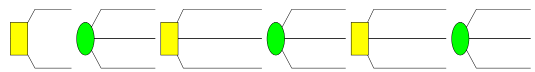
Incorporating Learning Models in Structuring and Valuing R&D Projects



Decision Analysis Affinity Group

San Francisco, CA

February 26, 2004

Phil Beccue

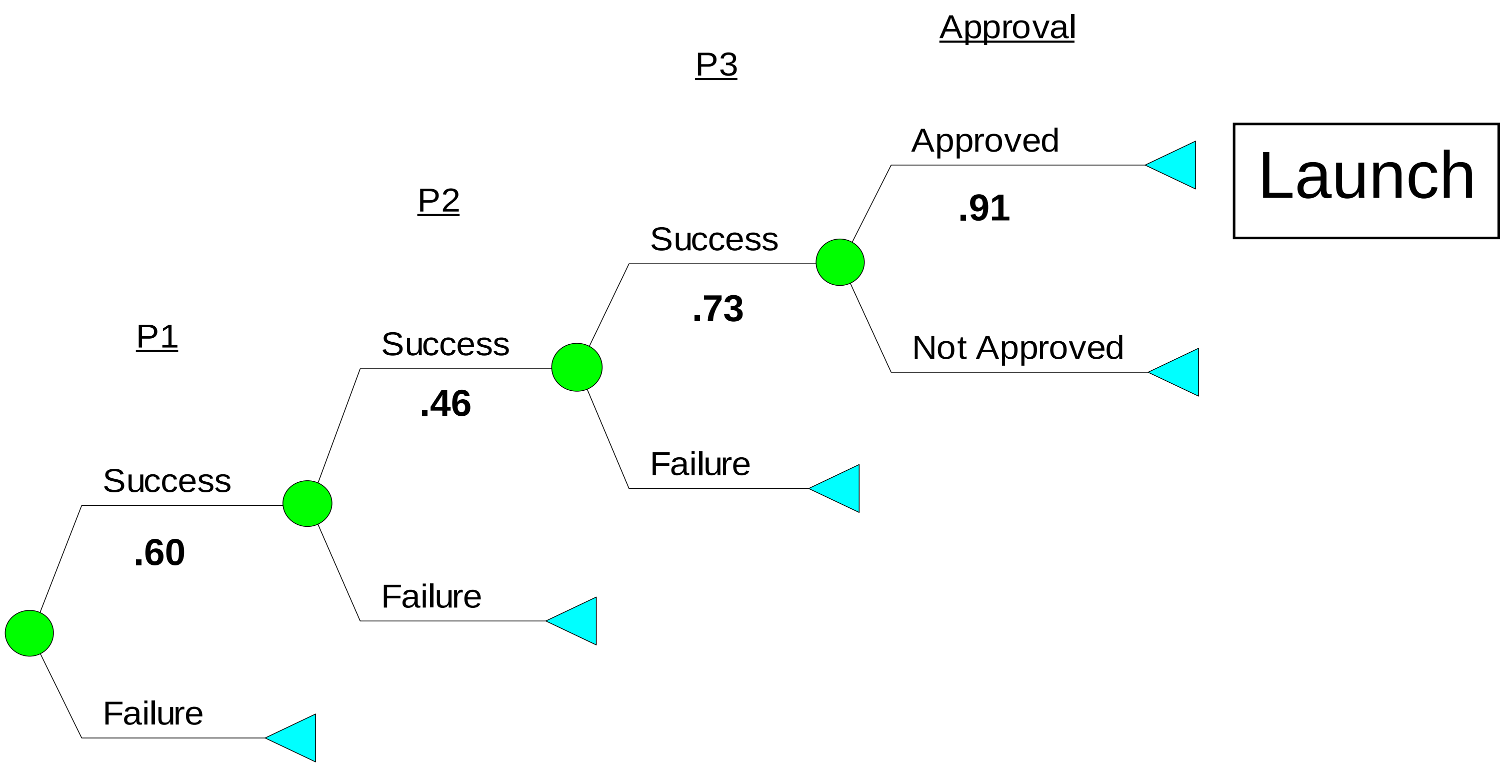
Baxter Bioscience

Agenda

- Motivation
- Case Study
  - Background
  - Constructing a learning model
  - Integrating the learning model into a real-options analysis
  - Results
- Conclusions

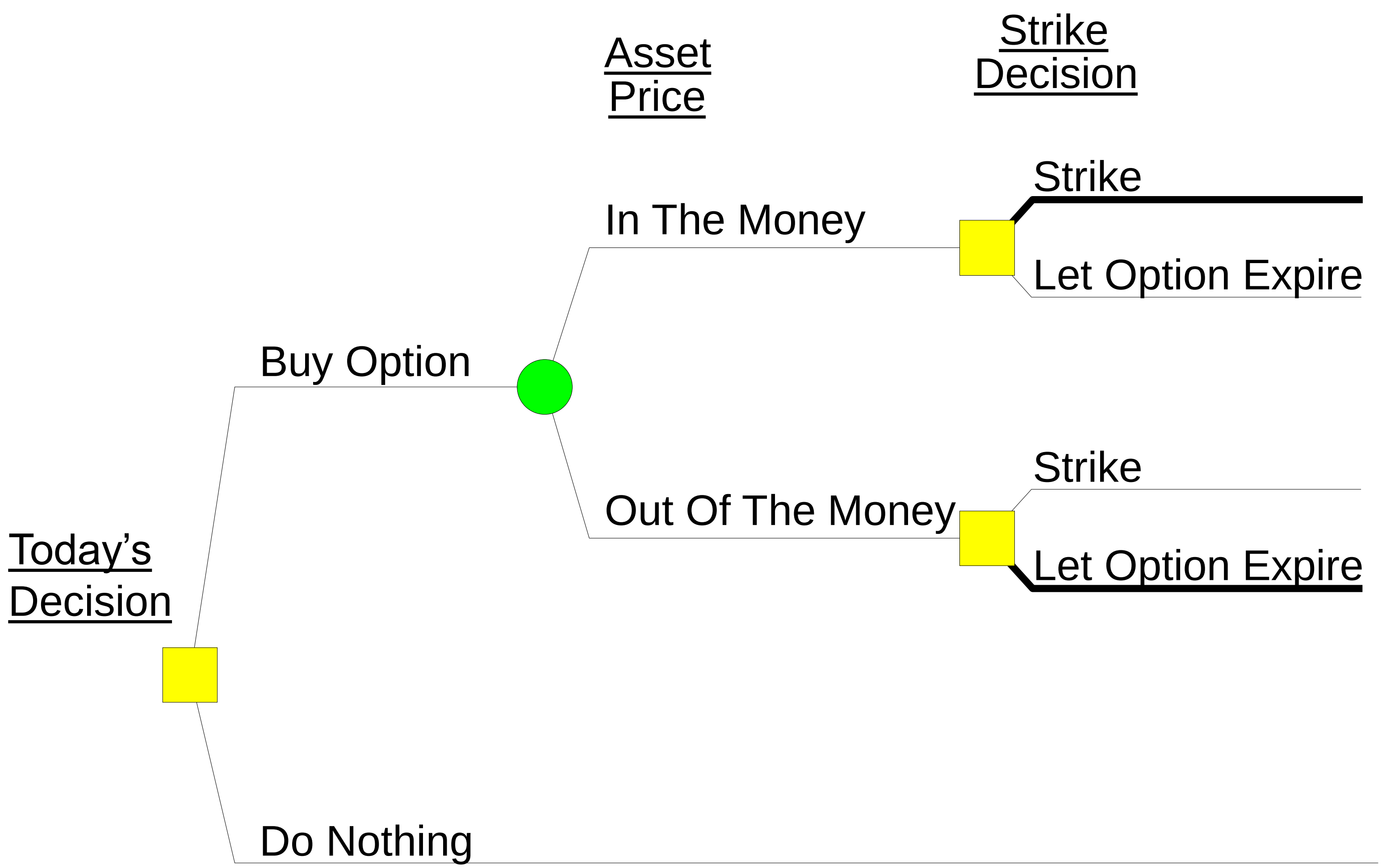
Note: All data presented are modified to preserve confidentiality.

