ASSESSING THE FINANCIAL VIABILITY OF STRATIFIED MEDICINE USING DECISION TREE ANALYSIS

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Abstract

The cost of developing pharmaceutical drugs is rising to $1 billion and more per new drug (Herper 2013). Throughout the development process, if a pharmaceutical company finds itself in the situation where it cannot pass a certain clinical trial, it may have the option to pursue a stratified medicine opportunity from that point in development further. The potential market size for these stratified medicine opportunities is much smaller than empirical medicine (for example, one stratified drug, Kalydeco®, has the potential to help only 4% of people with cystic fibrosis), which deters pharmaceutical companies from developing these opportunities because these drugs are not financially viable for the company (FDA 2012).

Current valuation techniques (NPV analysis) for determining the financial feasibility of these opportunities are often recommending against the development of the stratified medicine opportunity. We wanted to take a different approach to valuating the feasibility of these stratified medicine opportunities (decision tree analysis) to more closely simulate the pharmaceutical company's drug development process and incorporate dynamic decision making into the valuation so pharmaceutical companies may have a more comprehensive set of tools to decide whether to pursue the stratified medicine opportunity.

We created two decision tree models to reflect the scenario when a pharmaceutical company does not have the option to pursue stratified medicine and when it does have this option. We evaluated the financial viability of five drugs using the traditional techniques and our models to compare the tools' recommendations. We also determined scenarios for when a drug may be determined viable and recommended to be developed further if stratified medicine is an option, but where the drug would be unviable if stratified medicine is not an option.

Table of Contents

List of Tables

List of Figures

Introduction

Throughout the drug development process, a drug must go through several clinical trial phases before the pharmaceutical company applies for FDA approval of the drug to bring it to market. Phase I of clinical trials typically takes two years to complete and involves testing the safety of the drug. Phase II typically lasts two years long and tests the effectiveness of the drug. Phase III typically takes three years to complete and tests the effectiveness of the drug as compared to the standard treatment. Once a drug passes all three phases of clinical trials, it can apply for FDA approval. If the drug gains FDA approval, the pharmaceutical company will then begin to commercialize the drug. Sometimes, companies are required to enter phase IV of clinical trials (post-FDA approval) in order to further test the long-term effects from the drug (FAQ 2008). The determination of whether a drug successfully passes a clinical trials phase depends on the p-values obtained from the statistical analysis on the results of the clinical trials. The standard p-value of 0.05 suggests borderline statistical significance of a clinical trial's results, but p-values less than 0.01 suggest confident statistically significant results (What Researchers 2005).

Sometimes, a drug going through clinical trials has results with p-values greater than 0.01, suggesting that the drug has failed this particular clinical trial phase, because the results were not confidently statistically significant. At this point in the development process, a pharmaceutical company may discover that the drug is very effective for a subset of the population being tested, but not effective for other subsets of the population. From here, the pharmaceutical company can make the decision to pursue development of a drug to help the subpopulation for which it has effective results, or the company can decide to stop development of the drug completely.

With pharmaceutical companies spending from hundreds of millions to over one billion dollars to research and develop (R&D) new potential drug entities, the decision of whether it would be financially viable to pursue the stratified drug opportunities is even harder (Herper 2013).

Motivation

In recent years, research to investigate the opportunity for stratified medicine has been on the rise as technology improves and costs increase. The Massachusetts Institute of Technology's (MIT's) Center for Biomedical Innovation has established a research program to investigate the economics of stratified medicine, with Mark Trusheim leading the program. Trusheim assesses the financial viability of stratified medicine using NPV (net present value) analysis and concludes, "stratified medicine initiatives create likely uneconomic product development incentives (negative NPVs) in many, perhaps most, cases" (Trusheim 2012). The Academy of Medical Sciences, namely Sir John Bell, FRS HonFREng PMedSci have also studied the financial feasibility of stratified medicine, concluding, "Existing systems…are still not set up to enable the effective widespread adoption of stratification, let alone realize and maximize the potential it offers" (AMS 2013).

Research completed in the field of stratified medicine has mostly concluded that the development of stratified medicine is economically disadvantageous. However, the most research done in this area, by Trusheim, has used a specific approach in NPV analysis to value stratified medicine opportunities. We would like to investigate the use of a different approach, specifically, decision trees, that employ the use of sequential decision making to see how the option of implementing stratified medicine affects the total expected NPV and the decision to go through clinical trials for the drug.

Contributions

This paper goes beyond clinical NPV analysis to assess stratified medicine's viability by incorporating decision trees over traditional techniques. We created two decision tree models, one for the case where empirical medicine is the only option of developing a drug, and the other model for the case where stratified medicine is an option to pursue throughout different phases in the development process. By using our new models, pharmaceutical companies can utilize another tool to help them decide whether to pursue potential stratified medicine opportunities. We used our tools to valuate several stratified drugs already on the market, including Herceptin®, Vectibix®, Zelboraf®, Xalkori®, and Kalydeco®. Our models valued these drugs with positive expected values to support the recommendation that these drugs should be developed. Further, we investigated the different conditions that would make a stratified drug viable or unviable. We created two plausible drugs to analyze the potential for a drug to have negative expected values and recommend for development to be stopped on the drug if it can only be developed as an empirical drug and negative expected values but the recommendation to continue development of the drug if it has the option of being developed as a stratified drug throughout development. The hope is that by using this model, pharmaceutical companies will feel more inclined to develop stratified medicine to ultimately help more people that are suffering get the help they might not otherwise receive.

Traditional Financial Viability Valuation

NPV analysis is the traditional technique used to evaluate the financial feasibility of stratified medicine. This valuation technique provides negative NPV's for some potential stratified drug opportunities, mostly stratified opportunities for small cancers (effecting fewer than 20,000 patients per year) (Trusheim 2012). These negative NPV's recommend against pharmaceutical companies pursuing stratified medicine development.

Basic NPV Analysis Background

NPV analysis for stratified medicine evaluates a drug's ability to make up its development costs on a time-dependent basis. Specifically,

$$NPV = \sum_{t=0}^{n} \frac{CF_{in} - CF_{out}}{(1+i)^t}$$

where

$$CF_{in} = Positive\ cash\ flows\ (e.g., revenue)$$

$$CF_{out} = Negative\ cash\ flows\ (e.g., costs)$$

$$i = Discount\ rate$$

$$t = Time\ period\ of\ the\ cash\ flows$$

$$n = Total\ number\ of\ time\ periods$$

Estimating future costs and revenues of the drug is required, but the value given to the drug from the NPV tool can help pharmaceutical companies decide whether it is cost effective to pursue development of that drug. Typically, negative NPVs suggest companies to not pursue the stratified medicine opportunity, while positive NPVs suggest companies to pursue the opportunity.

Expanded NPV Analysis

We created our own NPV model to expand upon the basic model described above. Positive cash flows include sales revenues, negative cash flows include development costs, time periods are valued in years, and we set the total number of years to twenty to account for the standard patent life of a drug. In addition, we considered the transition probabilities of progressing from one phase of clinical trials to another. Although still a basic NPV model, our expansion considers the general developments costs for a drug, but not for one drug in particular.

