Assessing the Economic Case for Stratified Medicine

By

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Abstract

The goal of this study is to explore the economic conditions that favor the joint development of therapeutics and companion diagnostics. I hypothesize that predictive biomarkers can generate economic value in drug development by increasing success rates. I construct an economic model of the development of a hypothetical new therapy, and devote particular attention to parameters regarding safety, efficacy, cost, and market size, within a decision-theoretic framework.

The results include a characterization of the dynamic net present value trade-offs between stratum size and biomarker success, as well as the identification of two complementary concepts of stratified medicine, namely, disease reclassification and value-based reimbursement. I also identify a strong potential incentive mechanism in the hands of public policy makers that could facilitate a resolution of the tension between patient interests and the interests of pharmaceutical sponsors.

The conclusion is that a biomarker can compensate for smaller sratum by increasing success probabilities. However, the effects of longer development time due to biomarker inclusion counter the effects of improved success probabilities. Longer exclusivity periods for stratified medicine may be required in order to resolve the tension between patient interests and the interests of pharmaceutical sponsors.

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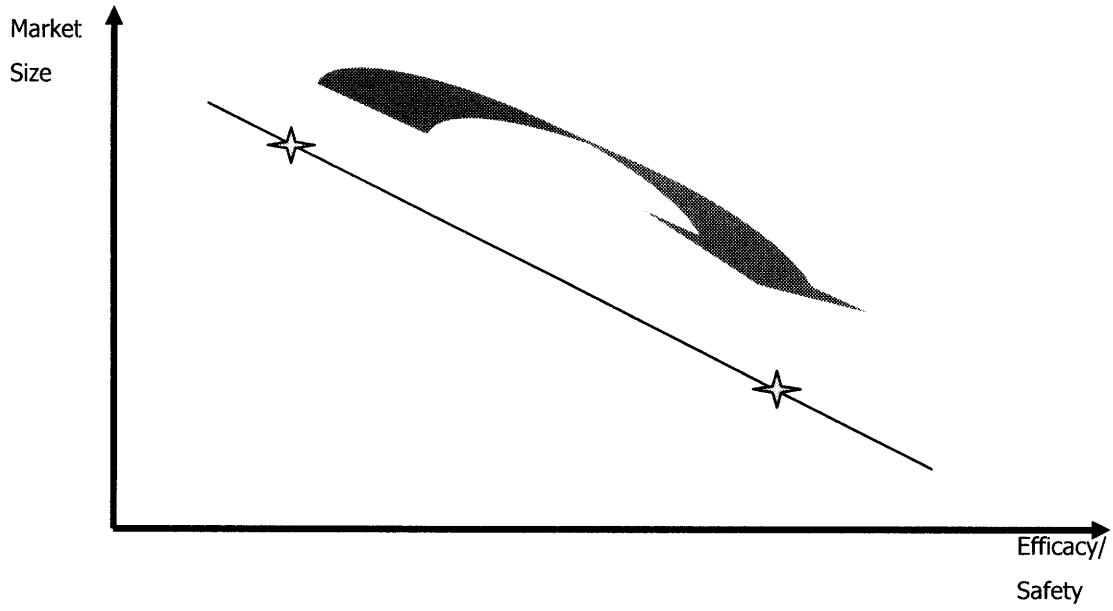
Background

Stratified medicine[1] as opposed to empirical medicine is the practice of using biomarkers or diagnostic tests to guide the choice of therapeutic treatments. In a simple case, a predictive diagnostic test stratifies the patient population to responders and non-responders for a certain treatment, where by contrast, in empirical medicine all patients would receive the same treatment. By stratifying the diagnostic test helps increase efficacy[2 3] and/or reduce toxicity[4] in the treated stratum but at the same time it reduces the addressable patient population for the treatment within a predefined disease space. For example, a more effective and safe medicine that would better serve the interests of patients would have this effect only in a small number of the patients with the disease it was designed to address. As a result, if the approved indication of this medicine is limited to the better responding stratum, the sponsor that develops the medicine would face a smaller market size, other things being equal.

Figure 1 - Stratification Tension



This double pronged effect would, in principle, create tension between patient interests and the interests of pharmaceutical sponsors, as is illustrated in Figure 1 - Stratification Tension. The vertical axis represents market size while the horizontal axis

represents efficacy and/or safety. The function line represents a continuum of market size, safety and efficacy combinations. Stratified medicine is demonstrated relative to empirical medicine by transition on the continuum from a point of larger market size with lower efficacy or safety to a point of smaller market size with higher safety or efficacy.

Review of the Literature

Stratified medicine[5] has previously been dubbed personalized medicine, pharmacogenomics, pharmacogenetics, prognostic diagnostics, or in short PgX, and also predictive or companion diagnostics. A predictive biomarker or diagnostic can predict response to therapy in which case it is defined as an efficacy biomarker. It can predict non-response in which case it is defined as a non-response biomarker. And finally, it can predict adverse reaction in which case it is defined as a safety biomarker.

Stratified medicine's promise of better therapies has inspired research regarding its economic value for society. Webster et al.[6] identified several potential applications for a predictive biomarker: First, it can be used to discover better drugs. Second, it can improve the safety of new drugs in development. Third, it can improve the efficacy of new drugs in development. Fourth, it can improve the safety of licensed drugs post-market, and fifth, it can improve the efficacy of licensed drugs post market. Phillips and Van Bebber's systematic review[7] documented that the cost-effectiveness of specific PGx tests will depend on many factors, including gene and disease prevalence, gene penetrance, and test sensitivity, specificity, and cost as well as individual preferences[8]. Phillips and Van Bebber[9] also concluded that crucial data for assessing the value of PGx with regard to its impact on clinical practice and outcomes are currently lacking.