Drug R&D is a series of growth options

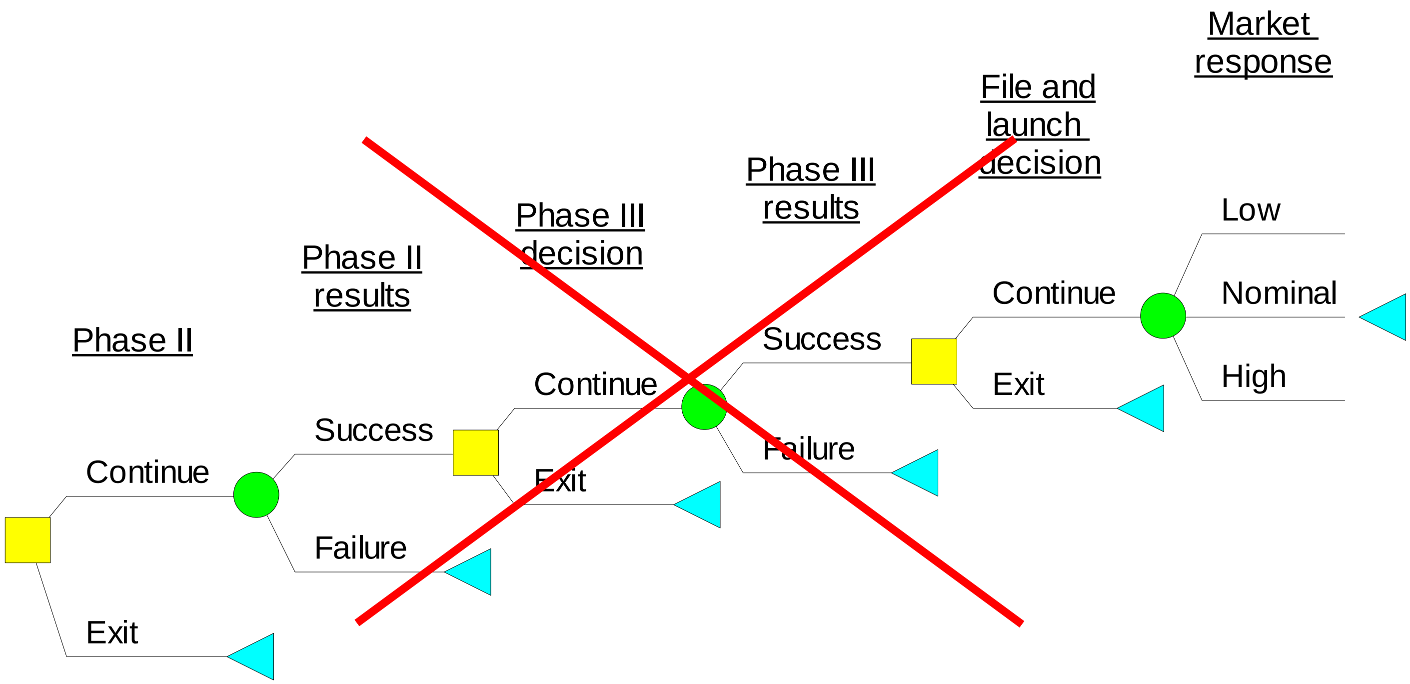


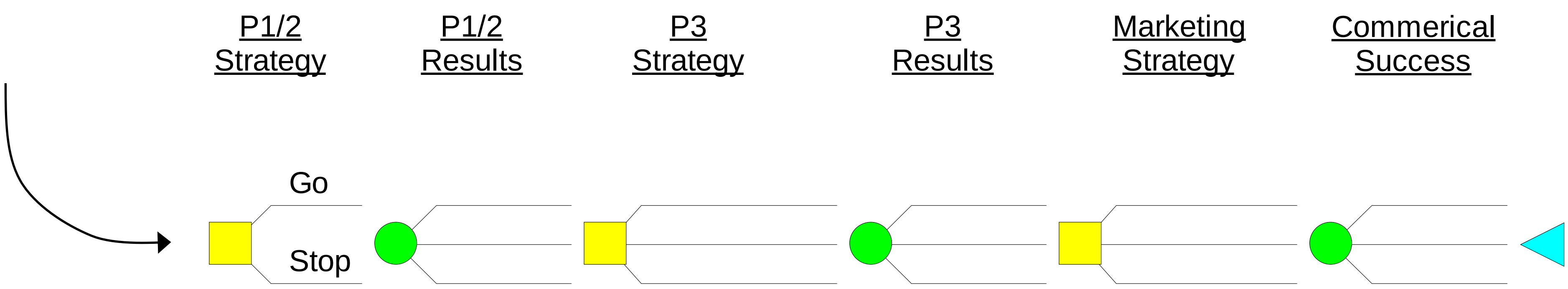
New, Active Substances (NAS)
CMR Int'l Data, 1997

Decision tree form of financial options



What if information is imperfect, and options are more than "go / no go"?

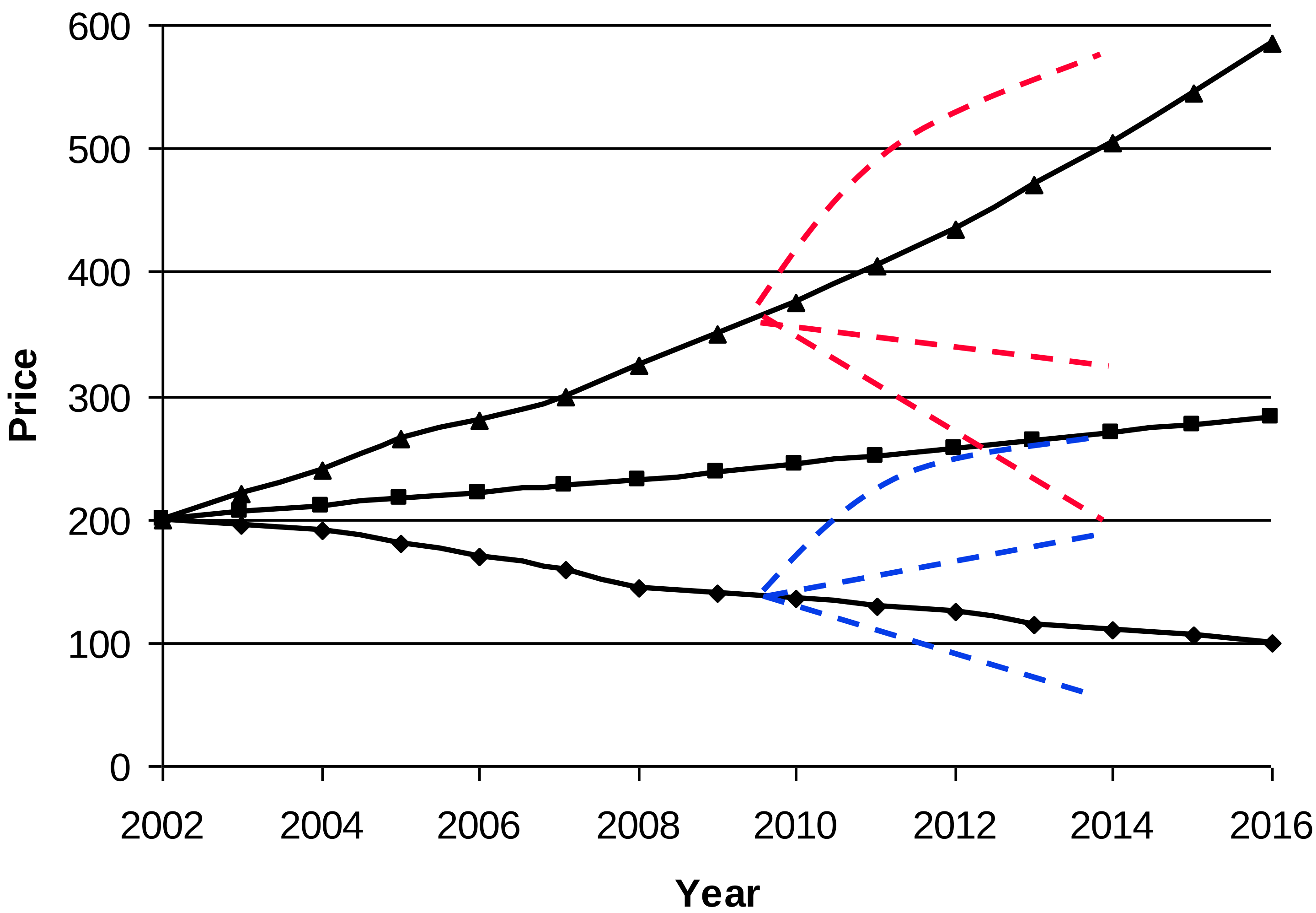




A real options approach often requires information that updates over time

A "learning model" provides conditional assessments needed for a real options approach

<u>Ex.</u> How does my forecast for 2014 change if in 2010 I observe prices are in their "high" state?



