Cost-effectiveness Analysis in Personalized Medicine: General Hypotheses and Corresponding Decision Tree Structures for Screening, Diagnostic, Predictive, Prognostic, Surveillance, and Monitoring Tests

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BACKGROUND

- Personalized medicine is characterized by an increasing number of tests and payer scrutiny over their value.
- The value of a test is intrinsically linked to the subsequent treatment(s) triggered by the test.
- Depending on the use of a test, health care costs and outcomes may change in predictable ways.

METHODS AND DISCUSSION

- Fundamental differences in target populations and test purposes lead to six distinct types of test: screening, diagnostic, predictive (or companion diagnostic), prognostic, surveillance, and monitoring (Table 1).
- Each test use is matched with general value hypotheses and a generic decision tree modeling framework that can be used to study the cost-effectiveness of the test.
- Specifying how each type of test is expected to affect health care costs and/or outcomes serves to clarify which test attributes, epidemiological factors, treatment data, and economic data are relevant to the test's cost-effectiveness.

Table 1. Target Populations and Purposes for Six Test Uses

Type of Test	Target Population(s) for Test	Purpose of Test
Screening	General population, possibly restricted by age or other risk factors	Identify those likely to have or develop a disease
Diagnostic	Individuals requiring a diagnostic procedure, either due to symptoms or the results of a screening test	Determine whether an individual has a disease
Predictive	Individuals who have been diagnosed with a disease	Predict response to or toxicity from a particular treatment
Prognostic	Individuals who have been diagnosed with a disease	Identify those likely to have a specific outcome, regardless of treatment choice
Surveillance	Individuals with no sign of disease at completion of treatment	Identify those likely to have or develop recurrence
Monitoring	Individuals who are undergoing or have completed treatment	Detect disease progression or response to treatment

General Value Hypotheses

Screening

New screening tests have the potential to:

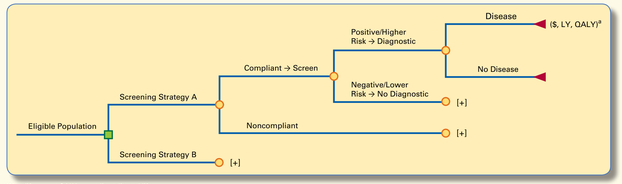
- Increase life expectancy and quality-adjusted life expectancy by identifying earlier and more accurately those individuals at risk for disease, thus facilitating earlier diagnosis.
- Reduce costs associated with unnecessary diagnostic testing by more accurately identifying low-risk individuals and reducing the occurrence of false positives.
- Improve compliance with a screening policy, thus increasing the magnitude of the aforementioned benefits by nature of being more acceptable to physicians and patients.

Diagnostic

New diagnostic tests have the potential to:

- Increase life expectancy and quality-adjusted life expectancy by more accurately identifying those with a disease and reducing the occurrence of false negatives.
- Reduce the costs of unnecessary treatments by more accurately identifying those patients without the disease and reducing the occurrence of false positives.

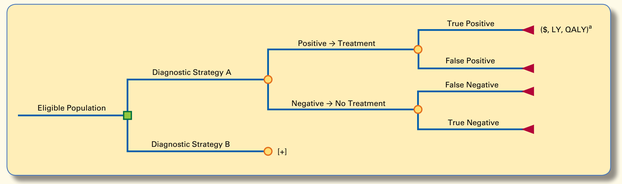
Figure 1. Decision Tree Structure for Screening Tests



LYs = life-years; QALYs = quality-adjusted life-years.

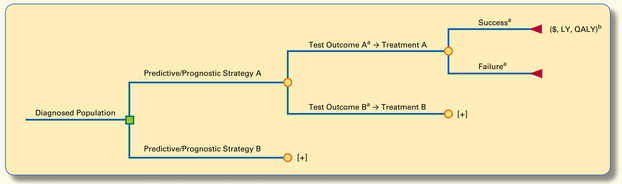
[a] Costs ($), LYs, and QALYs will vary by outcome.

