Introduction to Decision Analysis

Some statisticians might question whether Hamlet could have been saved by clinical decision analysis. In his famous soliloquy, Hamlet pondered: “To be or not to be—that is the question.” With some refinement, this existential questioning and the perceived consequences could be simplified into a decision analysis tree, perhaps allowing our protagonist to make a more informed decision. Decision analysis—the application of prescriptive quantitative methods to analyze decisions made under conditions of uncertainty—was first used in the financial and governmental sectors in the early 1940s, and by the 1960s was being applied to healthcare, particularly in countries with a single payer or social insurance fund system. Today, to stem exponentially rising healthcare costs, decision analysis in the US government has moved from arcane mathematical theory to the forefront in allocating healthcare expenditures. Furthermore, comparative effectiveness research (the umbrella term under which decision analysis falls) is becoming an attractive economic evaluation tool. Its methodology allows one to go from clinical observation to a decision tree framed in the form of either a cost-effectiveness or cost-utility analysis. A basic understanding of the mechanics of decision analysis is crucial as this form of comparative effectiveness will likely play a larger role in the future of healthcare in the US. Following guidelines from the Panel on Cost-Effectiveness in Health and Medicine, we were able to demonstrate that, compared with not testing for von Willebrand disease (VWD), universal screening for VWD in adolescents with menorrhagia is a cost-effective strategy, despite some minor data uncertainty.

Identify Whether Your Research Question Is Appropriate for Decision Analysis

At minimum, two criteria must be met for a particular research question to be deemed appropriate for clinical decision analysis:

- there is uncertainty about competing clinical strategies in a given health state; and
- there is a meaningful trade-off in the strategies.3

Once an appropriate decision problem is chosen, one must define the patient population and evaluate at least two relevant treatment/intervention strategies.3 Currently, it is unknown whether menorrhagia in adolescent females warrants an evaluation for VWD. The prevalence of VWD in women with menorrhagia ranges from 5 to 20 % compared with 1 % in the general population.7 First-line treatment for anovulatory bleeding, common in early adolescence, and VWD-associated menstrual bleeding is with estrogen-containing oral contraceptive pills (OCPs).5 In 2001, the American Congress of Obstetricians and Gynecologists (ACOG) recommended in a committee opinion that all adolescent females with menorrhagia be screened for VWD, based solely on retrospective diagnoses of VWD in adult women with gynecologic-procedure-related bleeding.6 In 2009, this statement was refined to suggest VWD evaluation if a clinical bleeding history is “strong.”7 The specific research question we posed was: ‘Is it cost-effective to screen...
all adolescent females with menorrhagia for VWD prior to the initiation of OCPs? The trade-offs include both the high cost of evaluation for VWD, $519 (median 2007 cost), and possible delays in treatment, since exogenous estrogen can mask a diagnosis, versus avoidance of future surgical bleeding and acute menstrual bleeding that necessitates blood transfusions or von Willebrand factor (VWF) replacement. The compared strategies for the proposed clinical scenario were not testing for VWD, the current practice, despite the ACOG recommendation, and universal strategies for the proposed clinical scenario were not testing for VWD, the current practice, despite the ACOG recommendation, and universal screening for VWD. ‘Selective’ screening for VWD was not performed, since no data support this strategy.

Construct a Decision Tree Based on the Decision Problem
Prior to the construction of a decision tree, there are two primary factors to take into consideration:

- the decision problem should be simple enough to understand but complex enough to capture clinically important events; and
- a proper time-frame should be chosen to capture future events.

A decision tree is then constructed, moving from left to right, as a pictorial representation of the temporal sequence of competing events. It begins with a hypothetical patient, and a decision, represented by a square node, is made. Branching off from that decision are probabilities, depicted by circular ‘chance’ nodes. Markov modeling was chosen to capture future events and costs. The M node, in this scenario, depicts five chosen Markov states. This model was greatly simplified for display purposes.