The clinical utility of a predictive biomarker increases with the toxicity of the treatment and decreases with the efficacy of the treatment[10]. For example, a drug that is very effective for almost all patients with no side effects would not be a good stratification candidate. On the other hand, a toxic drug with limited efficacy may require stratification for toxicity, efficacy or both. The prevalence of the disease and relative size of the stratum also affect the value of a predictive biomarker[11]. For example, if the better responding stratum is expected to be very small it might not justify the development of a diagnostic test and the ongoing testing of the full patient population. Severity of the

disease affects what type of biomarker, safety, efficacy or non-response is most clinically beneficial.

Other research has focused on the adoption of companion diagnostics by industry and the incentives that exist for their development. Robertson et al.[12], Webster et al.[13], and Califf[14] concluded that most large pharmaceutical companies focus their PGx investments on improving the efficiency of drug development, and that they have limited interest and incentive for PGx investments for currently marketed medicines[15]. Danzon and Towse[16] argued that current marketplace incentives, particularly drug price inflexibility once a drug is launched, give manufacturers little commercial motivation to invest in biomarkers that would result in a narrower indication[17]. Garrison and Austin[18] suggested that health system reforms that promote value based, rather than cost based, flexible reimbursement for innovative, patent-protected diagnostic and therapeutic products are critical to create stronger economic incentives for the development of personalized medicine. Seiguer[19] also concluded that there is very little if any incentive for industry to invest in companion diagnostics. Trusheim et al.[20] pointed out the risks for industry in continuing to pursue an unsustainable blockbuster model. They also identified a few compensation mechanisms that financially offset smaller strata due to improved safety and efficacy. For example, higher price, better compliance and increased market share within a stratum can offset the effect of a smaller market size on revenues. In addition, when the decision to stratify is made *a priori*, clinical trials can potentially be both smaller and shorter, which can improve a drug development project net present value (NPV) through lower investment and shorter time to revenues. On the other hand, more narrowly defined inclusion criteria may lead to lengthier recruiting, the need for additional sites, and higher costs.

Trusheim et al. also broadened the discussion on stratified medicine by defining clinical biomarkers to include any diagnostic test or clinical observation that indicates a preferred or contraindicated treatment for a patient subpopulation. Such tests can be based on gene expression patterns, individual proteins, proteomic patterns, metabonomics, histology, imaging, physicians' clinical observations and even self-reported patient surveys. In other words, they define a clinical biomarker not by its technology or biological basis, but rather by its reliable, predictive statistical correlation with differential patient responses.

The incremental value of U.S. medical spending has been decreasing as evidenced by the continual increase in cost per year of life gained[21]. At the same time it has been recognized that there is a pharmaceutical R&D productivity problem[22 23] as evidenced by the ~50% increase of investment per successful compound[24]. One of the possible causes for this productivity problem is the decline in drug development success rates for new molecular entities entering clinical development from 14% in the late 90's to 8% in the period 2000-2002[25].

In this study I hypothesize that predictive biomarkers can generate economic value in drug development by increasing success rates. I construct an economic model of the development of a new therapy, and devote particular attention to parameters regarding safety, efficacy, cost and market size, within a decision-theoretic framework.

Methodology

I begin with a baseline economic model that compares the Net Present Value (NPV) of a stratified medicine case with that of an empirical medicine case. The model is populated with numbers from the literature[26 27]. I conclude, as others have before me[28 29], that there is little if any economic incentive for drug developers to make stratification decisions *a priori*. The reason is that even when the stratified medicine has a superior risk adjusted NPV, its success NPV is still inferior to that of the empirical medicine. This is important since risk adjusted NPV, which is a weighted average of failure NPV and success NPV, does not represent an actual outcome. In reality the firm would get either the success NPV or the failure NPV. Consequently, a firm would be likely to keep an option for the full market with the larger success NPV rather than limit itself up front to a stratum with lower success NPV. In cases where both the success NPV and risk adjusted NPV are superior for the stratified medicine it is clear that stratification is the better alternative. This outcome may occur when the stratum is relatively large and other offsetting mechanisms exist such as shorter clinical trials, higher price for the marketed drug, better compliance and higher share within the stratum[30] such as in the case of imatinib mesylate (Gleevec: Novartis, Switzerland). In this study I focus on cases where the success NPV for the stratified medicine is inferior to that of the full population since those are the ambiguous cases that call for clarification of the economic dynamics.

In addition to these economic considerations for not stratifying upfront, the availability of strata for a given treatment is rarely known early in the development process. Rather, in most cases it is one possible outcome of clinical trials that combine hypothetical stratifying biomarkers. Consequently, I ask, rather than upfront stratification, what is the value of having the option to stratify as a fall back or as a project salvage option? In other words, what are the drivers and conditions that justify the investment in companion diagnostics as stratification options[31]?