Development Costs

We calculated the development costs for each phase of drug development in order to have a sense of the costs incurred to develop a drug in general, not for one specific drug. By considering cost estimates from researchers including Joseph A. DiMasi (of the Tufts Center for Drug Development) (DiMasi March 2003), Christopher P. Adams and Van V. Brantner (of the Bureau of Economics, FTC) (Adams CP 2006), SM Paul (of Eli Lilly & Co.) (Paul SM 2010), John LaMattina (former President of Pfizer Global R&D) (LaMattina 2012), and more, we were able to determine the following costs associated with each development phase as summarized in Table 1.

Table 1: Development Costs by Researcher & Development Stage

	DiMasi, et al. ($M 2000)	Adams, Brantner ($M 2009)	Paul, et al. ($M 2009)	LaMattina ($M 2012)	**Average $M 2014**
Preclinical	121	164.6	284.4		**217.91**
Phase I-IV	282	383.7	599.2		**484.77**
FDA Approval				1.84	**1.87**
Total	403	548.3	883.6		**702.68**

The costs from Table 1 for the four clinical trial phases are not divided amongst the individual phases. Table 2 shows the per-patient costs for each of the four phases of clinical

trials from the Cell Therapy Blog (Clinical Trial Costs 2011) and Elio Evangelista (from Cutting Edge Information) (Evangelista 2013) as compiled in Table 2 below (all units in $).

Table 2: Per-Patient Costs for Clinical Trial Phases

	Cell Therapy Blog	Evangelista	**Average**	**Percentage of Total**
Phase I	21,883	20,000	**20,942**	**17%**
Phase II	36,070	35,000	**35,535**	**29%**
Phase III	47,523	47,000	**47,262**	**39%**
Phase IV	17,042	17,000	**17,021**	**14%**

Development costs to be used in the model for each of the development stages were calculated from the previous information. First, the development costs from Table 1 were adjusted to 2014 $USD considering inflation rates, and averages were both the preclinical and combined clinical trials stage. From Table 2, the average per-patient costs and the percentages of total per-patient costs for each phase were calculated. These percentages from Table 2 were applied to the calculated average combined clinical trials costs from Table 1. The results for a pharmaceutical company's development costs per new drug (in general) broken down into the development stages are shown in Table 3 below:

Table 3: Reconciled Development Phase Costs

Stage	**Costs ($USD M)**
Preclinical	217.91
Clinical Trials	
Phase I	84.07
Phase II	142.65
Phase III	189.73
FDA Approval	1.87
Phase IV	68.33
Total	**704.56**

Phase Transition Probabilities

Considering conditional phase transition probabilities between stages of drug development from Tufts's Center for the Study of Drug Development (Tufts CSDD 2013), Ken

Getz (Director of Sponsored Research Programs for the Tufts CSDD) (Getz n.d.), DiMasi (DiMasi March 2003), and more, we were able to determine the average phase transition probabilities as shown in Table 4.

Table 4: Phase Transition Probabilities

From Stage	To Stage	Tufts CSDD	Ken Getz	DiMasi, et al.	**Average**
Phase I	to Phase II	0.706	0.70		**0.70**
Phase II	to Phase III	0.454	0.33		**0.39**
Phase III	to FDA Approval	0.593	0.80	0.685	**0.69**

Herceptin® NPV Example

Herceptin® (trastuzumab) is the most familiar success story of a pharmaceutical drug that was developed as a case of personalized medicine. Herceptin® is a targeted therapy originally developed for HER2 Positive Metastatic Breast Cancer (accounting for about 25% of breast cancer patients). It was developed by Genentech and granted official FDA approval in September 1998 (Kurian 2007). Herceptin® U.S. sales were $1.879 billion in 2013, with Avastin (an empirical drug used to treat certain other types of cancers) having 2013 U.S. sales of $2.617B, for context (IMS Health 2014). Herceptin® is a blockbuster drug that emerged as an "ideal situation" of stratified medicine, since it can help a large subpopulation with a specific gene (over 700,000 patients per year) (The American Cancer Society 2013).

Using the NPV model we created for a general drug, we valued Herceptin® at ($58.51M), seen in Figure 1 below, which recommends against pharmaceutical companies developing the drug.

Figure 1: Herceptin® NPV Analysis

Phase Transition Probabilities		Pre-->Ph1	Ph1-->Ph2	Ph2-->Ph3	Ph3-->Ph4	Hurdle
		1	0.7	0.39	0.69	0.11
	Year	Costs	Sales	"Cash Flow"	Probability	NPV
Preclinical	0	-217.91		-217.91	1.00	-217.91
Phase 1	1	-42.04		-42.04	1.00	-37.87
	2	-42.04		-42.04	1.00	-34.12
Phase 2	3	-71.33		-71.33	0.70	-36.51
	4	-71.33		-71.33	0.70	-32.89
Phase 3	5	-63.24		-63.24	0.27	-10.25
	6	-63.24		-63.24	0.27	-9.23
	7	-63.24		-63.24	0.27	-8.32
FDA Approval	8	-1.87	30.50	28.63	0.19	2.34
Commercialization	9	-13.67	183.70	170.03	0.19	12.52
Ramp-up	10	-13.67	249.70	236.03	0.19	15.66
	11	-13.67	315.40	301.73	0.19	18.03
	12	-13.67	344.90	331.23	0.19	17.83
	13	-13.67	406.00	392.33	0.19	19.03
Commercialization	14		479.00	479.00	0.19	20.93
Steady-State	15		747.20	747.20	0.19	29.42
	16		1234.00	1234.00	0.19	43.77
	17		1287.00	1287.00	0.19	41.12
	18		1382.00	1382.00	0.19	39.78
	19		1382.00	1382.00	0.19	35.84
	20		1382.00	1382.00	0.19	32.29
					NPV:	-58.51

Trusheim's NPV analysis for Herceptin® considers several extra parameters on top of the basic NPV analysis. He employs parameters concerning population distribution (including 11% expected responders to the drug), indication market size (including 384,556 incidence for the launch year, and 2% patient growth), and $25,000 base price, to name a few. Trusheim's NPV model for Herceptin® calculates $2.019B NPV and $323M risk-adjusted NPV (also using an 11% hurdle rate) (MIT CBI 2014). These positive NPV's are consistent with the recommendation to develop the stratified drug opportunity.

Proposed Financial Viability Valuation

NPV analysis is helpful for providing a straightforward calculation of the overall value of a potential stratified medicine opportunity. It incorporates the drug's expected costs and revenues, likelihood of entering each successive stage of drug development, and time-dependency considerations. However, a major disadvantage of NPV analysis is that it only values the potential economic feasibility of stratified medicine at the onset of the development opportunity, and therefore does not capture the company's ability to make decisions throughout the time horizon considered. Calculating a potential drug's NPV recommends to the pharmaceutical company at the preclinical stage whether to pursue development. It does not account for the potential for deciding to pursue an opportunity at the end of a phase of development – a scenario that is more realistic and useful to consider since the opportunity to pursue stratified medicine can arise during any stage of drug development.

