, NC, United States

OBJECTIVE

- To describe the methods used and lessons learned during the external validation of a health economic model for a complex, chronic, progressive disease, using a population-level model for diabetic retinopathy (DR) screening as an example.

BACKGROUND

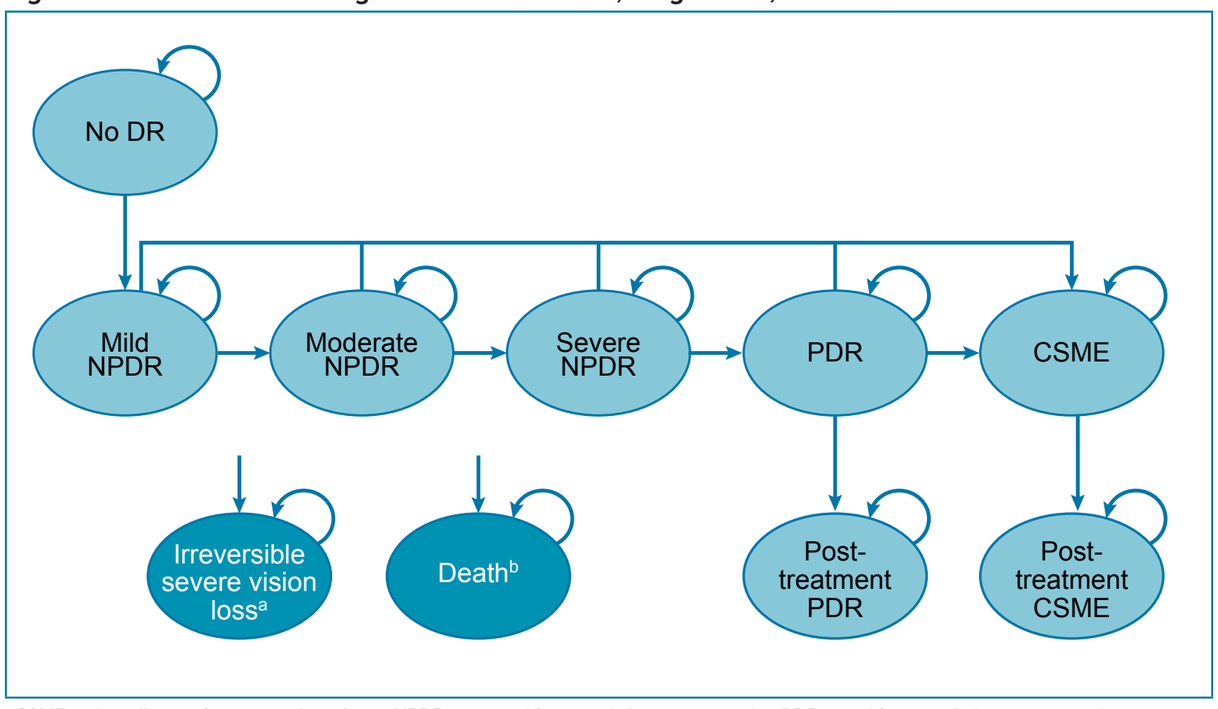
Model Validation

- The ISPOR-SMDM Modeling Good Research Practices Task Force guidelines for model validation, defined as a set of methods for judging a model's ability to make accurate predictions, stress the importance of face validity (confirming the approach, sources, and assumptions with experts), internal validity (quality-checking the parameter values and calculations), and external validity (comparing the results with other studies).[1]
- External validation of health economic models involves comparing various outcomes across multiple sources, while accounting for potential differences in study populations and standards of care across study settings.
- External validation can be more challenging for models of complex chronic diseases, especially when the data used to populate the model are drawn from studies spanning a period of time marked by significant advances in care.

DR Screening Model

- DR and related diabetic eye diseases are leading causes of blindness in the United States (US), and annual screening for DR is recommended for all patients with diabetes.[2]
- A decision-analytic model was developed to study the cohort- and population-level health and economic impact of novel DR screening devices in the US.
- The model structure depicting the incidence, progression, and treatment of DR is presented in Figure 1; a cycle length of 1 year was used in the model to track transitions among health states.

Figure 1. Model Structure Diagram for DR Incidence, Progression, and Treatment



CSME = clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

[a] Accessible from all PDR and CSME health states; [b] Accessible from all health states.

- The foundational epidemiologic data for the incidence and progression of DR were collected during large observational studies (e.g., Wisconsin Epidemiologic Study of Diabetic Retinopathy [WESDR]) and clinical trials (e.g., Early Treatment of Diabetic Retinopathy Study [ETDRS]) initiated over 30 years ago.[3-5]
- Research has shown that several characteristics of the diabetes patient population (most notably, duration of diabetes, glycemic control, and blood pressure) influence the rates of DR incidence and progression (Table 1).[6]
- Over the 30 years since the WESDR and ETDRS cohorts were enrolled, the standard of care for diabetes in the US has shifted (most notably with improved diagnosis and management), leading to a corresponding shift in these key population characteristics (Table 1).[3,4,7]
- Initial external model validation efforts applied unadjusted DR incidence and progression data from WESDR to a contemporary diabetes population, resulting in a shift in the DR health state distribution over time that would be unexpected in the absence of further changes to the standard of care.
- To address this challenge and successfully validate the model required a systematic and iterative process designed to identify the parameters leading to the unexpected model behavior, to revisit and adjust model parameters based on available evidence, and to calibrate selected parameters where evidence was uncertain.