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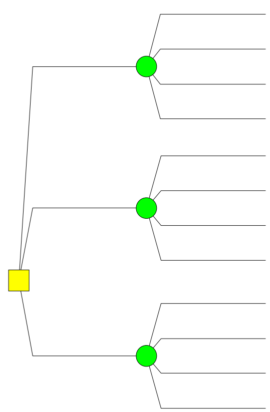
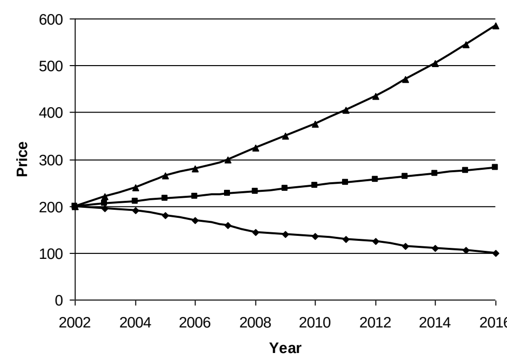
There are a variety of methods for developing learning models

Direct assessment

Stochastic processes





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This case example illustrates the application of a real options framework to an R&D project

- Product X is already marketed for one indication, and is currently in P1 development for a second indication
- Preclinical research studies is known, and the safety profile has been well established
- Significant uncertainty remains in terms of efficacy and tolerability in the new patient population
- Immediate question: “Should we proceed to P2?”

We began with a brainstorming session to identify key issues

We categorized issues into decisions, uncertainties, and values.

DECISIONS
- Positioning
  - Reduce background therapy
  - Refractory to current 2nd line failures
- P2 trial design
- P3 trial design
- Commercialization
  - Outlicense
  - CSO
  - Internal sales force
  - Co-promote
- Pricing

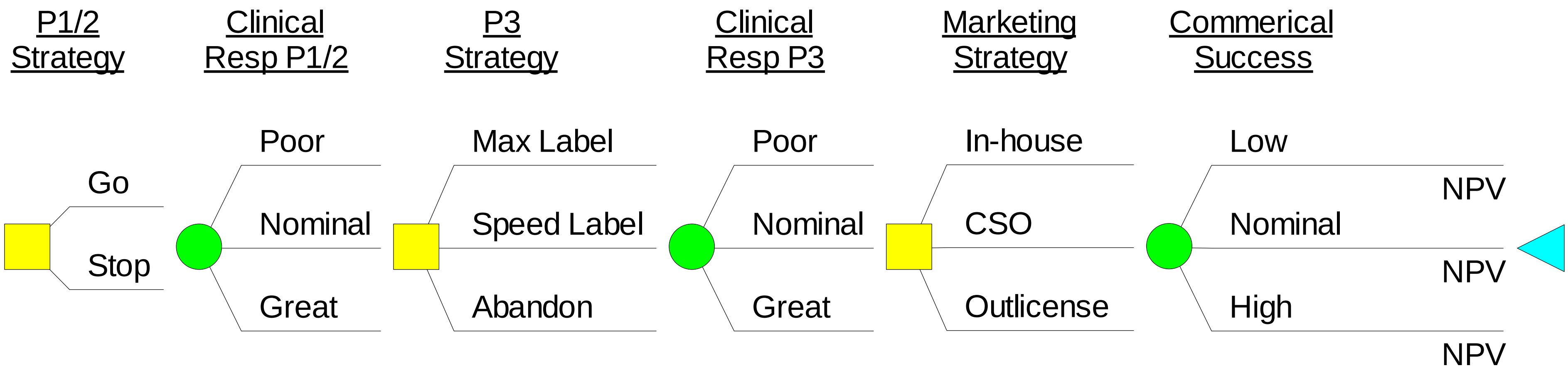
UNCERTAINTIES
- Product profile
- Response rate
- Safety profile
- Frequence of dosing
- Maintenance of remission at 12-wks
- Market share
- Market size
- Competition
- Regulatory approval
- COGS
- R&D costs
- S&M costs
- Outcome of P2
- Outcome of P3

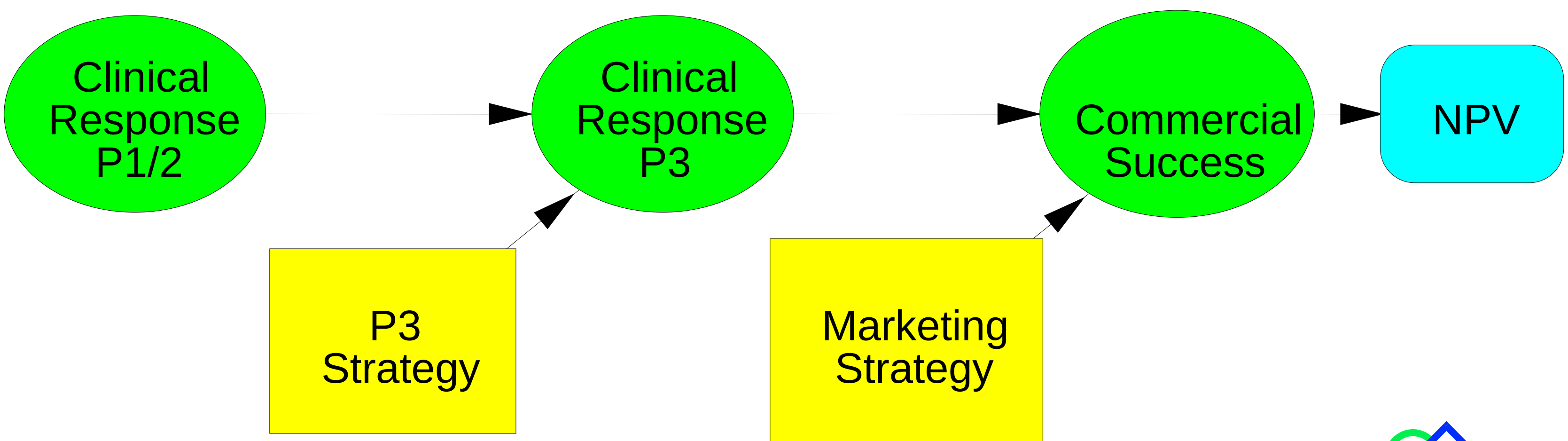
VALUES
- Shareholder value
- Peak Revenue
- NPV
- 5th-year sales

To understand the true value and best course of action to take, we must first uncover the options embedded in the project

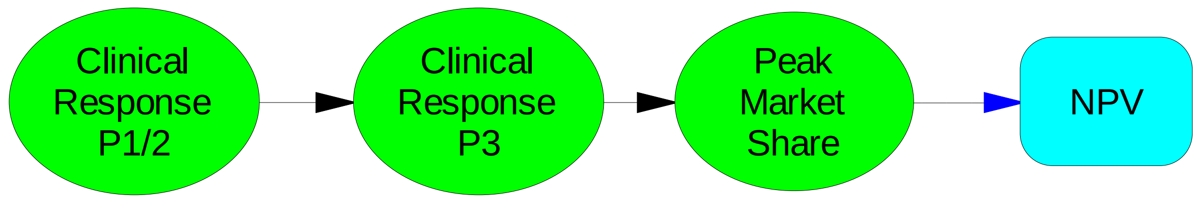
We developed a model of the key strategic decisions, and the information that would inform them

Constructing a schematic tree helped define the “learning-decide-learning-decide” structure



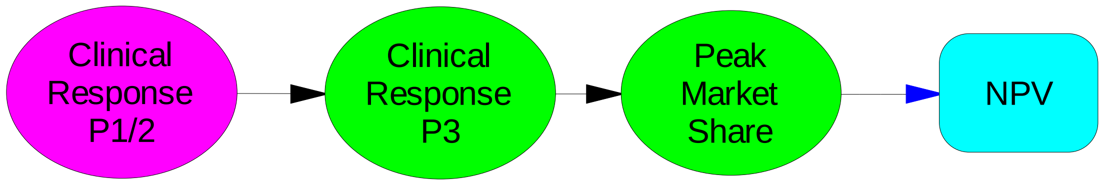


Process for developing the "Learning Model"