Figure 2. Decision Tree Structure for Diagnostic Tests



[a] Costs ($), LYs, and QALYs will vary by outcome.

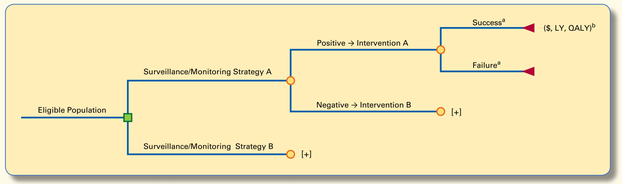
Figure 3. Decision Tree Structure for Predictive and Prognostic Tests



[a] Definitions of test outcomes, success, and failure will vary by test, disease, disease severity, and/or treatment.

[b] Costs ($), LYs, and QALYs will vary by outcome.

Figure 4. Decision Tree Structure for Surveillance and Monitoring Tests



[a] Definitions of success and failure will vary by test, disease, disease severity, and/or intervention.

[b] Costs ($), LYs, and QALYs will vary by outcome.

Predictive

New predictive tests have the potential to:

- Improve response rates and increase life expectancy and quality-adjusted life expectancy by more accurately identifying those patients likely to respond to a particular treatment.
- Reduce toxicity rates and increase quality-adjusted life expectancy by more accurately identifying those individuals likely to experience serious adverse events from a particular treatment.

Prognostic

New prognostic tests have the potential to:

- Improve response rates and reduce costs by identifying individuals at risk for a specific outcome and informing an appropriate treatment approach.

Surveillance

New surveillance tests have the potential to:

- Increase life expectancy and quality-adjusted life expectancy by identifying earlier and more accurately those individuals experiencing (or likely to experience) disease recurrence and thus requiring additional interventions.
- Reduce costs and increase quality-adjusted life expectancy by reducing ongoing testing that is unnecessary or unlikely to be beneficial.

Monitoring

New monitoring tests have the potential to:

- Increase life expectancy and quality-adjusted life expectancy by identifying earlier and more accurately those individuals experiencing (or likely to experience) disease progression and thus requiring changes in interventions.
- Reduce costs and increase quality-adjusted life expectancy by reducing ongoing interventions and/or testing that are likely to be unnecessary or ineffective.

Decision Tree Modeling Framework

Screening

- Two competing screening strategies, each comprising a screening test, a level of test compliance, and a follow-up diagnostic procedure that is automatically triggered by a positive screening result (Figure 1).
- In the case of noncompliance or a negative screening result, patients may be diagnosed with disease through other methods (e.g., triggered by symptoms rather than screening results).

Diagnostic

- Two competing diagnostic strategies, each comprising a diagnostic test and a follow-up treatment that is triggered by a positive diagnostic result (Figure 2).
- Patients with a negative result do not receive immediate treatment, but may be diagnosed with disease at a later date (after a corrective diagnosis, which is not modeled explicitly).

Predictive or Prognostic

- Two competing predictive or prognostic strategies, each comprising a test, the result of which informs use of a treatment (Figure 3).
- Test accuracy is modeled implicitly in the treatment success and failure outcomes associated with each pathway. The definitions of success and failure vary depending on the test, disease, disease severity, and treatment (e.g., failure may indicate disease recurrence for a curative treatment or progression for a treatment designed to prevent disease spread).

Surveillance or Monitoring

- Two competing surveillance or monitoring strategies, each comprising a test for disease recurrence or progression (or the likelihood thereof), the result of which informs the follow-up intervention (which may include continued testing) (Figure 4).
- Test accuracy and the effectiveness of the follow-up interventions are modeled implicitly in the success and failure outcomes associated with each possible pathway. As with the predictive or prognostic model, the definitions of success and failure vary depending on the test, disease, disease severity, and intervention.

The test attributes, epidemiological data, and treatment and/or intervention data required for each model are shown in Table 2.