Decision tree analysis (DTs), our proposed method, incorporates dynamic decision-making that considers new information throughout the development process. Where NPV analysis values a stratified medicine opportunity by one number that the company calculates at the preclinical stage of development, DTs value the drug opportunity at each stage of development, providing a way to evaluate the financial viability based on different scenarios of development.

Decision Tree Analysis Background

DT analysis is a valuation tool that accounts for risks and decisions made throughout the drug development process. It considers future potential decisions and the potential for abandonment during any phase within the process. DT analysis evaluates each potential outcome, gives the value of the drug at each phase within the process, and lastly, it gives the

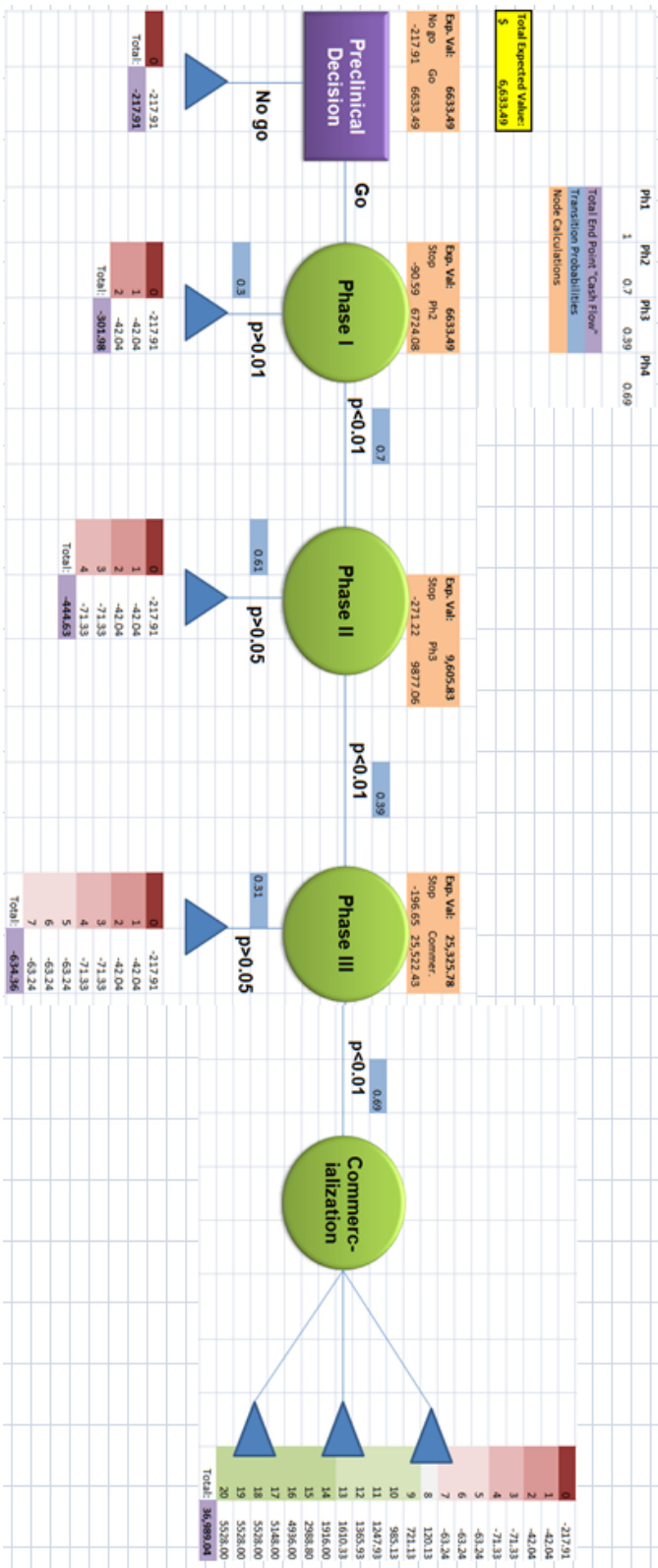
expected value of the whole development process to give pharmaceutical companies insight into the viability of the drug. Where DT analysis considers every potential outcome (all potential decisions, changes in the sequence of the traditional development process phases, abandonment outcomes, and market outcomes), NPV analysis values the drug by assuming a standard development process where the drug is granted FDA approval as a stratified medicine and taken to market.

The DT models we created for determining the financial feasibility of stratified medicine come in two types: (1) one assumes developing a drug as empirical medicine is the only option; (2) the other assumes stratified medicine is always an option throughout the drug development process. We compared the proposed decisions of whether to pursue a stratified medicine opportunity using the (2) DT model with the basic NPV analysis, in order to investigate the advantages/disadvantages of using one type of model over another. We also compared the two different DT models with each other to determine if the potential for pursuing stratified medicine at all, at any point during the development process, is worth it. We used the same development costs and phase transition probabilities that we calculated for our expanded NPV analysis.

Decision Tree Analysis – Empirical Medicine Only

The simpler of the two different decision tree models is the "empirical medicine only" case, whereby the decision for pharmaceutical companies to pursue a particular drug entity only considers the potential for the drug to work for large populations (e.g., all people with Alzheimer's) or else the company will withdraw development completely. Modeling this case is helpful to use as a benchmark for comparing to the case where stratified medicine could be an option for the pharmaceutical company to pursue. Figure 2 below shows an "empirical medicine only" decision tree analysis case for Herceptin®, which has an expected value of $6.633B.

Figure 2: DT Empirical Only Herceptin®



This DT model has only one potential market outcome (the full FDA approval of the drug as an empirical medicine) and four abandonment outcomes (only one of which is possible through an explicit decision). While the p-values drive the determination of a drug passing or failing a clinical trial phase, the phase transition probabilities from Table 4 take into account the probability of the p-values being significant enough for a drug to continue onto the next phase. Development costs from Table 3 are used to value each potential outcome. The development costs for each specific outcome are totaled according to the phases through which the drug would have been developed. Then, considering the phase probabilities of entering the phases before an outcome, the expected value of each phase and decision are calculated above the phase itself.

The only explicit decision to be made in this DT is during the preclinical stage (in the purple box), where the DT values both avenues from the preclinical decision (the total value of not pursuing the drug at all versus the total value of pursuing the drug to any other outcome) to suggest to the pharmaceutical company which avenue will create the most value for the company. In theory, negative DT expected values should result in the pharmaceutical company not pursuing development at all and positive DT expected values should suggest them to continue development.