1) Define the information learned at each stage
2) Determine the mutually-exclusive states (potential outcomes) for each uncertainty
3) Assess a probability distribution for the "unconditioned" uncertainty (with no influencing arrows pointing to it)
4) For the remaining uncertainties, assess the conditional probability of being at each state, given a particular state of the predecessor event
5) Finally, assess NPV as a function of peak market share

We defined 3 states to represent the potential outcomes for the P1/2 study



P1/2 study description:
- 150 patients
- 3-month trial
- 3 doses in study
  - 5 mg/kg
  - 10 mg/kg
  - 20 mg/kg

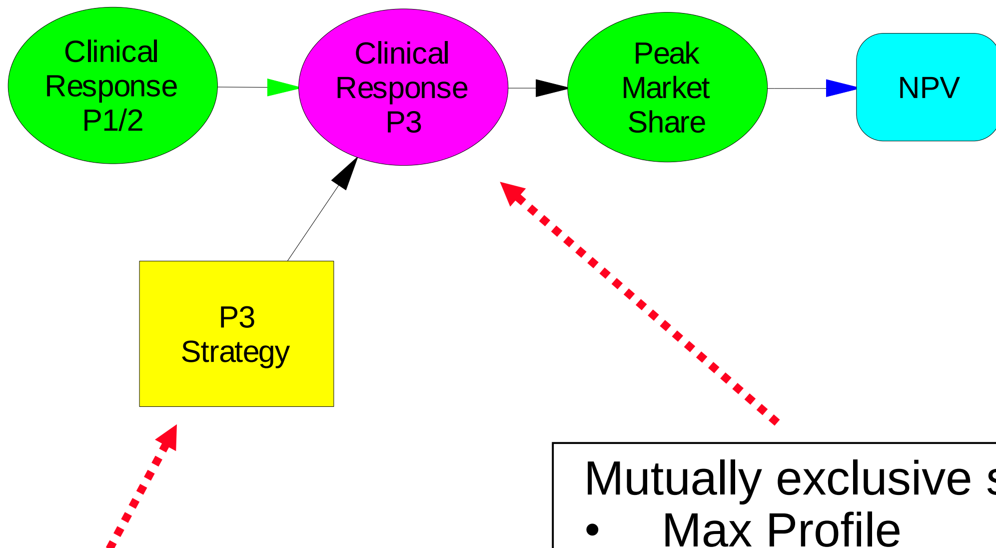
P1/2 endpoint:
Percent of patients who achieved a reduction in SS score of >= 70 points at 4 weeks

Response Rate

Dose (mg/kg)	State 1	State 2	State 3
5	**20%**	**5%**	**60%**
10	**40%**	**10%**	**40%**
20	**60%**	**20%**	**20%**
	40%	40%	20%

The marginal probability distribution was assessed from experts, based on best clinical evidence

To assess the P3 study outcomes, we defined four potential profiles, and two P3 strategies



Mutually exclusive states for P3 outcome:
- Max Profile
- Speed-to-Market Profile
- Minimum Registration Profile
- Fail

P3 Strategy

Max Label Strategy
- 600 patients, 1-year study
- Endpoints are
  - Clinical response
  - Clinical remission
- Dev Costs: $40M

Speed Label Strategy
- 200 patients, 6-month study
- Endpoints are
  - Clinical response
  - Clinical induction and maintenance of remission
- Dev Costs: $25M

We assessed conditional uncertainty assessments for P3 Clinical Response

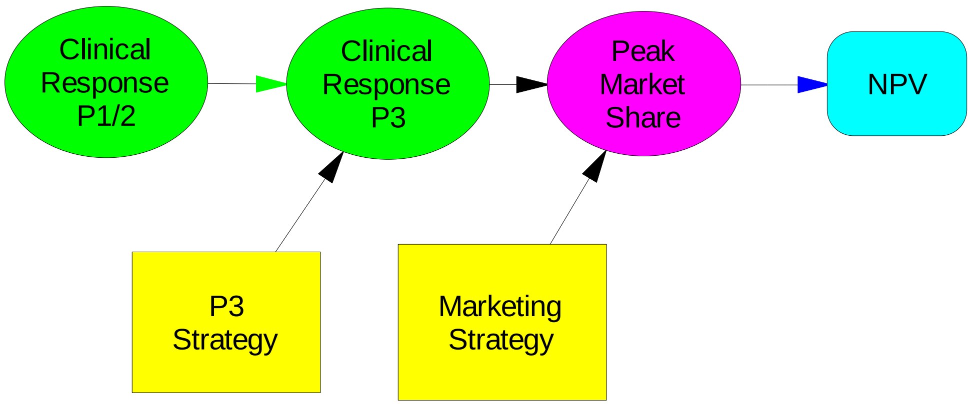
P3 Strategy: Max Label

Clin Resp P1/2	Clin Resp P3	
RR=20,40,60	Max	49%
	Speed	18%
	MinReg	3%
	Fail	30%
RR=5,10,20	Max	4%
	Speed	6%
	MinReg	10%
	Fail	80%
RR=60,40,20	Max	10%
	Speed	20%
	MinReg	10%
	Fail	60%

P3 Strategy: Speed Label

Clin Resp P1/2	Clin Resp P3	
RR=20,40,60	Max	10%
	Speed	53%
	MinReg	7%
	Fail	30%
RR=5,10,20	Max	3%
	Speed	9%
	MinReg	18%
	Fail	70%
RR=60,40,20	Max	10%
	Speed	20%
	MinReg	10%
	Fail	60%

Before estimating Peak Market Share, we need to think about commercialization alternatives

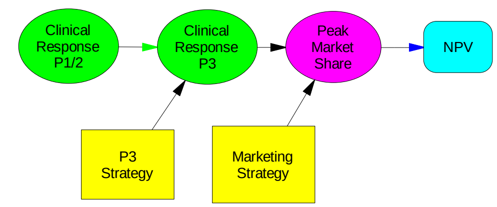


- We narrowed the Commercialization strategies into 3 options:
  - In-house sales force
  - CSO plus in-house sales force
  - Outlicense
- We assumed the CSO could possibly provide an increase in share by "double-dipping," but this is not guaranteed
- We could outlicense the product to an organization with an existing sales force that would substantially increase share, but we would only take a portion of the value in royalty fees

Peak Market Share estimates depend on Marketing Strategy and P3 Clinical Response

Market Share Assessment (%)