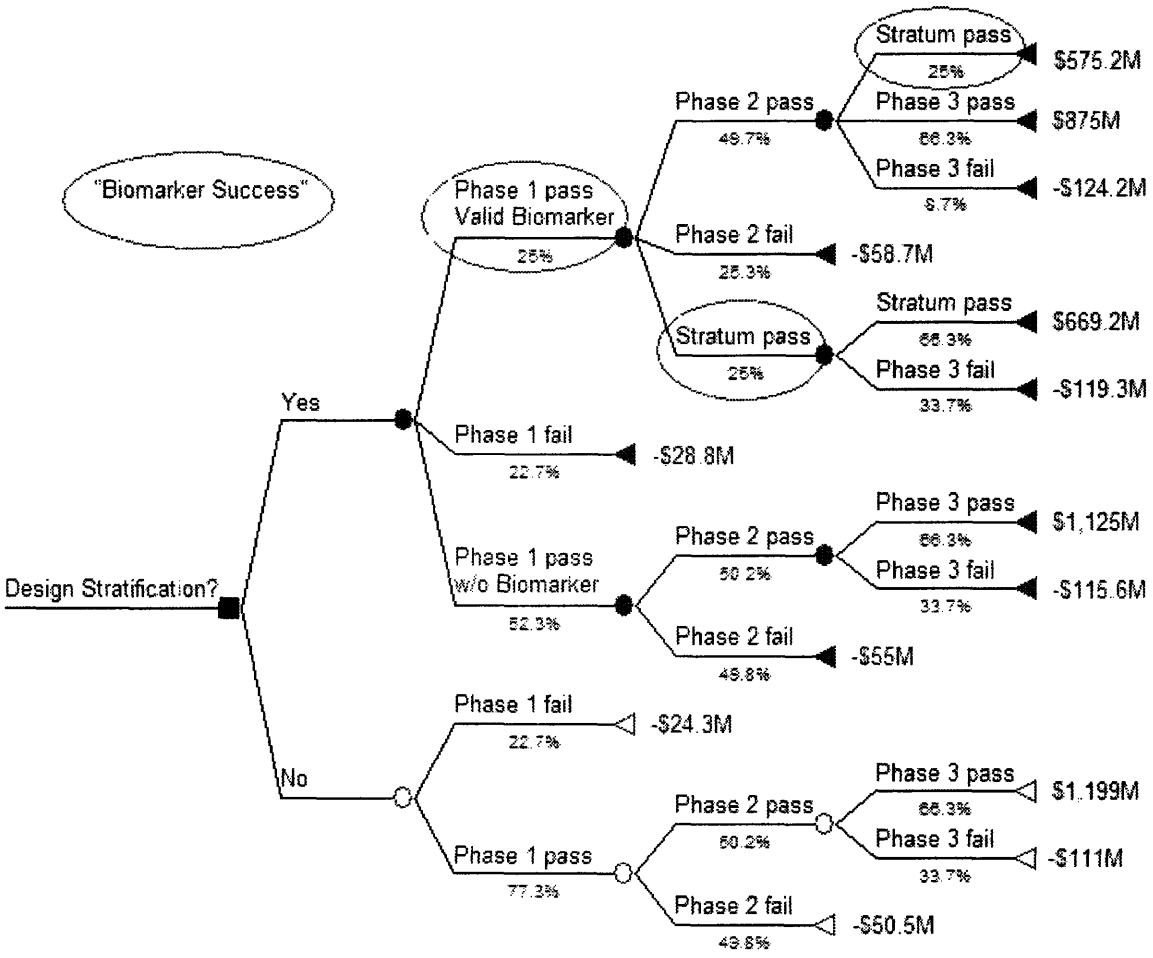
In order to answer this question I add a decision analysis[32] layer of complexity to the model. This stochastic layer adds the success probability over development phases as demonstrated in Figure 2 – Companion Diagnostic Decision Tree. Based on the decision analysis model I conduct sensitivity analyses that are the basis for the results reported in this study.

In order to validate the model and the results, I also conduct qualitative interviews with some of the stakeholders including personnel in academia, at the U.S. Food and Drug Administration, and in industry. Some of the interviews were the result of a predefined set of cases but most were based on networking with key representatives of the above stakeholders.

Model

The following decision trees represent comparisons between two approaches. The first approach is that of stratified medicine, which uses companion diagnostics as "real options"[33] in a drug development hedging strategy. The second approach is that of empirical medicine, which does not use biomarkers.