Decision Tree Analysis – Stratified Medicine Option

This DT assumes stratified medicine is always an option throughout the drug development process. The model has three market outcomes: the case where the drug is developed as empirical medicine; the case where the drug is developed as stratified medicine after phase II of the first round of clinical trials; and the case where the drug is developed as stratified medicine after phase III of the first round of clinical trials. This DT also has several abandonment outcomes, three of which are possible through an explicit decision. The same p-

value significance rules are used, except that from phase II and phase III in the first round of clinical trials, p-values of 0.05 or higher suggest abandoning development and p-values between 0.01 and 0.05 open the opportunity for stratified medicine to be pursued. The stratified medicine decisions (in purple boxes, like the preclinical explicit decision) depend on whether the avenues leaving from the decision produce positive or negative expected values. Again, at the preclinical phase decision point, the expected value of pursuing drug development at all is compared with the option of stopping development, and negative DT expected values suggest not pursuing development and positive DT expected values suggest pursuing development. The "stratified medicine option" DT model for Herceptin® is shown in Figure 3 and gives Herceptin® an expected value of $6.987B.

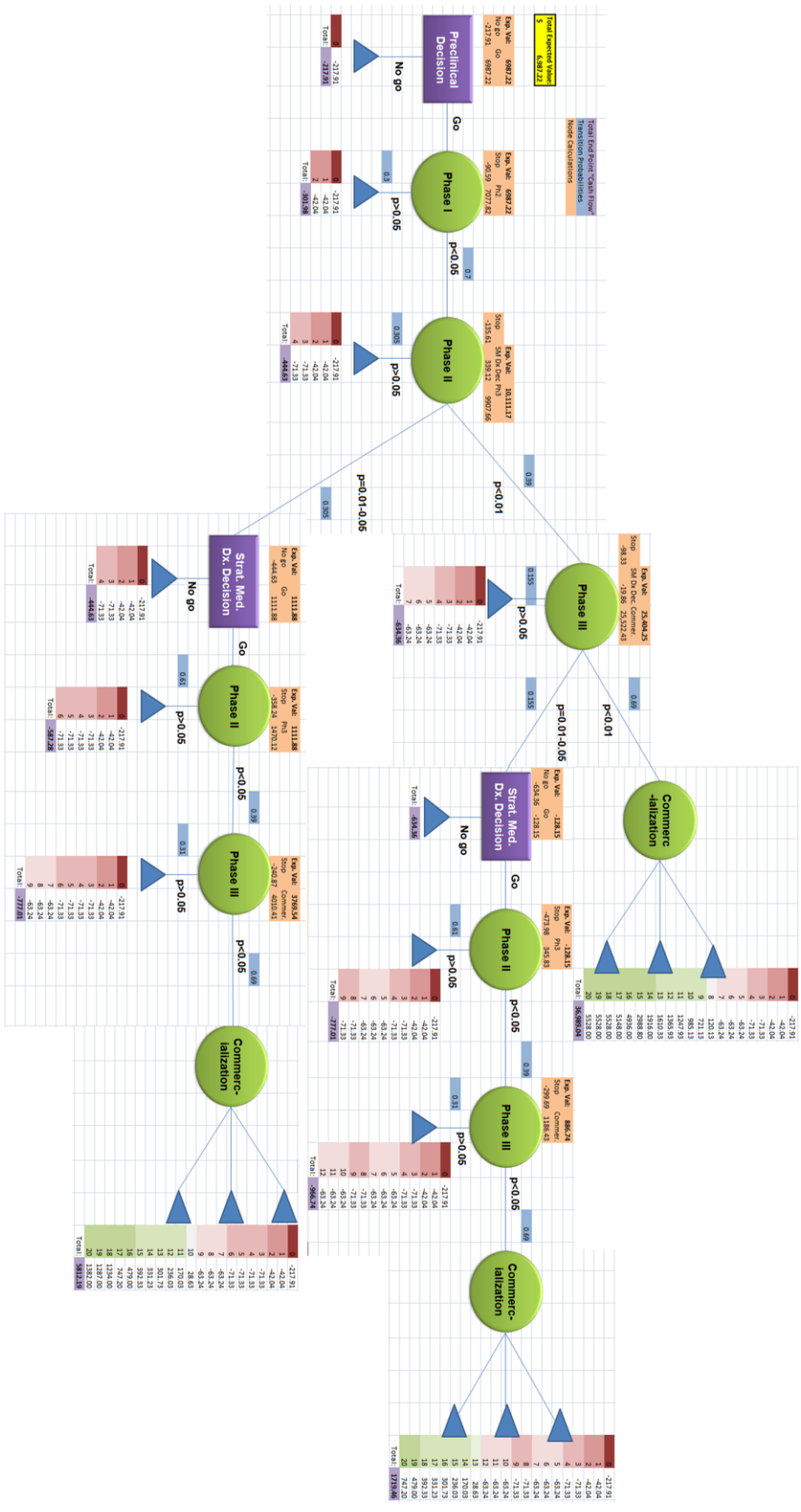


Figure 3: DT Stratified Medicine Option Herceptin®

Drug Valuation Examples

As previously stated, Herceptin® is known as a "blockbuster" stratified medicine drug since it can help over 700,000 patients per year, and Trusheim has valued this drug at an NPV of $2.019B. Our expanded NPV model values Herceptin® at ($58.51M), our DT empirical drug only model values Herceptin® at $6.663B, and our DT stratified medicine option model values Herceptin® at $6.987B.

Vectibix® (panitumumab) is a drug used for the treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal carcinoma (mCRC), helping about 50% of people with colorectal cancer, or over 550,000 patients per year (Amgen, Inc. 2014) (Medscape 2014) (The American Cancer Society 2013). It was developed by Amgen Inc. and received FDA approval in 2006 (Drugs.com 2014). Trusheim has valued Vectibix® at an NPV of $566M (MIT CBI 2014). We valued Vectibix® at an NPV of ($319.38M), DT empirical model expected value at $109.18M, and DT stratified model at $70.31M.

Results are not shown for NPV analysis that Trusheim performed on drugs other than Herceptin® and Vectibix®, but we ran our models through three more drugs, Zelboraf®, Xalkori®, and Kalydeco®.

Zelboraf® (vemurafenib) is used to treat melanoma patients with a BRAF gene mutation (about 50% of patients), affecting nearly 450,000 patients per year (Gonzalez 2013) (The American Cancer Society 2013). It was developed by Roche Molecular Systems and received both priority review and fast track designation (see section "Other Development Parameters to Consider on pp. 33-34 for further explanation) from the FDA before being fully FDA approved in 2011 (FDA 2014) (FDA 2012). We investigated Zelboraf® because it received priority review and fast track designation from the FDA.

Xalkori® (crizotinib) was developed by Pfizer, Inc. and received accelerated approval from the FDA before being fully approved in 2011 for the treatment of patients with non-small cell lung cancer (NSCLC) that are ALK-positive, accounting for nearly 13,000 patients per year (Pazdur 2013) (O'Bryant 2013) (The American Cancer Society 2013) (FDA 2012). We investigated Xalkori® because it received accelerated approval from the FDA.

Kalydeco® is a stratified drug used to treat patients with cystic fibrosis that have the G551D mutation in the CFTR gene, accounting for only 1,200 patients per year. Vertex Pharmaceuticals Inc. developed Kalydeco® and received full FDA approval for the drug in 2012 (FDA 2012). We investigated Kalydeco® because its potential market is much smaller than the other drugs we have investigated (only 10% of the Xalkori® market and less than 1% of the Zelboraf® market).