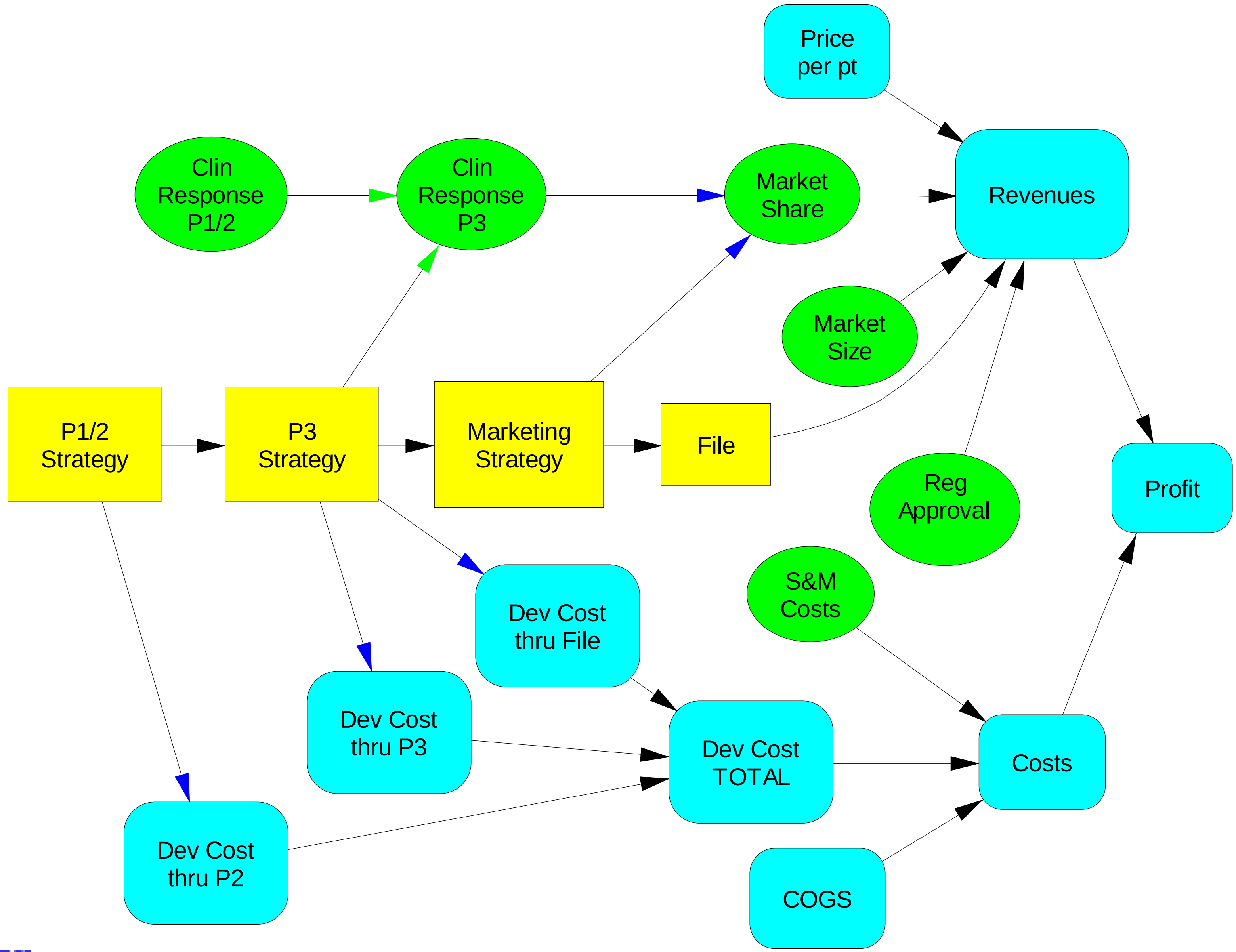
Marketing Strategy	Clin Resp P3	*Low 10th*	*Nominal 50th*	*High 90th*
In-house	Max Profile	5	10	15
	Speed Profile	3	7	10
	Min Reg Profile	1	3	5
	Fail			
CSO	Max Profile	5	10	16
	Speed Profile	5	8	15
	Min Reg Profile	1	3	7
	Fail			
Out-license	Max Profile	14	18	26
	Speed Profile	12	16	21
	Min Reg Profile	10	14	16
	Fail			



Assumptions:

- 2nd to market
- 6-months lag time
- Safety is superior to competition
- No reimbursement

The influence diagram summarizes the relationships of the key uncertainties and decisions



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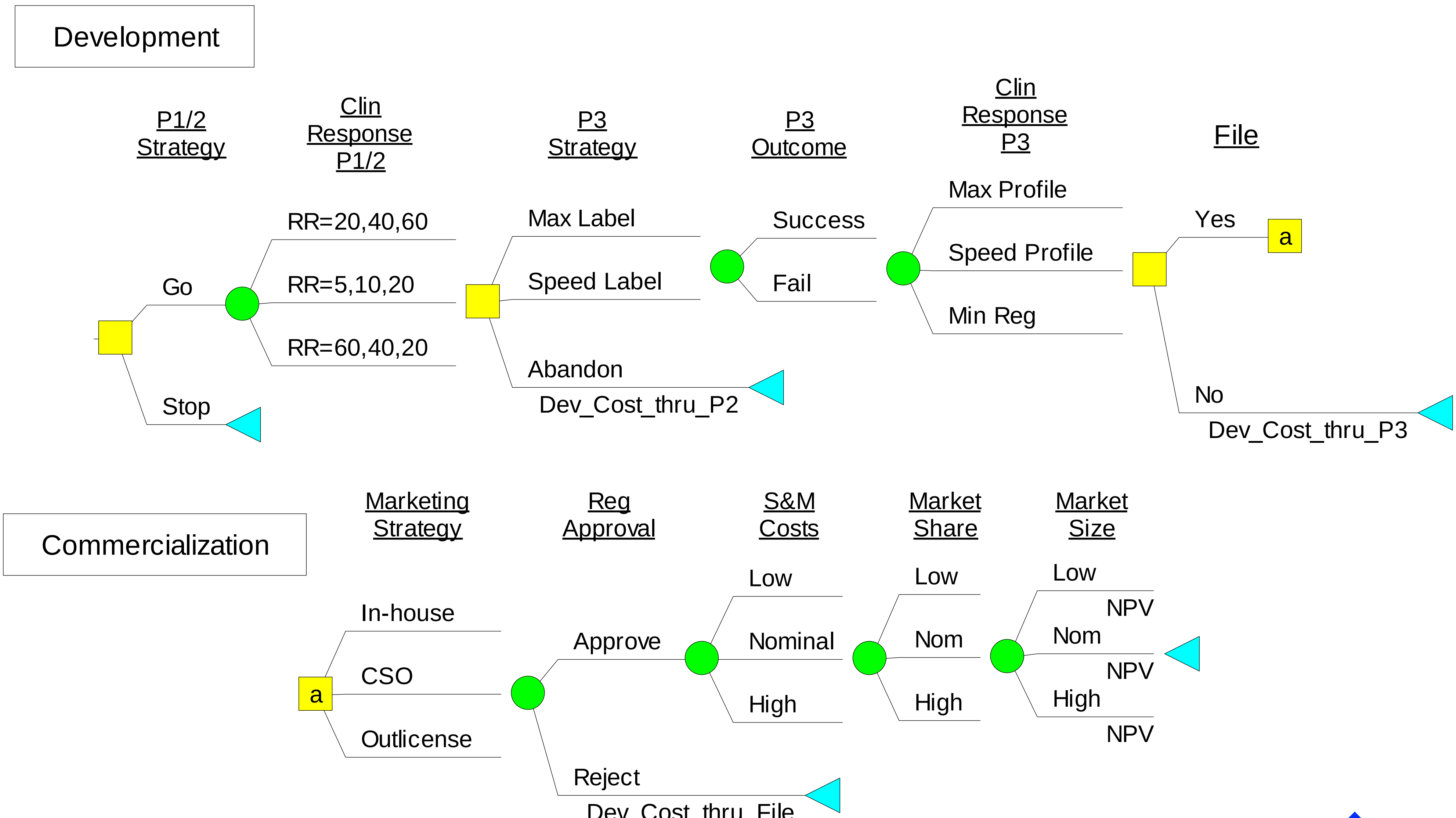
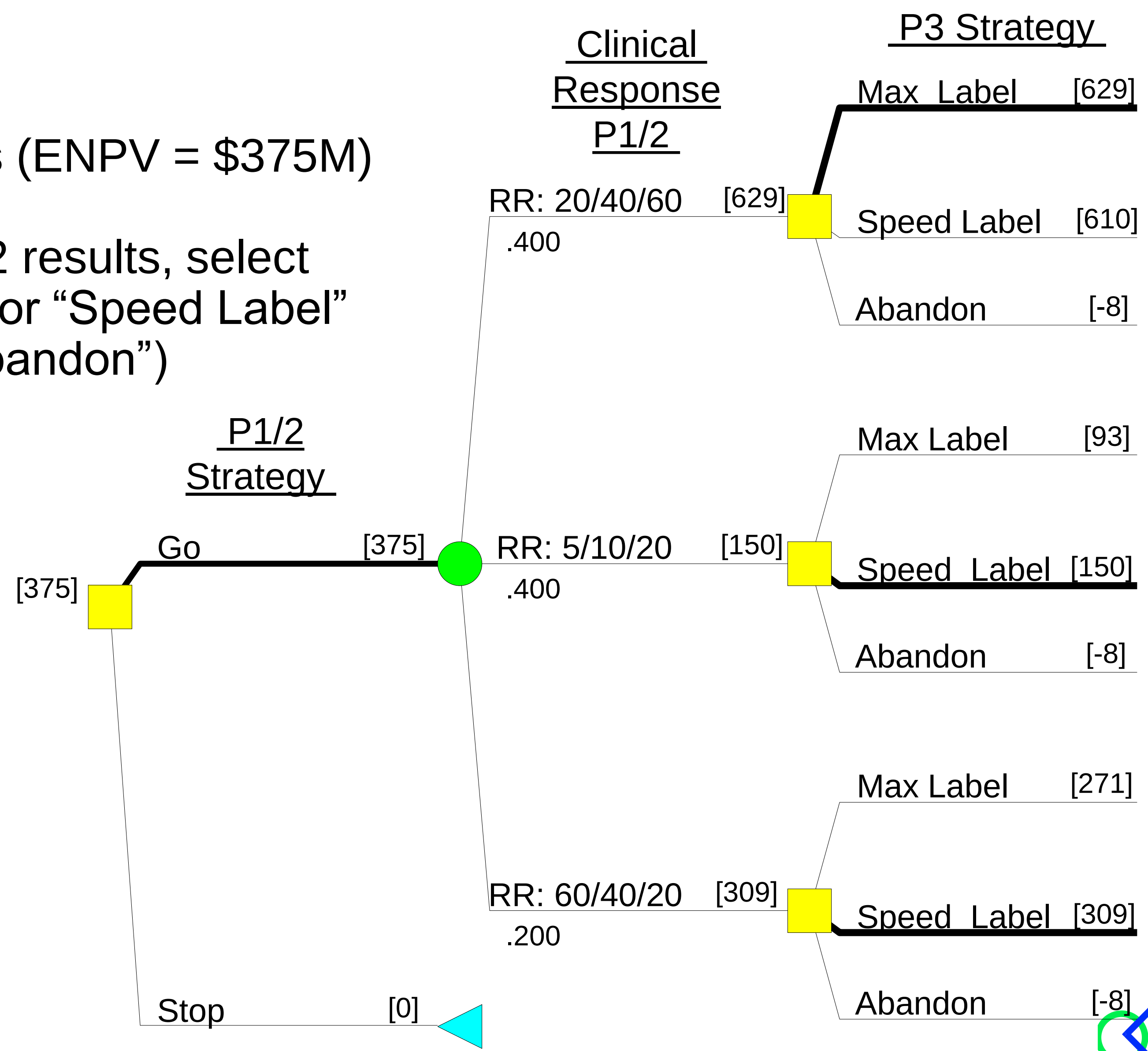
The decision tree identifies options and all scenarios to be analyzed