Estimate the Probabilities, Costs, and Utilities to Be Used in the Decision Tree
With the basic structure of the model complete, the next step is identification of available data from the literature. Costs, probability events, and health utility data need to be gathered and input into every decision tree branch following the decision node. A vigorous literature review is critical since the strength of the model depends on the quality of the data supporting it. Event probabilities can typically be obtained from literature, cost (direct and indirect) data from drug reference books, and Medicare/Medicaid reimbursement and procedure coding data from the Bureau of Labor Statistics. Health utilities can be obtained from various compiled lists of validated health utilities as well as from condition-specific, health-related quality-of-life instruments. It is important to differentiate between costs, preferred for use in decision analysis, and charges, which are arbitrarily set. Health utilities are based
Von Willebrand Disease

Identify the Preferred Strategy or Overall Expected Value and Interpret the Results

Prior to interpreting the results of the decision tree, sensitivity analysis should be performed to evaluate for the presence of structural or technical errors. All early versions of a decision tree have ‘bugs’ that need to be identified and eliminated. The recommended procedure is one-way sensitivity analysis in which the value for an individual variable is varied, using an acceptable clinical range. Additionally, extreme one-way sensitivity analysis, modifying variable input data from 0 to 1, is performed to evaluate whether the expected value makes clinical sense. For example, with the proposed research question, if the prevalence of VWD is 100 %, one would expect that it would always be cost-effective to screen for VWD in all adolescent females with menorrhagia. By contrast, if the prevalence of VWD is 0 %, universal screening would never be a cost-effective strategy. All analyses should be performed using comparative base case values or best estimates for probabilities, utilities, and costs for variables in the model. One-way sensitivity analysis can be displayed as a tornado diagram, which presents the model variables in decreasing order of their effect on the outcome (see Figure 2). A ‘robust model’ is not affected by small changes in a variable and can withstand minor uncertainty in the base case estimate.

Once the decision tree is free of all apparent bugs, it is appropriate to generate the expected values for each decision branch. ‘Folding back’ the tree is performed in each decision branch by adding all the costs and dividing the total by the sum of the utilities, or the multiplied product of the utility and the time spent in a certain health state. The process is repeated in the remaining decision branches. Although computations can be undertaken by hand, they are typically performed by computer software. The result or overall expected value is presented as cost per clinical state avoided or obtained (for CEA) or cost per QALY gained (for CUA). Generally, a base or reference case is chosen—typically the current clinical strategy—and a competing strategy is compared and presented as an incremental cost-effectiveness ratio (ICER). This is the net effect of substituting a new strategy for the previous strategy. It is calculated by subtracting the base case cost from the competing strategy cost divided by the base case utility subtracted from the competing utility. If a strategy costs more but is less effective, it is ‘dominated’ and removed from further analysis. An ICER of $50,000–$100,000/QALY is generally considered an economically feasible strategy, or cost-effective. There is, however, no such absolute economic threshold in cost-effectiveness analysis, making its findings more difficult to interpret.

The chosen reference strategy for this case was not testing for VWD and the competing strategy was testing for VWD. One-way sensitivity analysis was performed on all variables in the model and extreme one-way sensitivity analysis was used to evaluate model functionality. In the CUA, utilizing the base case estimates, the ICER was $62,791/QALY. This means that the additional cost of choosing the competing strategy was $62,791 per QALY gained. As previously noted, this would be considered a cost-effective strategy if the willingness to pay threshold was $100,000/QALY. One-way sensitivity analysis of the input variables showed that variations in the probabilities of acute menstrual bleeding

Figure 2: Tornado Diagram of Testing versus Not Testing for von Willebrand Disease

![Tornado Diagram of Testing versus Not Testing for von Willebrand Disease](image-url)

Cost-Effectiveness in Health and Medicine, the outcome is measured as life-year saved. In CEA, the outcome is measured in a clinical state resulting in, for example, cost per joint bleed prevented or cost per life-year saved. In CUA, the recommended analysis by the Panel on Cost-Effectiveness in Health and Medicine, the outcome is measured as a utility, for example cost per quality-adjusted life-year (QALY) gained. The latter allows comparison between different diseases and funding programs. CUA can help reduce costs and present policy-makers with the consequences of selecting a specific strategy.