The results of running these drugs in our NPV model, DT empirical model, and DT stratified model are included below in Table 5 (all units are in $M).

Table 5: Models Comparison

	NPV	DT Empirical	DT Stratified
Herceptin®	(58.51)	6,633.49	6,987.22
Vectibix®	(319.38)	109.18	132.53
Zelboraf®	(306.50)	159.71	197.32
Xalkori®	(314.05)	35,545.44	36,042.71
Kalydeco®	(191.65)	19,839.43	20,016.73

For all drugs, our NPV model is giving negative NPV's, which recommends pharmaceutical companies to not develop the drug, whereas the DT stratified model gives positive expected values, suggesting for the development of the drug. Also for all drugs, the DT stratified model shows larger expected values than the DT empirical model, due to the added

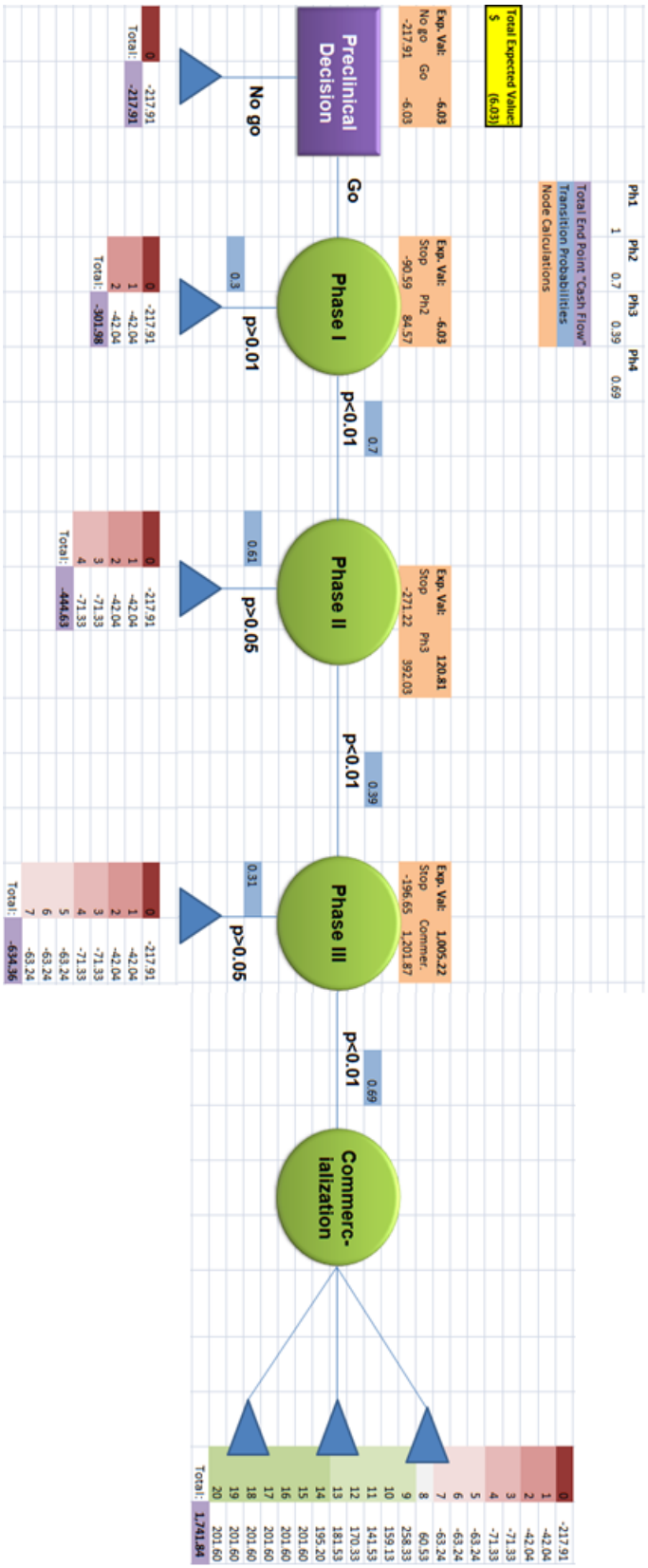
upside of developing a stratified drug to address patients' needs, which the decision-maker only pursues if it adds a net financial gain (if it increases the expected value).

Plausible Drug Examples

We created two plausible drugs that have the same characteristics as stratified drugs on the market today and evaluated them according to the models to mimic two different situations pharmaceutical companies may face in making the decision of whether to pursue a stratified medicine opportunity.

The first situation simulates a drug that has a negative NPV, a negative expected value from the DT empirical model, but a positive expected value from the DT stratified model. This situation suggests that through the use of DT analysis, a drug may end up having a positive expected value through development only if the option of developing it as a stratified medicine is possible. The drug used for this situation is assumed to have completed the standard FDA approval process (did not use any accelerated development mechanisms) and its two DT models are shown below in Figures 4 and 5. For plausible drug #1, the NPV is ($333.26M), the DT empirical model expected value is ($6.03M), and the DT stratified model expected value is $2.38M.