The expected NPV of Product X is $375 M

Optimal Policy:

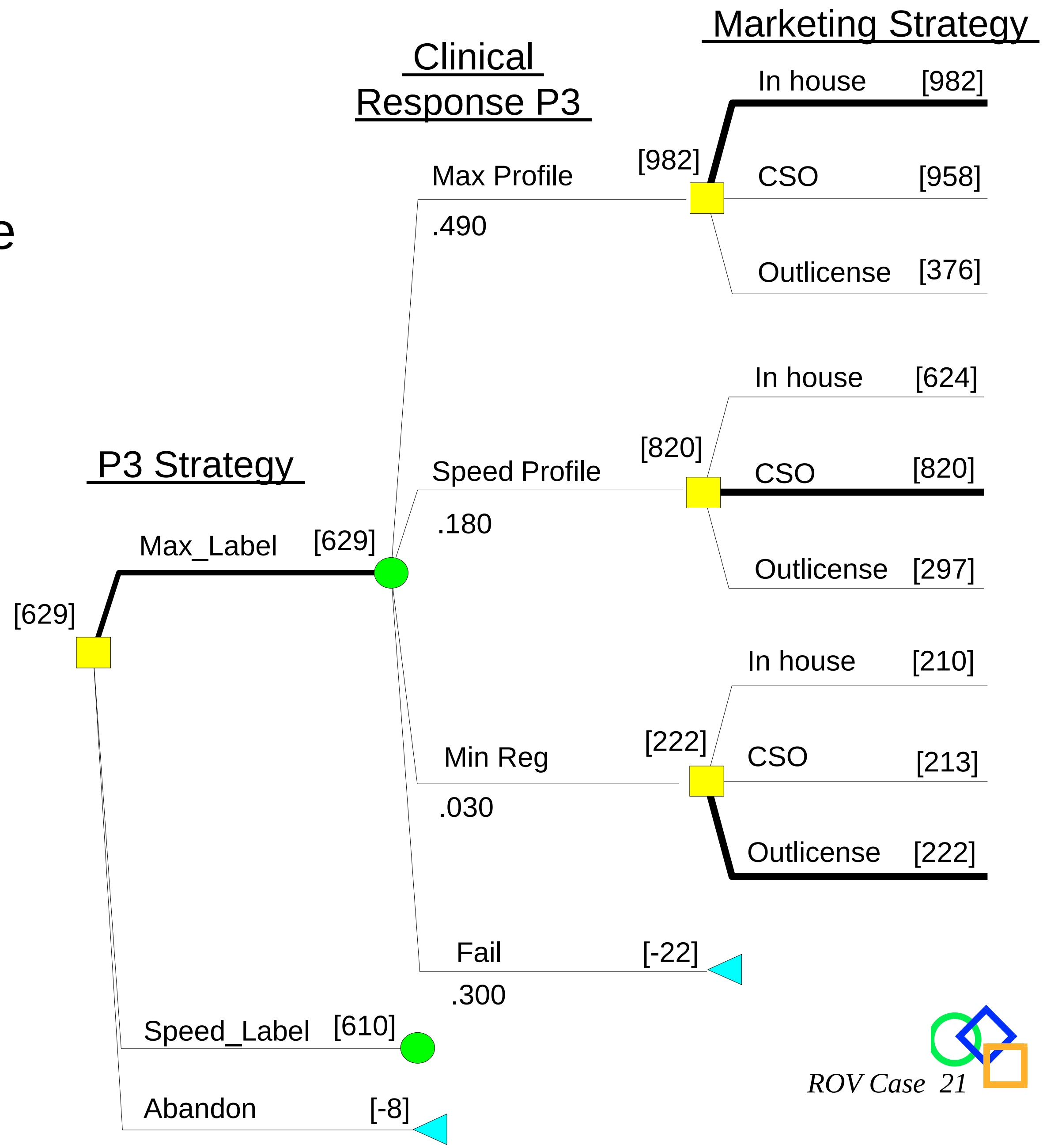
- Conduct P1/2 trials (ENPV = $375M)
- Depending on P1/2 results, select either "Max Label" or "Speed Label" strategy (never "Abandon")



We have a clear management plan after learning P3 results

Optimal Policy:

- Always file for regulatory approval unless P3 failure
- Our marketing strategy is contingent on the P3 trial results:
  - If Max Profile: In-house
  - If Speed Profile: CSO
  - If Min Reg: Outlicense