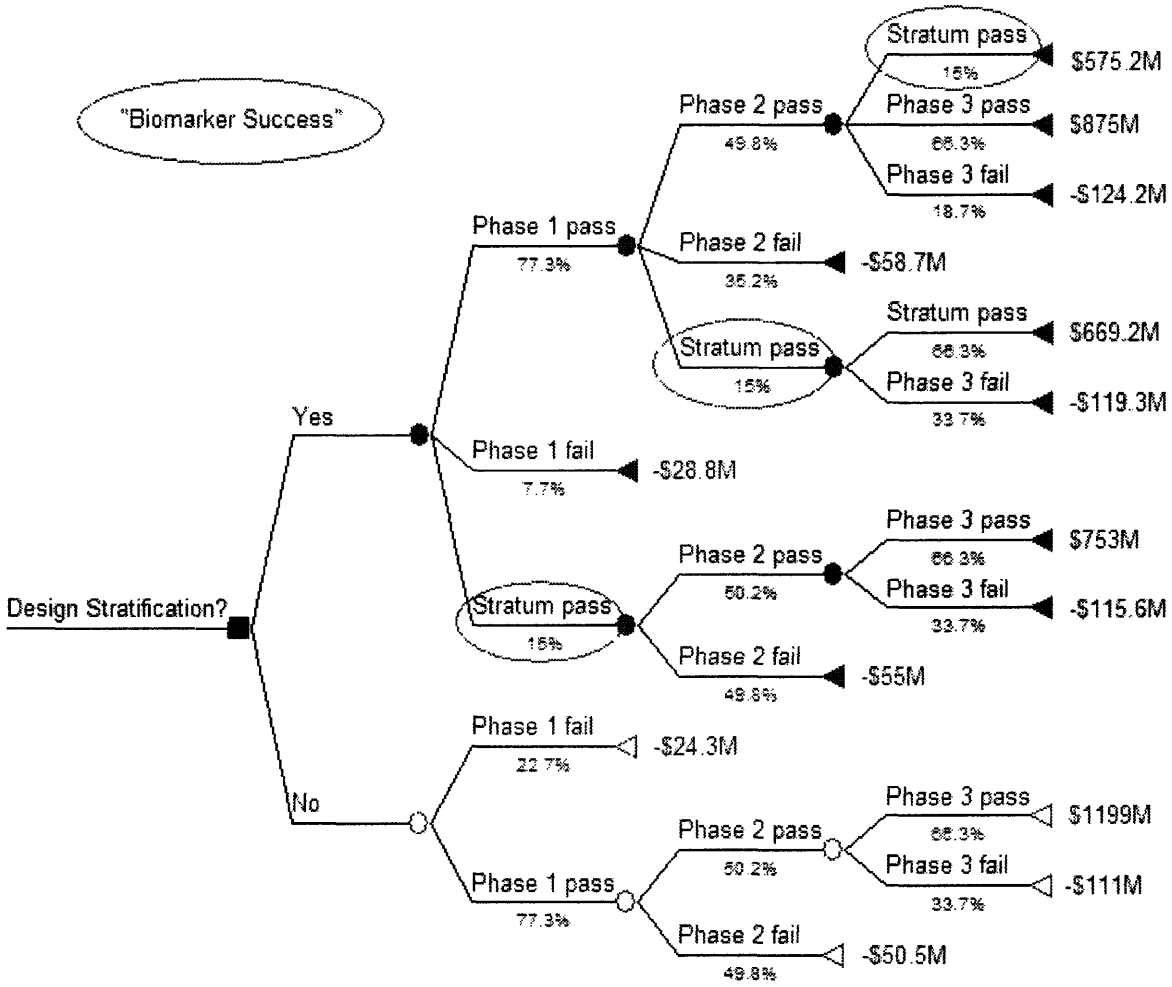
Figure 2 – Companion Diagnostic Decision Tree – Efficacy Biomarker



In Figure 2 – Companion Diagnostic Decision Tree – Efficacy Biomarker, the lower tree branch ("No") represents empirical medicine where the probabilities of success and failure in each clinical phase are the average industry probabilities. The outcomes are based on average clinical phase costs and on the assumption of $1B peak revenues. In the upper branch ("Yes"), more alternatives are generated by the use of biomarkers. Instead of only success or failure, stratified success or biomarker success is

an additional salvage alternative, whose probability is deducted from the failure probability. The outcomes at the end of each branch are the result of a sequence of clinical and financial scenarios. For example, the first outcome on this tree is an NPV of $575.2 million, which is a result of a decision to use an efficacy biomarker, identification of a valid biomarker in phase I, success in the full population in phase II and success only in the stratum in phase III. The overall probability for this outcome is 3% (25%X49.7%X25%) and hence, the contribution of this possible outcome to the overall NPV of the decision to use an efficacy biomarker is 3%X$575M=$17.9M.

Figure 3 - Companion Diagnostic Decision Tree - Safety Biomarker



In Figure 3 - Companion Diagnostic Decision Tree - Safety Biomarker, for example, the second outcome is an NPV of $875 million, which is a result of a decision to use safety biomarker, identification of a valid biomarker in phase I, success in the full population in phase II and success in the full population in phase III. The overall

probability for this outcome is 25.5% (77.3%X49.8%X66.3%) and hence, the contribution of this possible outcome to the overall NPV of the decision to use an efficacy biomarker is 25.5%X$875M=$223.3M.

The structures of the decision trees incorporate a number of assumptions, especially regarding the stratified medicine cases. These structural and other base case assumptions are specified here, but in the results section I also report findings from some sensitivity analyses in which I modify these structural assumptions.

Structural Assumptions

1) The decision point in time, which is the analysis reference point, is just prior to the clinical development stage.
2) In clinical phase I the biomarker is identified. The assumption is that patient enrichment is implemented for a safety biomarker and that a phase IB study is performed for an efficacy biomarker. The implication is that the time and cost of clinical phase I are increased relative to a phase I without stratification (assumed to be 120% in the baseline scenario and subject to a sensitivity analysis).
3) "Biomarker success" in phase I means either transition to phase II with an identified efficacy biomarker or transition to phase II only with an identified stratum based on a safety biomarker. The probability of such an event is deducted from the overall probability of success in the case of an efficacy biomarker and from the overall probability of failure in the case of a safety biomarker. In Figure 2 – Companion Diagnostic Decision Tree – Efficacy Biomarker, the 25% biomarker success probability is circled and called "stratum pass". It reduces the full market success probability in phase I from 77.3% to 52.3%. In Figure 3 - Companion Diagnostic Decision Tree - Safety Biomarker, the 15% success probability is circled and called stratum pass. In this case it reduces the failure probability in phase I from 22.7% to 7.7% due to the ability of a safety biomarker to "save" a phase I trial.
4) If phase I is successful but no efficacy biomarker is identified, then the phase II and III studies continue as in the empirical medicine case. If phase I is successful but only in a stratum defined by a safety biomarker, phase II and III continue as in the empirical medicine case but result in smaller stratum revenues.