Figure 4: Plausible Drug #1 DT Empirical



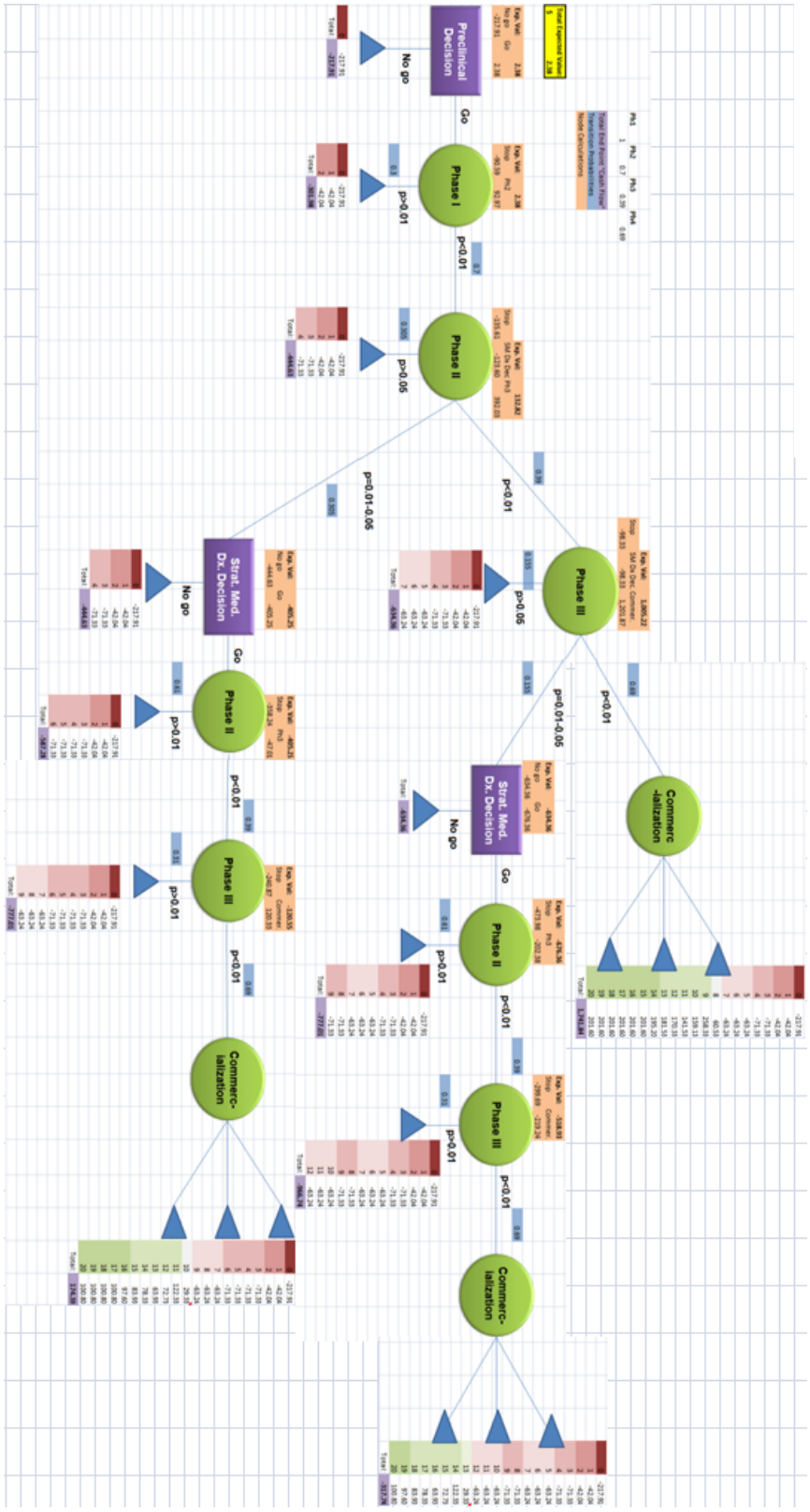
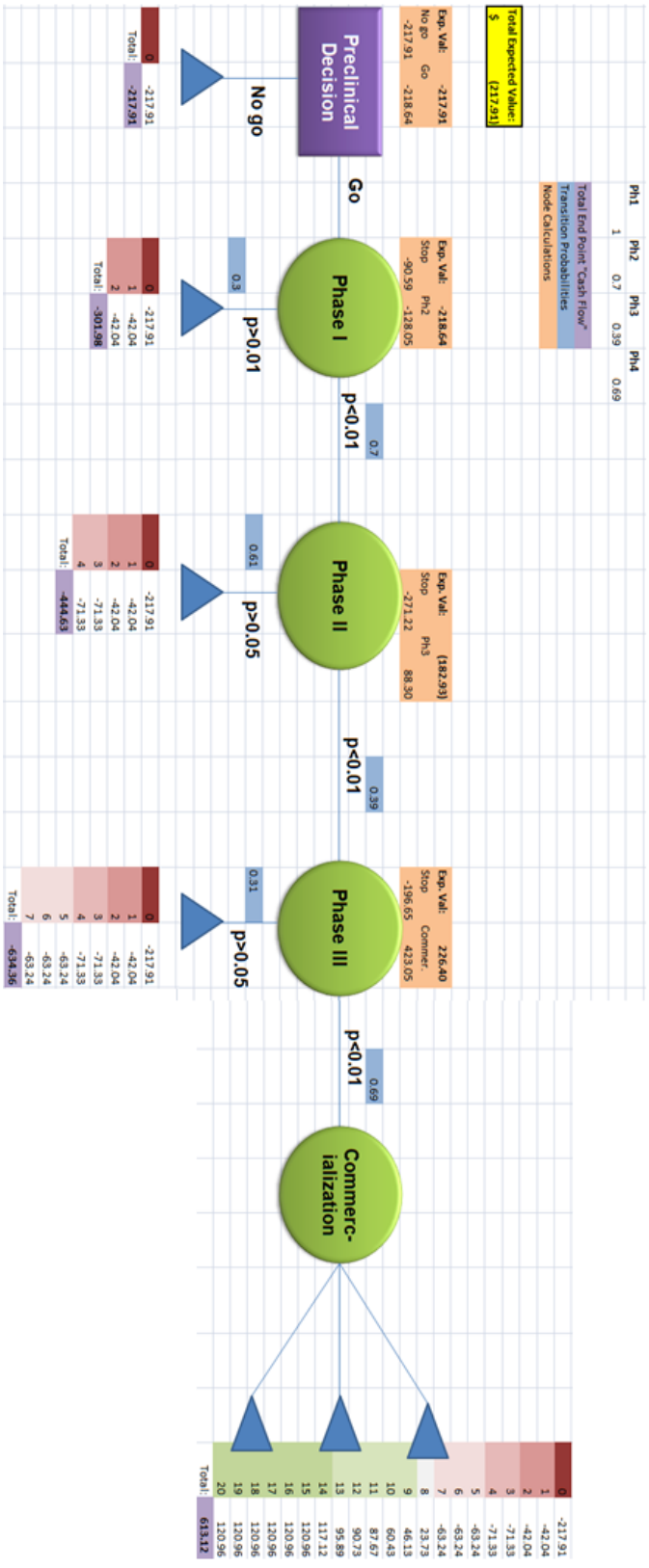


Figure 5: Plausible Drug #1 DT Stratified

The second situation simulates a drug that has a negative NPV, an expected value from the DT empirical model that suggests for the company to not develop the drug at all, and an expected value from the DT stratified model that recommends that the company proceed with development of the drug. This situation suggests that through the use of DT analysis, a drug may only be financially viable if stratified medicine is an option for the drug to pursue, and the drug would not be financially viable if developing the drug as an empirical medicine is the only option for development. The drug used for this situation is also assumed to have completed the standard FDA approval process and its two DT models are shown below in Figures 6 and 7. For plausible drug #2, the NPV is ($341.29), the DT empirical model expected value is ($217.91M), (the cost of stopping development after the preclinical phase), and the DT stratified model expected value is ($216.40).