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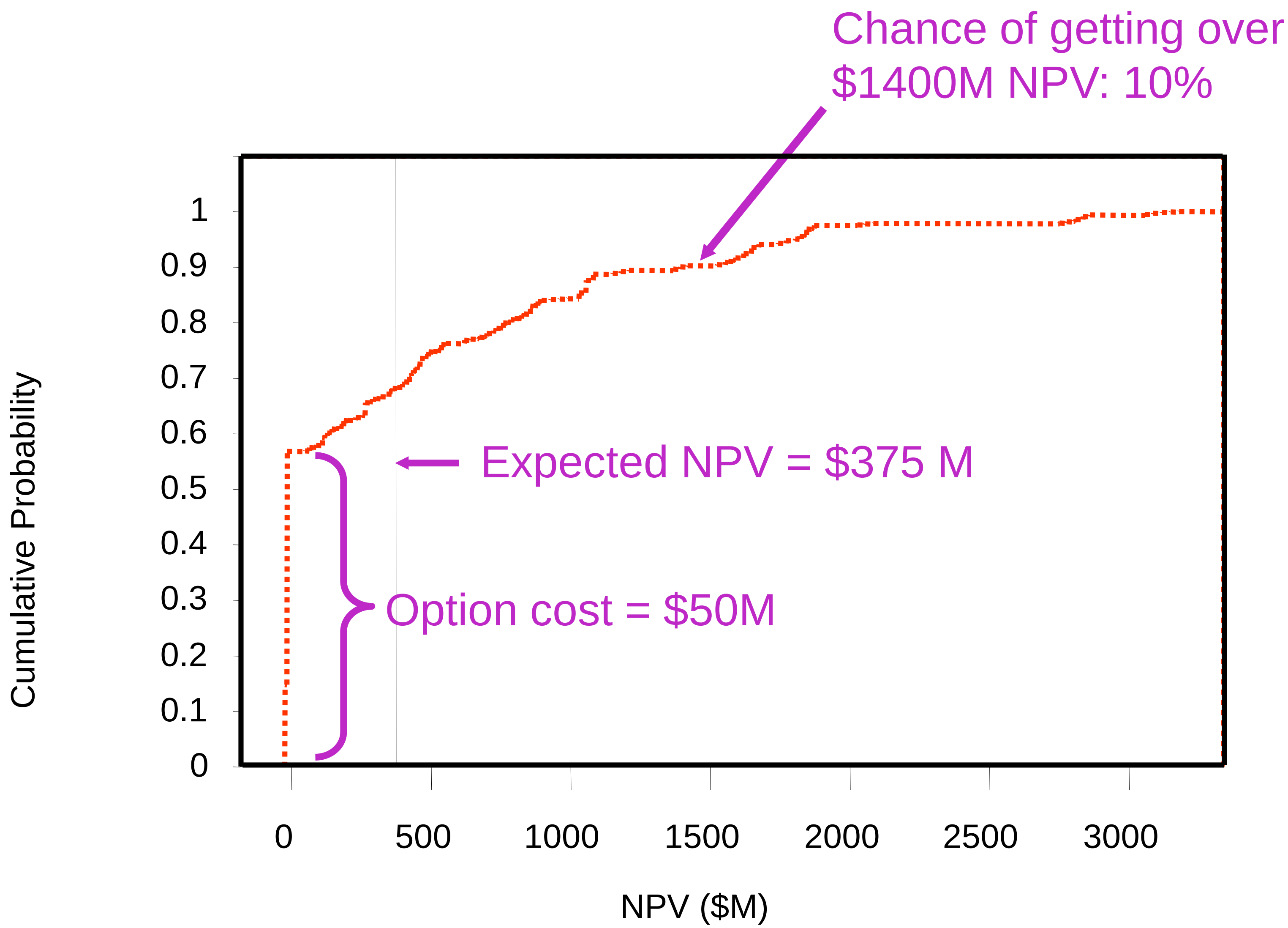
The risk profile for the optimal strategy shows the full range of possible outcomes



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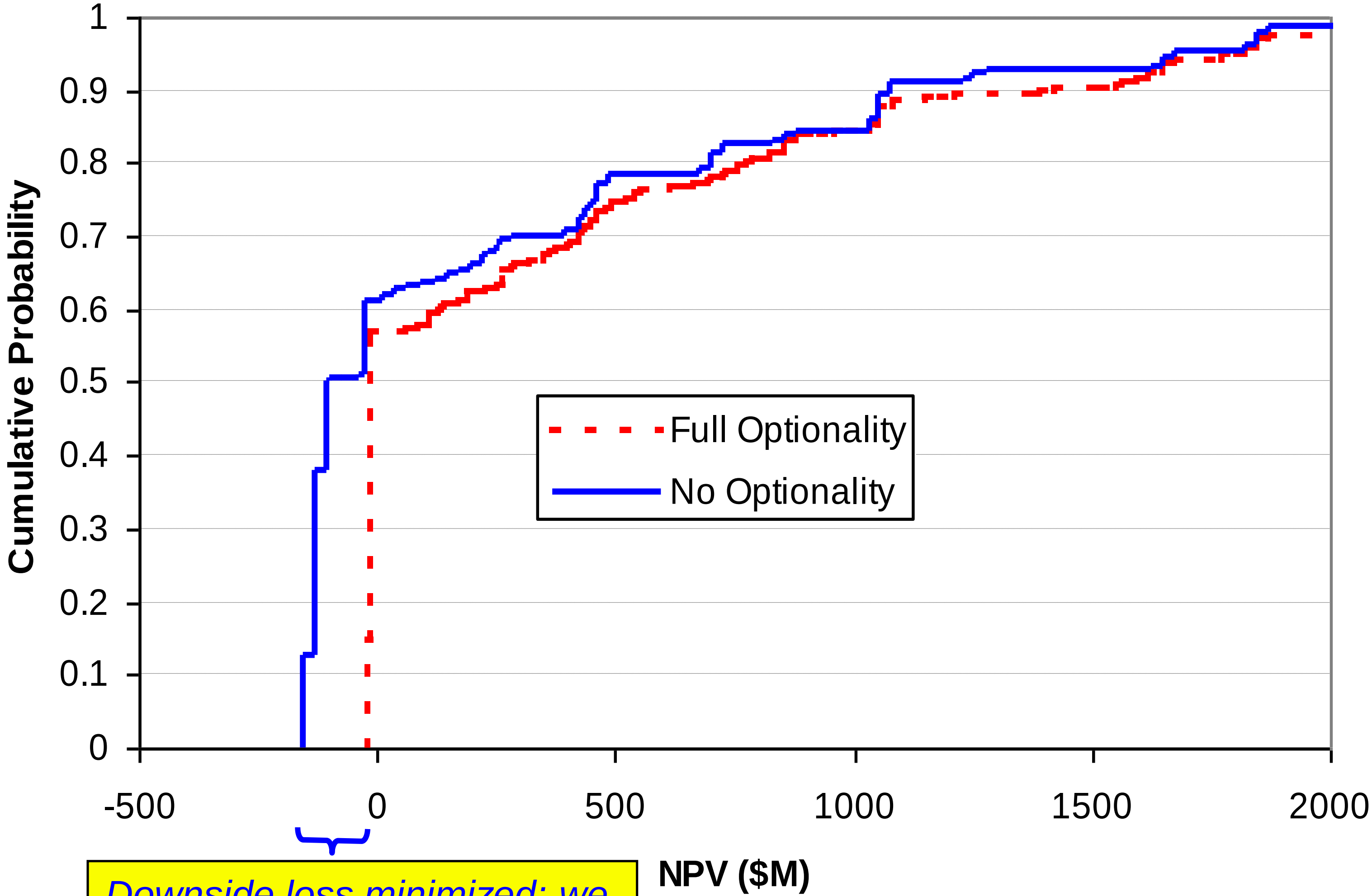
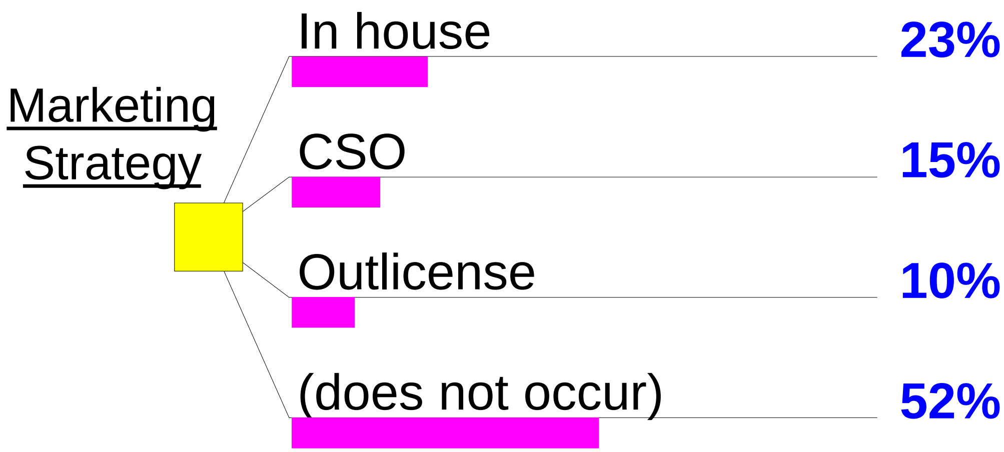
Accounting for optionality increases expected return and mitigates downside losses