If, however, phase I is successful for the full population with an identified biomarker, then:

5) Phase II time and cost are increased relative to the empirical medicine case (assumed to be 120% in the baseline scenario and subject to a sensitivity analysis) in order to power both for the full population and for the potential stratum.
6) Phase II "biomarker success" or "stratum pass" represents transition to phase III but only with a responding stratum as identified by the biomarker. The probability of such an event is deducted from the failure probability.
7) If phase II is successful only in the biomarker defined stratum, phase III continues as in the empirical medicine case.
8) If phase II is successful for the full population, phase III time and cost are increased relative to the empirical medicine case (assumed to be 120% in the baseline scenario and subject to a sensitivity analysis) in order to power both for the full population and for the potential stratum.
9) Phase III "biomarker success" or "stratum pass" represents transition to marketing but only with a responding stratum as identified by the biomarker. The probability of such an event is deducted, again, from the failure probability.

Financial Assumptions

The outcome at each end node is computed through a financial scenario. These scenarios can be found in Appendix 2 – Scenarios. The data that is shared between the scenarios and data related assumptions can be found in Appendix 1 – Data (DiMasi et al. 2003[34] and 2007[35], all recalculated in 2005 dollars).

The baseline peak revenues for the empirical medicine are chosen to be $1B to represent a typical "blockbuster". Following one common convention used in venture capital[1], I use the following formula to assess the peak revenue value multiple: Multiple = 1.5 + (years of exclusivity/2). I assume that it takes five years from launch to reach peak revenues and that for empirical medicine it leaves seven years of patent exclusivity resulting in a peak revenue multiple of five (1.5+7/2 = 5). This multiple is consistent with

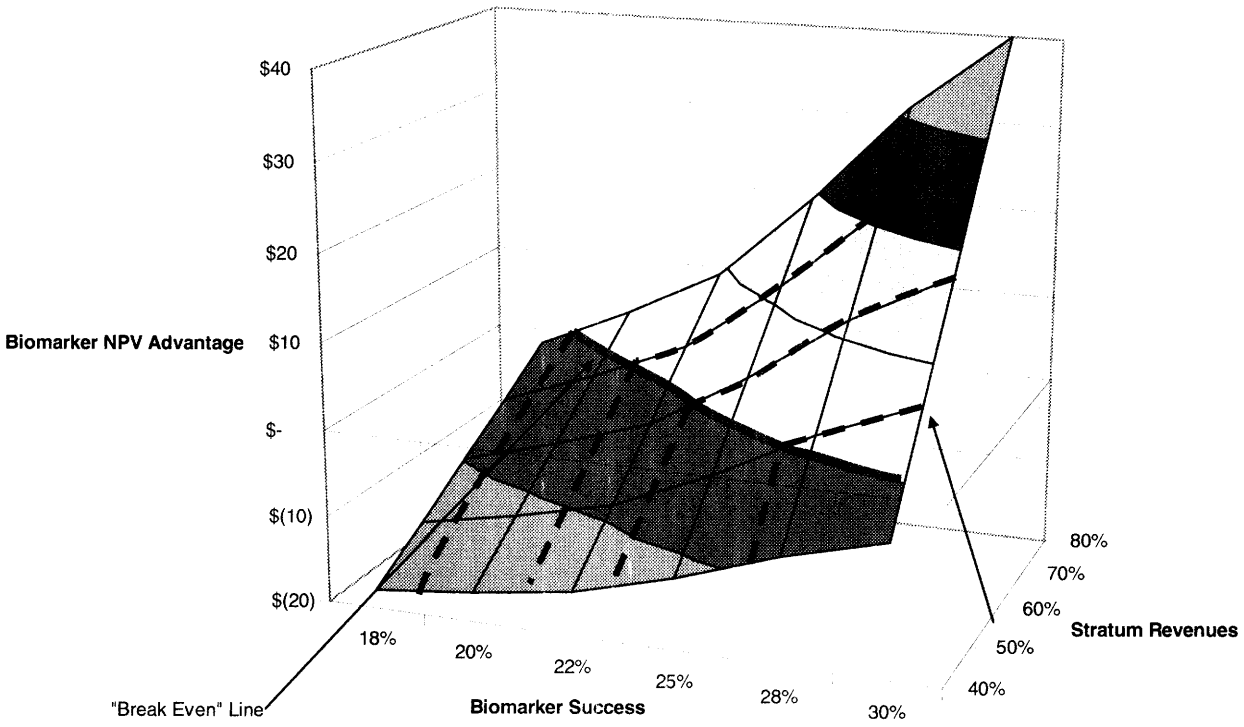
[1] Personal communication: Dr. Thomas Roberts (Noonday Asset Management, NC)

the value paid by pharmaceutical companies to acquire new products in several recent acquisitions. In the biomarker arm of the model, lengthier development time in the baseline case results in less exclusivity time and longer time to peak revenues. This in turn, results in lower present values of revenues for the biomarker arm. A sensitivity analysis for the effect of time is discussed later in the results section.