Figure 6: Plausible Drug #2 DT Empirical



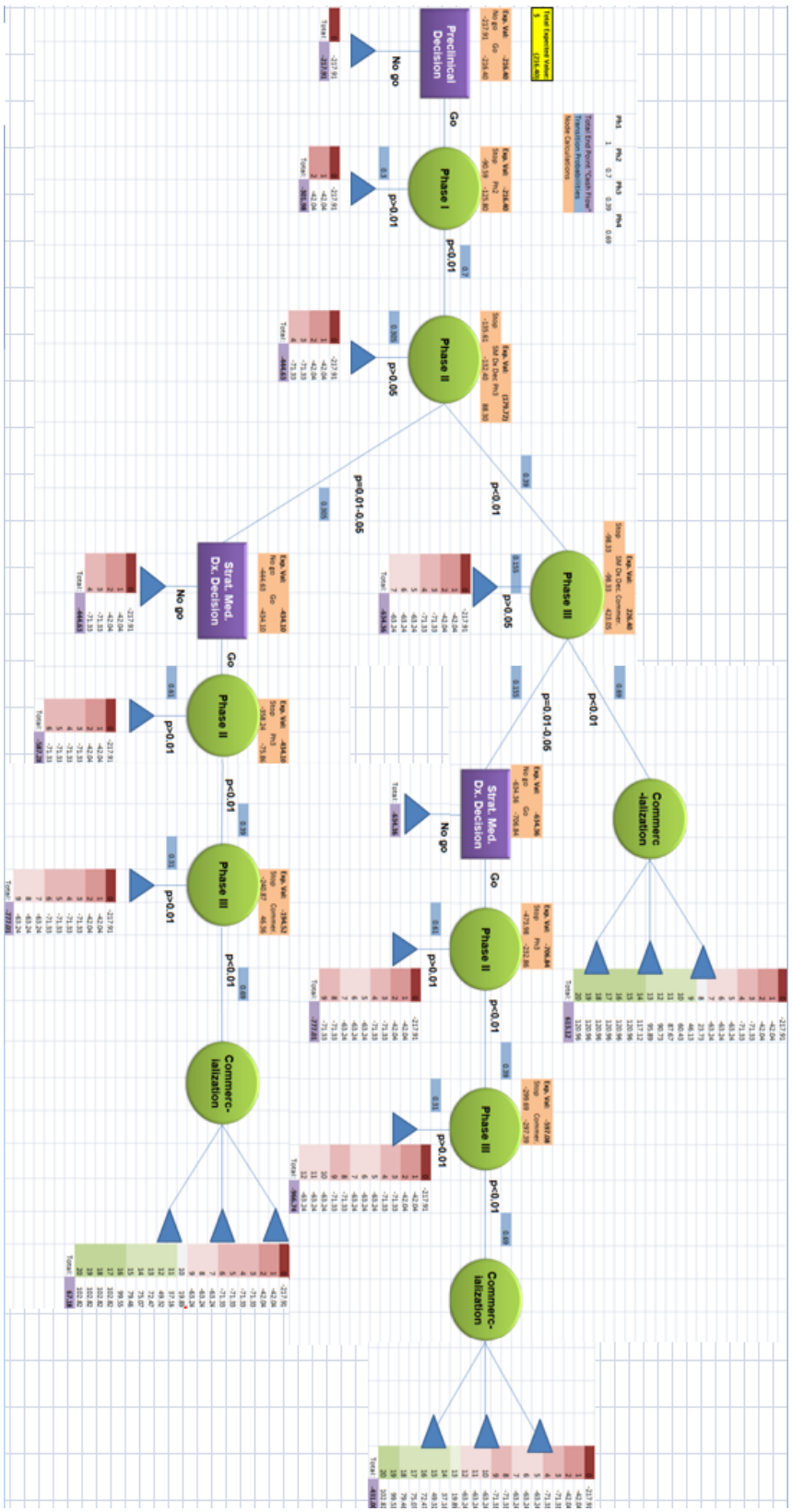


Figure 7: Plausible Drug #2 DT Stratified

Sensitivity Analysis

The major parameters used in our models include the development costs and the clinical trial phase transition probabilities. We performed sensitivity analysis on both the plausible drug #2's DT empirical and DT stratified models to determine how much the expected value of the models change with changes in these parameters.

Development Costs

Changing the preclinical phase development costs from the average we calculated above to Paul's preclinical costs and converting to 2014 $M gives us $310.00M for the preclinical phase. For the DT empirical model, the expected value decreases to ($310.00M) from ($217.91M) and this recommends pharmaceutical companies to not pursue development for the drug. For the DT stratified model, the expected value decreases to ($308.49M) from ($216.40M), suggesting for pharmaceutical companies to pursue development. We also changed the preclinical costs to DiMasi's costs ($164.32 in 2014 $M), which increased the DT empirical model to ($164.32M) and the DT stratified model to ($162.81M), while still making the same recommendations to the pharmaceutical companies as before. Changing the preclinical phase costs to ($219.63M) for the DT empirical model changes the pharmaceutical company to a point of indifference between pursuing development of the drug and not pursuing development. There is no feasible point of indifference for the DT stratified model, (at best, the avenue to pursue development is $1.51 greater than stopping development completely), suggesting that it is always optimal to pursue development in this case.

We then changed the total development costs for the clinical trials phases I-IV to Paul's ($652.13M) total and distributed this amount the same as before within the different trial phases. The DT empirical model expected value stayed at ($217.91M) and the DT stratified model

expected value decreased to ($217.91M) from ($216.40M). Changing this number again to DiMasi's ($382.96M) changes the DT empirical model expected value to ($183.42M) and the DT stratified model expected value to ($175.81M), where both models now recommend for the pharmaceutical company to pursue development of the drug. The point of indifference between pursuing development or not pursuing development occurs for DT empirical when the total clinical trials phases I-IV costs decrease to $482.44M from $484.77M, or phase I costs $83.66M, phase II costs $141.96M, phase III costs $188.81M, and phase IV costs $68.00M. The point of indifference between pursuing development or not pursuing development occurs for DT stratified when the total clinical trials phases I-IV costs increase to $487.24M, or phase I costs $84.49M, phase II costs $143.38M, phase III costs $190.69M, and phase IV costs $68.68M. Table 6 summarizes these results, showing the percentage change of the expected values of both the DT empirical and DT stratified models from changes in the development costs (all costs units are in $M).

Table 6: Sensitivity Analysis on Costs Results

Factor	Current Value	Change to	% Delta	DT Empirical	DT Stratified
Preclinical	(217.91)	(310.00)	-42.3%	-42.3%	-42.6%
	(217.91)	(164.32)	24.6%	24.6%	24.8%
Phases I-IV	(484.77)	(652.13)	-34.5%	0.0%	-0.7%
	(484.77)	(382.96)	21.0%	15.8%	18.8%

Phase Transition Probabilities

We also changed the clinical trial phase transition probability from phase II to phase III from 0.39 to Getz's 0.33 keeps the DT empirical expected value the same as before at ($217.91M) and changed the DT stratified expected value from ($216.40M) to ($217.91M), changing the recommendation from pursuing development to not pursuing development. Changing the phase II-III probability from 0.39 to Tufts CSDD's 0.454 and the DT empirical

expected value changed from recommending to not pursue development ($217.91M) to ($188.58M) to now recommend pursuing development. This also changed the DT stratified expected value from ($216.40M) to ($181.77M), with the recommendation to pursue development remaining the same as before. The point of indifference between pursuing development and not pursuing development occurs when the phase transition probability from clinical trial phase II to phase III increases to 0.39155 from 0.39000 for the DT empirical model or if the probability decreases from 0.3900 to 0.3872 for the DT stratified model.