Table 2. Test Attributes, Epidemiological Factors, and Treatment/Intervention Data Used in the Decision Tree Model for Each Test Use

Parameter	Screening	Diagnostic	Predictive or Prognostic	Surveillance or Monitoring
Test attributes				
Sensitivity	Yes	Yes	Yes	Yes
Specificity	Yes	Yes	Yes	Yes
Positive predictive value	Yes	Yes	Yes	Yes
Negative predictive value	Yes	Yes	Yes	Yes
Compliance	Yes	—	—	—
Epidemiological factors				
Disease prevalence	Yes	Yes	—	—
Disease severity at diagnosis (separately for true positives, false negatives, and untested)	Yes	Yes	—	—
Outcome prevalence (e.g., progression or recurrence)	—	—	Yes	Yes
Life expectancy, by severity	Yes	Yes	—	—
Life expectancy, by outcome	—	—	Yes	Yes
Treatment/intervention data				
Probability of success	—	—	Yes	Yes
If unsuccessful, time to failure	—	—	Yes	Yes

Test attributes, while not "seen" in decision analysis models, relate to decision tree probabilities. Table 3 presents the standard 2x2 table used to categorize tests and the presence or absence of a condition. Table 4 presents the model parameters for the diagnostic test model and relates them to the standard 2x2 table, defining sensitivity, specificity, and all related attributes.

Table 3. Standard 2x2 Table Used to Categorize Tests[a]

	Condition Present	Condition Absent	Totals
Test positive	a	b	a + b
Test negative	c	d	c + d
Totals	a + c	b + d	a + b + c + d

[a] Sensitivity = a/(a + c); specificity = d/(b + d); positive predictive value = a/(a + b); negative predictive value = d/(c + d).

Table 4. Relationship of Diagnostic Model Parameters to Test Attributes and 2x2 Table

Model Parameter	Descriptive Definition	Definition, in Terms of 2x2 Table	Definition, in Terms of Possible Test Attributes
Probability of positive test	Positives / All tested	(a + b) / (a + b + c + d)	—
Given positive test, probability of true positive	True positives / All positive tests	a / (a + b)	Positive predictive value, influenced by disease prevalence
Given positive test, probability of false positive	False positives / All positive tests	b / (a + b)	—
Probability of negative test	Negatives / All tested	(c + d) / (a + b + c + d)	—
Given negative test, probability of false negative	False negatives / All negative tests	c / (c + d)	—
Given negative test, probability of true negative	True negatives / All negative tests	d / (c + d)	Negative predictive value, influenced by disease prevalence

Relationships and Insights

- The value of new screening and diagnostic tests is related to the identification and epidemiology of the disease among the undiagnosed population.
- The value of new predictive, prognostic, surveillance, and monitoring tests is related to the treatment and epidemiology of the disease among those diagnosed with the disease.
- Improving the accuracy of a screening or diagnostic test is beneficial only when there are differences in life expectancy and costs between disease severity levels, as well as differences in severity between true positives and false negatives.
- Improving the compliance of a screening test generates value only when there are differences in life expectancy and cost between disease severity levels, as well as differences in severity between those diagnosed after being screened and those diagnosed after not being screened.
- More accurate predictive and prognostic tests can generate value only when there are differences in life expectancy and costs between treatments and between treatment outcomes or when there are differences between treatments in how long it takes for treatment failure to occur.
- More accurate surveillance and monitoring tests can generate value only when there are effective interventions available to increase the life expectancy and/or decrease the costs associated with individuals experiencing or at risk for negative disease outcomes.

CONCLUSIONS

- Tests may be expected to affect health care costs and outcomes in predictable ways depending on the type of test, epidemiology of the disease, available treatments, and associated costs.
- The value hypotheses and modeling frameworks associated with the six distinct types of test highlight the importance of considering the differences between the test uses when studying their cost-effectiveness.
- The decision tree modeling structures for each test use and the types of data they require provide qualitative and quantitative means to identify drivers of cost-effectiveness and opportunities for new tests to add value.

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