Results

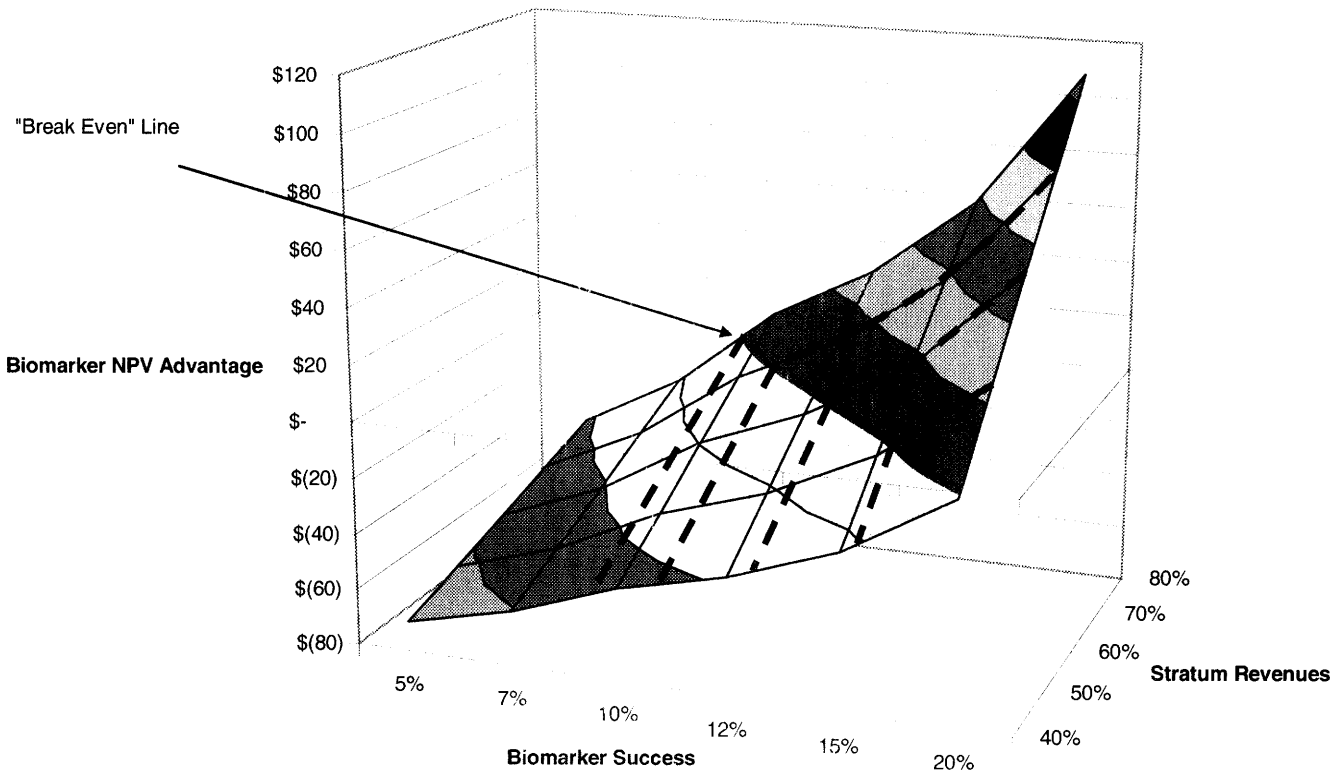
The hypothesis of this study is that predictive biomarkers can generate economic value in drug development by reducing failure rates. In order to qualitatively assess the ability of a predictive, stratifying biomarker to generate value that offsets the effect of a smaller market I also perform the following sensitivity analyses. Both the biomarker success probability and the relative size of stratum in revenues (% peak revenues) are allowed to change while all other factors are held constant. The result is the advantage, negative or positive, for the stratified medicine approach over the empirical approach computed as the stratified NPV less the empirical NPV.

Figure 4 - Sensitivity Analysis – Efficacy Biomarker



In Figure 4 - Sensitivity Analysis – Efficacy Biomarker, the trade-off between biomarker success and stratum revenues can be visualized, as I now describe. Lower stratum revenues (Y axis, right side) reduce the biomarker NPV advantage (Z axis, left side) while higher biomarker success (X axis, bottom) increase biomarker NPV advantage. The breakeven line shows the trade-off for zero biomarker NPV advantage. For example, if stratum revenues are expected to be 50% of full market revenues one would have to assume an above 27% efficacy biomarker success in order to justify the additional investment in a biomarker (based on a positive biomarker NPV advantage).

Figure 5 - Sensitivity Analysis - Safety Biomarker



In Figure 5 - Sensitivity Analysis - Safety Biomarker, the trade-off between biomarker success and stratum revenues can also be visualized, as I now describe. Lower stratum revenues (Y axis, right side) reduce the biomarker NPV advantage (Z axis, left

side) while higher biomarker success (X axis, bottom) increase biomarker NPV advantage. The break even line shows the trade-off for zero biomarker NPV advantage. For example, if stratum revenues are expected to be 50% of full market revenues one would have to assume an above 16% efficacy biomarker success in order to justify the additional investment in a biomarker (based on a positive biomarker NPV advantage).

Tables 1 and 2 below summarize the trade-off between stratum revenues and biomarker success along the above breakeven lines.