We assumed the prevalence of VWD in adolescent females with menorrhagia to be 13 % (range 5–20 %), and the sensitivity and specificity of VWD screening was 79 and 90 %, respectively. The length of hospitalization for an acute menorrhagia bleeding event or surgical bleeding or OCP complications (DVT) was obtained from the Healthcare Utilization Project, a longitudinal database of 17 US hospitals. The probability of surgical bleeding in a child with VWD was estimated to be 13 %, and 3.6 % in those without VWD, based on post-tonsillectomy hemorrhage rates, a high-risk bleeding event in patients with VWD. Acute menorrhagia bleeding probabilities in children with and without VWD were estimated from expert opinion, as data are lacking. We assumed 1 and 0.1 % risk, respectively. All costs were in 2007 dollars based on Medicare/Medicaid reimbursement. We assumed repeat VWD testing in all patients, and included the cost of a desmopressin 1-desamino-8-D-arginine vasopressin (DDAVP) challenge if at least one test was positive for VWD. Costs of VWD testing for a negative diagnosis of VWD were $519 compared with $852 for a positive diagnosis.

On a patient’s preference for a particular health state and the time spent in that particular health state.
at presentation, and in surgical bleeding in normal and in WWD (affected) patients, altered the outcome most significantly, followed by variations in the prevalence of WWD.

Consider Additional Mathematical Analysis
Secondary analysis of this model can be performed next. Currently, the recommended and most common type of secondary analysis is probabilistic analysis. To account for parameter uncertainty, Monte Carlo probabilistic analysis allows the use of input distributions rather than a single input data point. Through random sampling from the entered distributions and repeat iterations, thousands of ICERs are generated. From these data, an acceptability curve is generated that can demonstrate how often (in a percentage) the competing strategy is a cost-effective strategy.

Monte Carlo probabilistic analysis was performed using clinically acceptable distributions for all input variables. The model was cycled 10,000 times, and if one’s willingness to pay threshold is $100,000/QALY, universal screening for WWD in all adolescents with menorrhagia is a cost-effective strategy 56% of the time. Overall, these findings suggest that the competing strategy is economically reasonable, even in the face of minor parameter uncertainty arising from the stricter definitions of WWD. Using threshold analysis and sensitivity analysis, it was possible to determine the exact point at which the preferred strategy changed: as long as the prevalence of WWD in adolescents with menorrhagia was at least 10%, universal screening for WWD appeared to be a cost-effective strategy.

Summary
Although it may be debated whether appropriations for medical programs or treatments should be solely based on disaggregating a complex clinical scenario into a simplified decision tree, decision analysis is a powerful tool that can provide policy-makers with an understanding of the economic consequences of various diagnostic and treatment strategies. In the current debate on healthcare costs, decision analysis will likely contribute to future healthcare reform. Since 1997 there has been a concerted government-mandated effort to improve the quality of medical decision analysis. The Panel on Cost-Effectiveness in Health and Medicine provides the current guidelines, while numerous sources such as the five-part Primer on Medical Decision Analysis series address various practical issues. To that end, several publications provide for critical assessment of decision analyses and contribute to a better basic understanding of this methodology and its potential application. Optimally, as illustrated herein, the decision analysis is initiated by a clinical observation that frames this scenario into a decision problem followed by identification of parameter estimates, construction of a decision tree, and mathematical analysis to derive the cost-effective or cost-utility outcome. In this case, we demonstrated that universal screening for WWD in adolescents with menorrhagia prior to the initiation of OCPs is cost-effective.

References
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