Changing the phase III to FDA approval (or, post-approval phase IV trials) transition probability from 0.69 to Tufts CSDD's 0.593 does not change the DT empirical expected value from ($217.91M), but it does change the DT stratified expected value from ($216.40M) to ($217.91M), changing the recommendation for pharmaceutical companies to pursue development of the drug to not pursuing development of the drug. Changing the phase III to phase IV transition probability from 0.69 to Getz's 0.80 changes the DT empirical expected value from ($217.91M) to ($181.18M) to change the recommendation of not pursuing development from before to pursuing development of the drug now. This change also changes the DT stratified expected value from ($216.40M) to ($171.20M) without changing the recommendation to pursue development of the drug. The point of indifference between pursuing development and not pursuing development occurs when the phase transition probability from clinical trial phase III to phase IV increases from 0.6900 to 0.6921 for the DT empirical model or if the probability decreases from 0.6900 to 0.6863 for the DT stratified model. Table 7 summarizes these results, showing the percentage change of the expected values of both the DT empirical and DT stratified models from changes in the phase transition probabilities.

Table 7: Sensitivity Analysis on Phase Transition Probabilities Results

Factor	Current Value	Change to	% Delta	DT Empirical	DT Stratified
Phase II→III	0.39	0.33	-15.4%	0.0%	-0.7%
	0.39	0.454	16.4%	13.5%	16.0%
Phase III→IV	0.69	0.593	-14.1%	0.0%	-0.7%
	0.69	0.80	15.9%	16.9%	20.9%

Conclusions

Using decision tree analysis to assess the financial viability of stratified medicine opportunities has several advantages over the traditional NPV analysis. First, DTs more realistically simulate the drug development process for the pharmaceutical company, incorporating dynamic decision making throughout the valuation process. With DTs, companies can make the decision whether to pursue development of a stratified drug throughout the development process at the end of the different phases of clinical trials, where NPV analysis forces one decision to be made at the onset of preclinical development.

We created two DTs for analysis, one that considered only the empirical medicine development possibility and the other that considered the potential for stratified medicine to be developed throughout the development process. Valuating the drugs already approved and on the market showed negative NPV's, positive DT empirical expected values, and positive and larger DT stratified expected values, which suggests the potential for DT analysis to recommend the development of stratified medicine that NPV analysis would not.

We also created two plausible drugs and simulated their valuation through the NPV and DT analyses and determined a case for when NPV analysis recommends against developing the stratified medicine opportunity, the DT empirical model recommends against development, and the DT stratified model recommends the company to develop the opportunity. We created another plausible drug where its NPV was negative, suggesting against development, DT empirical was negative and suggested against development, and DT stratified was negative but suggested for development.

At least through our DT models, a pharmaceutical company can evaluate their own stratified medicine opportunity in a different approach than the traditional method to more

closely mimic their situation and help them make the decision of whether to pursue development. If a pharmaceutical company started developing a stratified drug from the start, NPV analysis will most likely suggest stopping development completely. DT analysis allows the pharmaceutical company to consider developing the drug as an empirical medicine at the onset and further to consider developing the drug as a stratified medicine throughout the development process if the drug does not pass through all clinical trial phases as an empirical medicine.

Future Work

We created very basic DT models to simulate the pharmaceutical companies' decisions of whether to pursue stratified medicine opportunities, but there are other steps that should be taken before a pharmaceutical company actually uses the models to evaluate their own opportunity. First, there are other parameters to consider adding to the model to make it more robust and realistic. Second, we should further investigate the potential market for the stratified medicine opportunities to include in the model more consideration to varying parameters affecting eventual stratified drug sales.

Other Development Parameters to Consider

There are several parameters that were not considered in the development of our models that should be investigated in future models including accelerated development mechanisms and academic research alliances.

Accelerated Development Mechanisms

Some pharmaceutical drugs are awarded certain accelerated development mechanisms by the FDA that speed up the approval process to allow drugs to enter into the market more quickly. In early stages of development, these potential drugs must show compelling results to researchers in order to be considered for one of these mechanisms. From here, the pharmaceutical company can apply for one of the three types: accelerated approval, priority review, or fast track designation.

Accelerated approval is the most valuable of the three types of accelerated development mechanisms. Drugs that are granted accelerated approval show p-values low enough in phase I of clinical trials that the FDA will allow the pharmaceutical company to legally run fewer trials in phase II and phase III. The fewer clinical trials required of these potential drugs save the

pharmaceutical companies the development costs of those trials that they no longer have to run. Xalkori® was developed under accelerated approval (FDA 2012).

Pharmaceutical companies receiving priority review for a developing drug are guaranteed a 6 month FDA review period instead of a 10-18 month review. This mechanism saves the pharmaceutical companies money by granting them sooner marketing rights, which allow them to sell the drugs earlier and realize earlier revenues and profits. Priority review adds an extra $300M to the pharmaceutical company's revenue (Emory University 2014). Zelboraf® was developed under priority review (FDA 2012).

Fast track designation is the last accelerated development mechanism where pharmaceutical companies hold more frequent communication with the FDA throughout development. Here, companies provide the FDA with updated results from trials as they are completed as well as news about potential drug developments. Fast track designation is considered a rolling review, and it allows drugs to be developed up to 2.5 years quicker so that the drug may be marketed earlier. Zelboraf® also used fast track designation during its FDA approval process (FDA 2012) (FDA 2013).

Academic Research Alliances

Pharmaceutical companies have been entering into contracts with academic institutions to help them develop new drugs. The pharmaceutical company contracts to pay a stipend to the academic institution over several years to start this partnership. The idea is that pharmaceutical companies can outsource some of their preclinical costs by paying an amount of it upfront to academia and academia will perform much of the preclinical research themselves to save the pharmaceutical company the extra costs associated with the preclinical research done by the academic institution.

For example, Gilead Sciences has entered into a contract with Yale School of Medicine for $100M over ten years; Pfizer, Inc. has contracted with UCSF for $85 over five years; and GlakoSmithKline has contracted with the Harvard Stem Cell Institute for $25M over five years (Lyman 2011). Sometimes these contracts specify an area of research for the academic institution to focus on through the alliance. For example, Roche, Eli Lilly, Servier, Janssen Pharmaceutica, and Pfizer entered into a contract with the King's College of London for $38.7M to specifically research Alzheimer's and Autism. Sanofi has partnered with UCSF for $3.1M to study diabetes. Merck has contracted with Calibr for $90M over seven years to research early-stage molecules (Toor n.d.).

Other Market Considerations

In addition to these development parameters that should be considered to make our models more comprehensive, potential market considerations should be taken into account, specifically the potential market sales/market share of the commercialized drug.

In our current model, we assume the sales of the drug are one scenario to determine the overall expected value of the model. Incorporating several scenarios of potential market sales/market shares that the pharmaceutical company would have once commercialized into the model and accounting for the likelihood of each scenario occurring would allow for several projected market shares/market sizes to be considered by the pharmaceutical company.

With these development and market considerations, the model will more accurately depict the pharmaceutical company's stratified medicine decision. The hope is that pharmaceutical companies will use this model to evaluate their own stratified medicine opportunities, and the models will recommend for them to pursue more of these opportunities so that more people can be helped that otherwise could not.

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