Table 1 - Efficacy Biomarker Breakeven NPV

Stratum Revenues	*Biomarker Success Required to Balance NPVs*
80%	19%
70%	21%
60%	23%
50%	27%
40%	NA

Table 2 - Safety Biomarker Breakeven NPV

Stratum Revenues	*Biomarker Success Required to Balance NPVs*
80%	9%
70%	10.5%
60%	13%
50%	16%
40%	NA

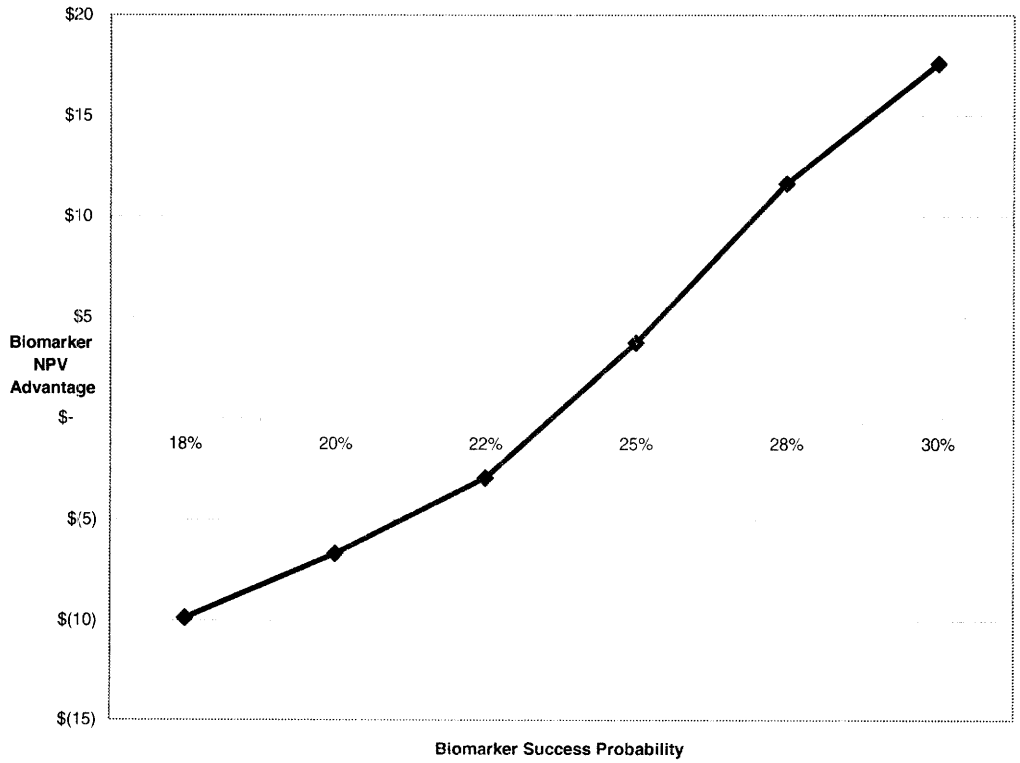
Note: NA means Not Applicable

Along the breakeven line, between the 50% and 80% stratum revenues, the arc elasticity of efficacy biomarker success with respect to stratum revenues is about -0.75, i.e., a 10% proportional increase in the stratum revenue percentage is associated with a 7.5% proportional decrease in the required biomarker success probability. In comparison, the analogous arc elasticity of safety biomarker success with respect to stratum revenues is larger (in absolute value) at about -1.2, i.e. a 10% proportional increase in the stratum revenue is associated with a 12% proportional decrease in the

required safety biomarker success probability. Hence, in terms of required biomarker success to offset revenue loss, the safety biomarker is more elastic than the efficacy biomarker.

The results support the hypotheses that a predictive stratifying biomarker can generate economic value by reducing failure rates through a project salvage option. Moreover, these results, and especially the break even line trade-offs, demonstrate the conditions that are required for such value to be created, thereby serving as a guideline for justifying investment in stratifying biomarkers on a case by case basis. The biomarker success probability that is required to balance stratum revenues reduction for a safety biomarker is much smaller than that required for an efficacy biomarker. This is due to the ability of a safety biomarker to "save" a project starting in clinical phase I where an efficacy biomarker can only begin "saving" in phase II. Neither a safety nor an efficacy biomarker can balance an above 50% reduction in revenues due to stratification under the assumptions of this study.