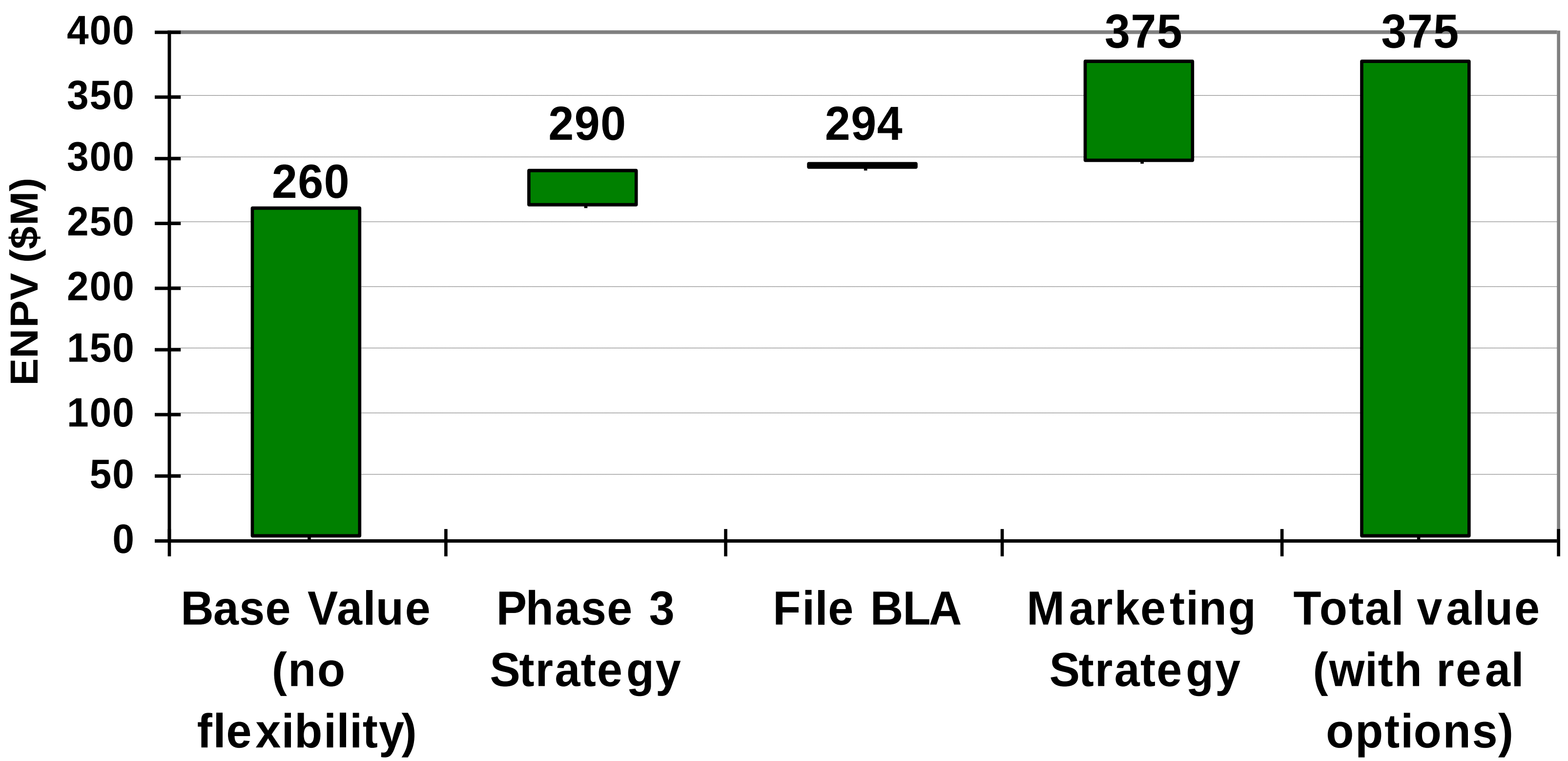
Downside loss minimized; we abandon when the option is "out-of-the-money"

A real options analysis allows us to show the likelihood of taking a particular course of action



- In this case, there is a 10% chance of Outlicense. If we are wise decision-makers, then 10% of the time the data will tell us that the preferred marketing strategy is Outlicense.

Each of the three options in our analysis contributes to overall product value



NPV is computed based on difference between having the option versus being required to make all decisions today

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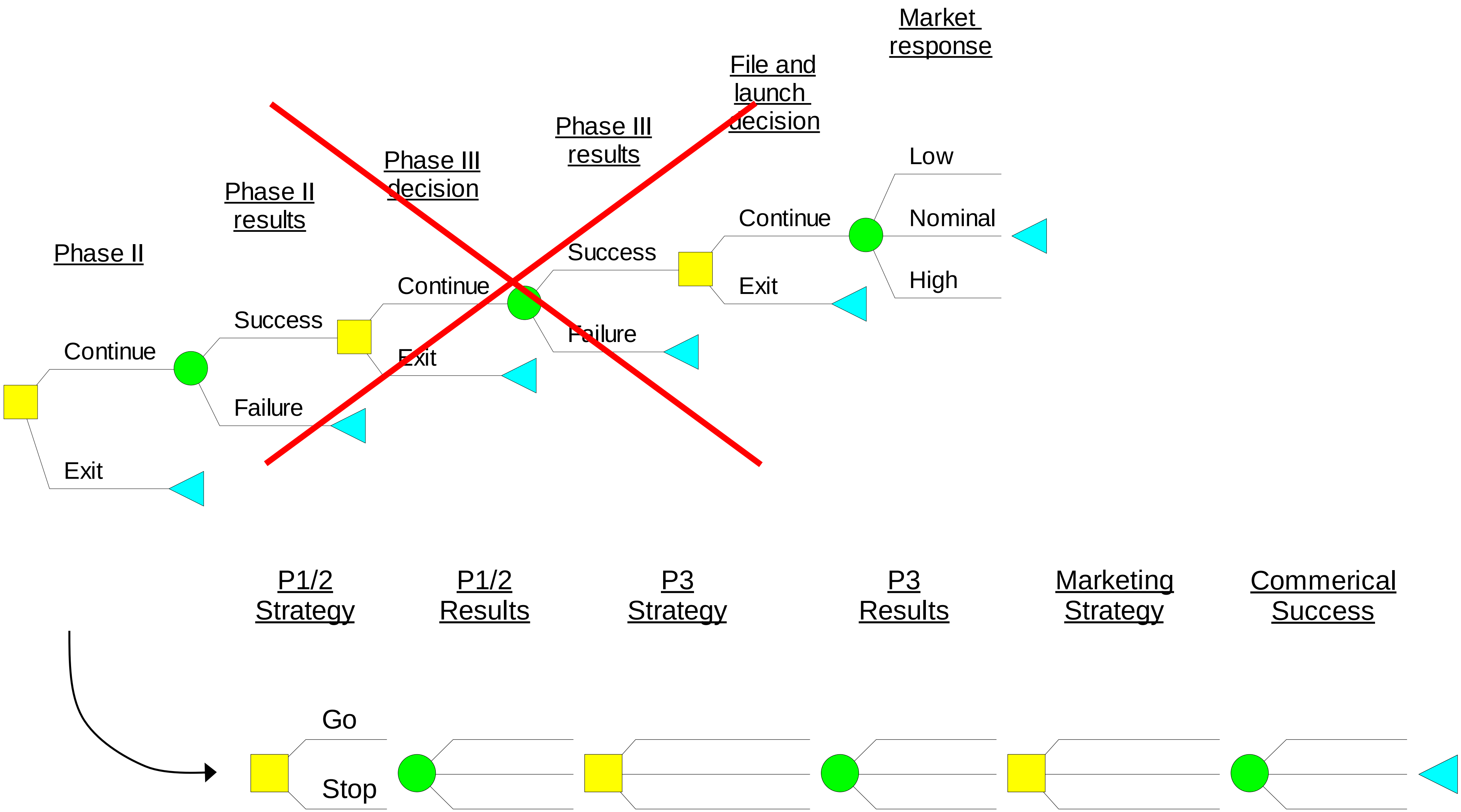
Valuing pharmaceutical R&D projects requires a real options mindset

- It is critical to frame the strategic choices in terms of today's decisions and future decisions
- A learning model must be developed that captures how information is revealed over time, and how that new information changes our future beliefs about relevant data
- To facilitate data assessment, the learning model should be designed to mimic how information is actually perceived by technical experts
- A dynamic financial model must be constructed that optimizes the firm's choices at each stage
- An explicit treatment of uncertainty is used both to trigger downstream decisions (when should we strike the option) and to characterize the true risks of a project

To properly value an option, three key features are fundamental

- Rigorous framing tools
  - Identifies sources of uncertainty
  - Identifies real options or future decision points
- A learning model
  - Captures changes in the level of an uncertainty over time as information is revealed
  - Drives the market value of the project
  - Based on actual clinical endpoints
  - Improved method to obtain the probability of technical success
- A dynamic decision model
  - Tree-based financial model that responds to new information and optimizes all downstream decisions (real options) conditioned by preceding uncertainties
  - Output provides management with a road-map to know how to act today and respond in the future, and provides risks of each alternative

Learning models are very effective in capturing the complexities of staged investments over time



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