Table 1. Comparison of Population Characteristics Linked to DR Incidence and Progression

Population Characteristics	RR of DR Incidence and Progression[6,a]	Shift in Characteristics Over Time	
		WESDR Estimates[3,4]	NHANES Estimates[7]
Duration of diabetes	1.062	11.6 years	9.5 years
Glycemic control (HbA1c)	1.163	11.2%	7.3%
Systolic blood pressure	1.014	143	131

HbA1c = glycated hemoglobin; NHANES = National Health and Nutrition Examination Survey; RR = relative risk.

[a] Relative risks were estimated from a multivariate regression analysis and applied in the model to DR incidence and to progression through the NPDR health states.

METHODS

- The external validation process consisted of four key steps spanning model conceptualization and parameterization through model finalization (Table 2).

Table 2. Model Validation Steps and Application to the DR Screening Model

Model Validation Steps	Application to the DR Screening Model
1. In anticipation of validation scenarios, identify relationships between key patient characteristics and disease incidence and progression, and include these relationships in model programming	• Coefficients from a multivariate analysis of the impact on key patient characteristics (duration of diabetes, glycemic control, blood pressure) on DR incidence and progression were identified • The model was programmed to automatically adjust DR incidence and progression parameters for populations with different baseline characteristics
2. Compare targeted cohort-level outcomes described in published studies (e.g., disease incidence at 5 years) with model outcomes for cohorts with matching characteristics and time horizons	• Baseline characteristics, including DR health-state distributions, were identified for 4 key WESDR studies reporting incidence outcomes at 4 years and for a UK population study reporting incidence outcomes at 10 years • Where baseline characteristics could not be matched precisely, a range of reasonable assumptions was tested
3. Assess population-level outcomes (e.g., distribution across health states) over time, while accounting for current population characteristics, the current standard of care, and new patients entering the population in subsequent years	• A prevalent cohort of current patients with diabetes in the US (i.e., patients eligible for DR screening) was combined with incident diabetic cohorts in later years to generate population-level estimates • Growth in the number of patients eligible for DR screening was compared with the projected growth in the number of patients with diabetes in the US • Stability in the prevalence of any DR and of PDR and CSME over time was assessed, based on the expectation that these measures would remain constant over time in the absence of significant changes to the standard of care
4. (If Needed) Informed by results of the cohort- and population-level comparisons, revisit model parameters and assumptions and consider calibrating selected parameters	• The unexpected shift in the DR health-state distribution over time was traced to a lack of alignment between the baseline population characteristics and progression data (both from WESDR) and the baseline health-state distribution (from contemporary data) • The baseline patient characteristics and DR progression data were updated to reflect contemporary data • The baseline health-state distribution was calibrated to generate the expected stability in population-level outcomes over time

UK = United Kingdom.

RESULTS

- By anticipating the required scenarios and programming the model to automatically adjust for differences in population characteristics, the validation process was able to demonstrate that cohort-level model outcomes were aligned with published outcomes.
  - Model estimates for DR incidence and progression over 4- and 10-year time horizons in matched cohorts were consistent with two large observational studies (Table 3).
  - Because the methodology for the population-level analysis layered together a prevalent cohort with future incident cohorts, establishing confidence in narrowly defined cohort-level outcomes was imperative prior to considering population-level outcomes.

Table 3. Comparison of Cohort-Level Model Outcomes With Published Studies

Outcomes	Published Studies	Model Outcomes[a]
Comparison with WESDR 4-year outcomes[3,4,8,9,b]		
DR incidence	34.4%-59.0%	44.0%
PDR incidence	2.3%-10.5%	5.1%
CSME incidence	2.9%-4.3%	3.2%
Severe vision loss	1.5%-3.2%	2.6%
Comparison with UK population 10-year outcomes[10,c]		
DR incidence	66.1%	56.0%-75.1%
PDR or CSME incidence	1.5%-2.7%	1.4%-3.0%

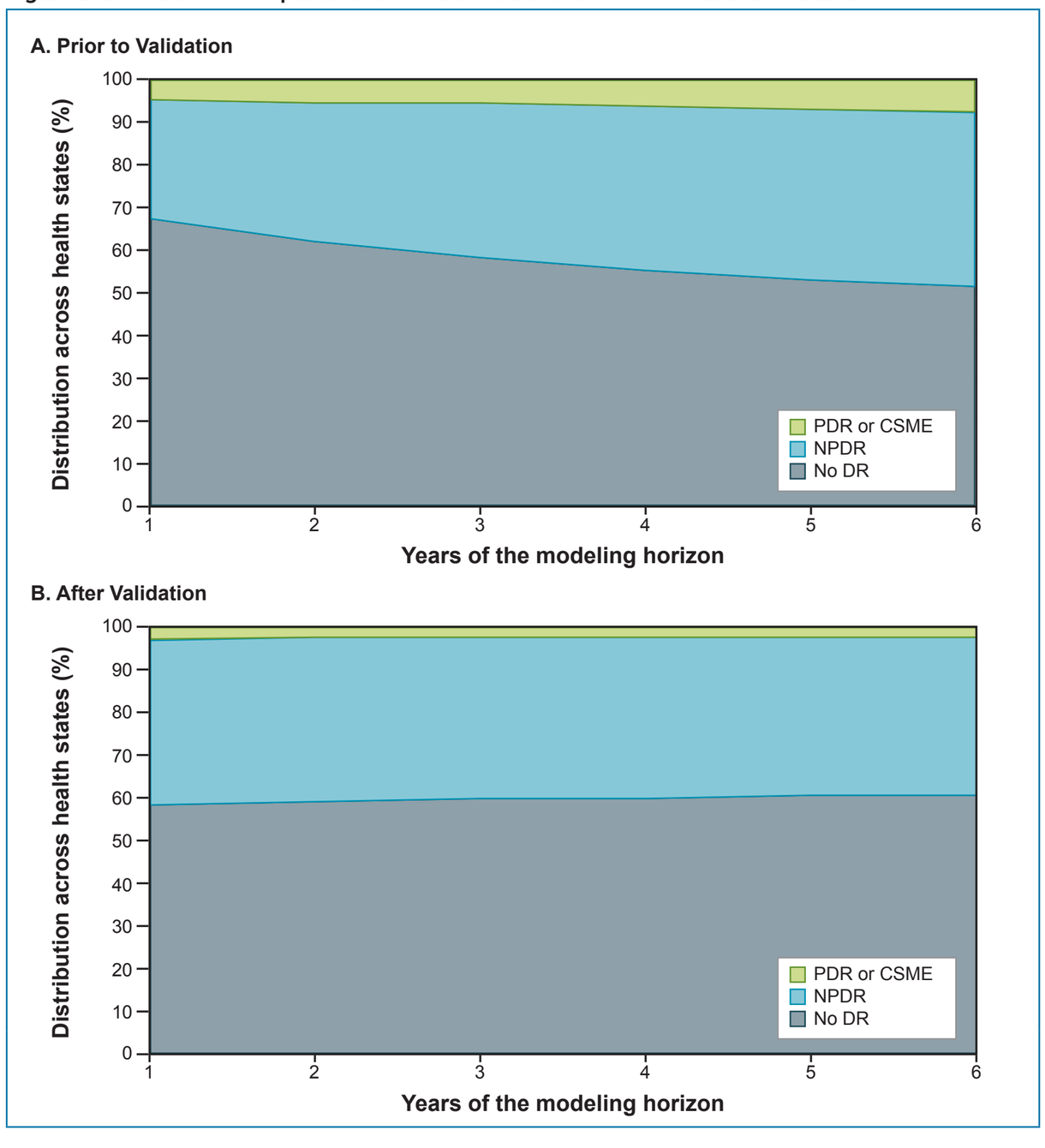
[a] Baseline characteristics in the model were adjusted to match the appropriate characteristics for each of the compared outcomes.

[b] The ranges of published outcomes for the WESDR studies reflected differences in the baseline ages of the WESDR cohorts (a proxy for type 1 vs. type 2 diabetes), a distinction that was not considered in the model outcomes.

[c] The ranges of model outcomes at 10 years reflected various assumptions about baseline characteristics (glycemic control and blood pressure) not reported in the UK study.

- Based on an unexpected trend in population-level model outcomes over time, selected model parameters and assumptions were revisited prior to model finalization.
  - The initial population-level outcomes revealed a marked increase over time in the prevalence of DR (and of PDR or CSME) (Figure 2A).
  - Without projecting a change in the standard of care for diabetes or DR, this shift was unexpected and raised concerns about the validity of the model.
  - The baseline patient characteristics and progression data were updated to reflect alignment with contemporary data, including reductions in DR incidence and progression based on improved glycemic control and lower blood pressure.
  - In the absence of similar contemporary data on the population distribution across DR health states, the baseline distribution was calibrated to generate the expected stability in population-level trends (Figure 2B).
- By demonstrating the model's ability to accurately predict cohort- and population-level outcomes over a range of time horizons, this systematic approach to external validation helped to promote confidence in model outcomes and in economic evaluations conducted using the model.

Figure 2. Distribution of Population Across DR Health States Prior to and After Validation



CONCLUSIONS

- External validation of models for complex, chronic, progressive diseases requires a systematic approach that integrates validation planning with model development and first targets narrow well-defined outcomes before considering broad interconnected outcomes.
- The methodology utilized and lessons learned during the external validation of a population-level model described in this poster can assist other researchers conducting validation of models in other similarly complex therapeutic areas.

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CONTACT INFORMATION

William L. Herring, PhD, MSc
Director, Health Economics

RTI Health Solutions
200 Park Offices Drive
Research Triangle Park, NC 27709

Phone: +1.919.541.6423
Fax: +1.919.541.7222
E-mail: wherring@rti.org

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