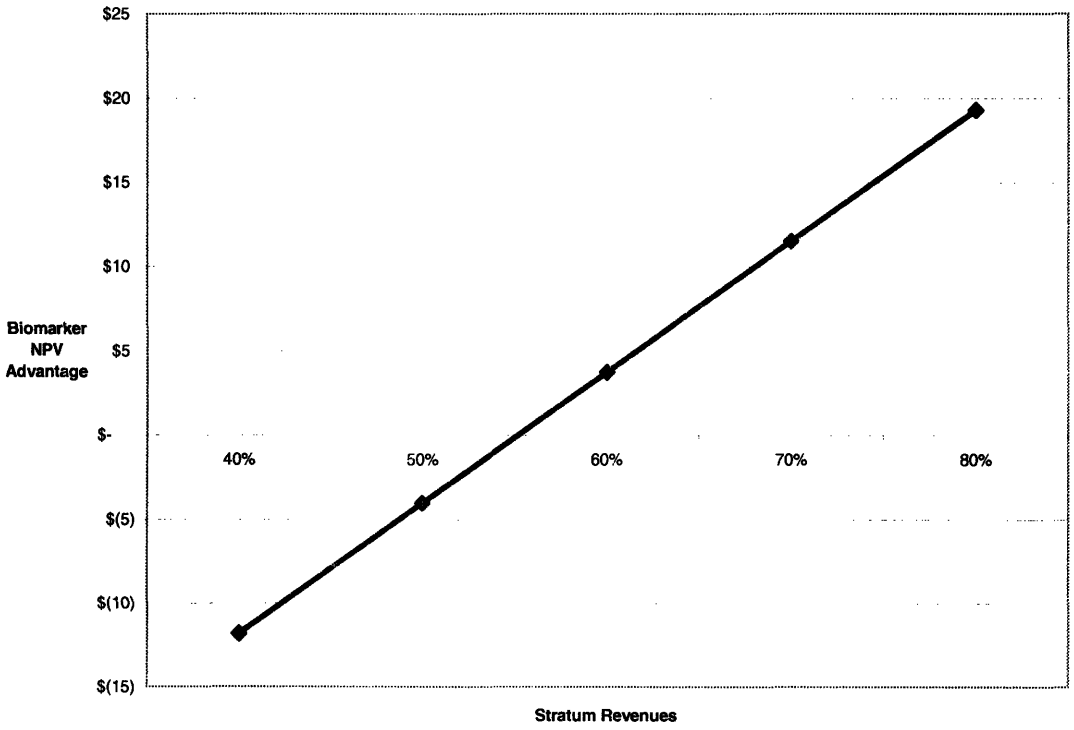
Figure 6 – Efficacy Biomarker Success Impact (at 60% Stratum Revenues)



As is evident from Figure 6, the relationship between biomarker success probabilities and biomarker NPV advantage is almost linear. Every one percent of biomarker success yields approximately $2.4M of biomarker NPV advantage.

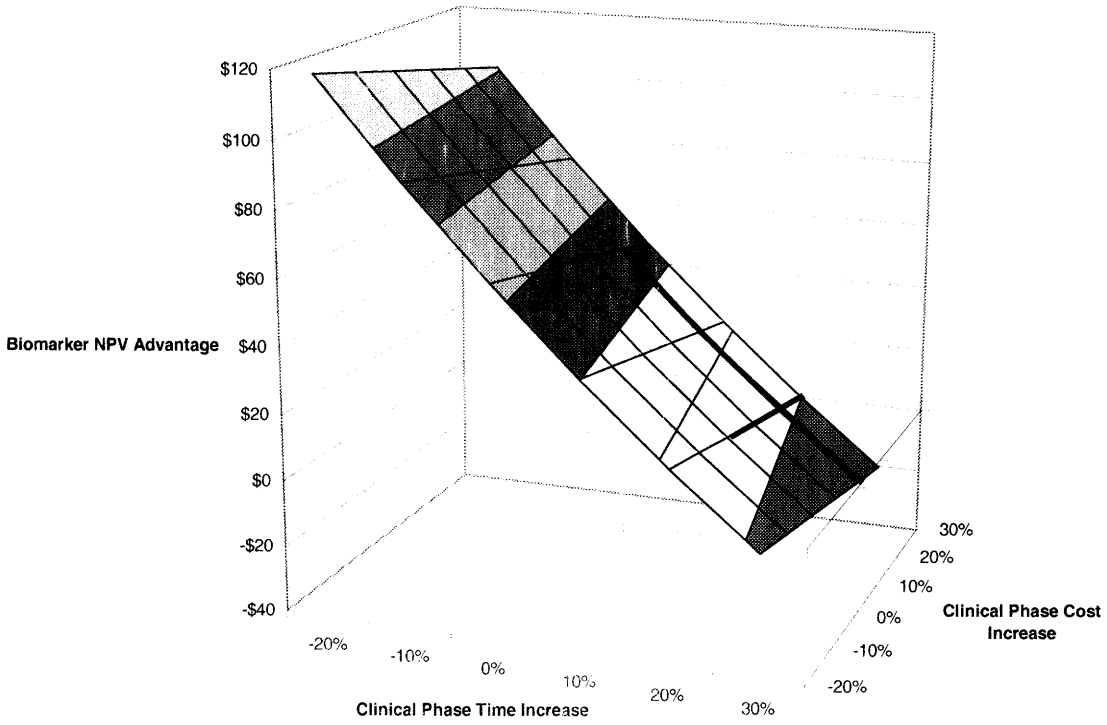
In Figure 7, the relationship between stratum revenues (as a percent of full market revenues) is linear with every one percent in stratum revenues yielding $0.775M. Around these values for an efficacy biomarker (60% stratum revenues and 25% biomarker success), one percent in biomarker success probability just offsets approximately three percent in stratum revenues. The linearity seems to be inherent to the model.

Figure 7 - Stratum Revenues Impact
(Efficacy Biomarker with 25% Success Probability)



These results turn out to be very sensitive to increases in clinical phase time but less so to increases in clinical phase cost. As demonstrated in Figure 8, biomarker NPV advantage (Z axis, right side) drops drastically with increases in clinical phase time (bottom). For example, an increase in the costs of clinical phases by 30% (from zero when phase time increase is held at 20%) reduces the NPV advantage from $12M to zero while an increase in the time duration of clinical phases by 30% (from zero when phase cost increase is held at 20%) reduces the NPV advantage from $50M to minus $18M.

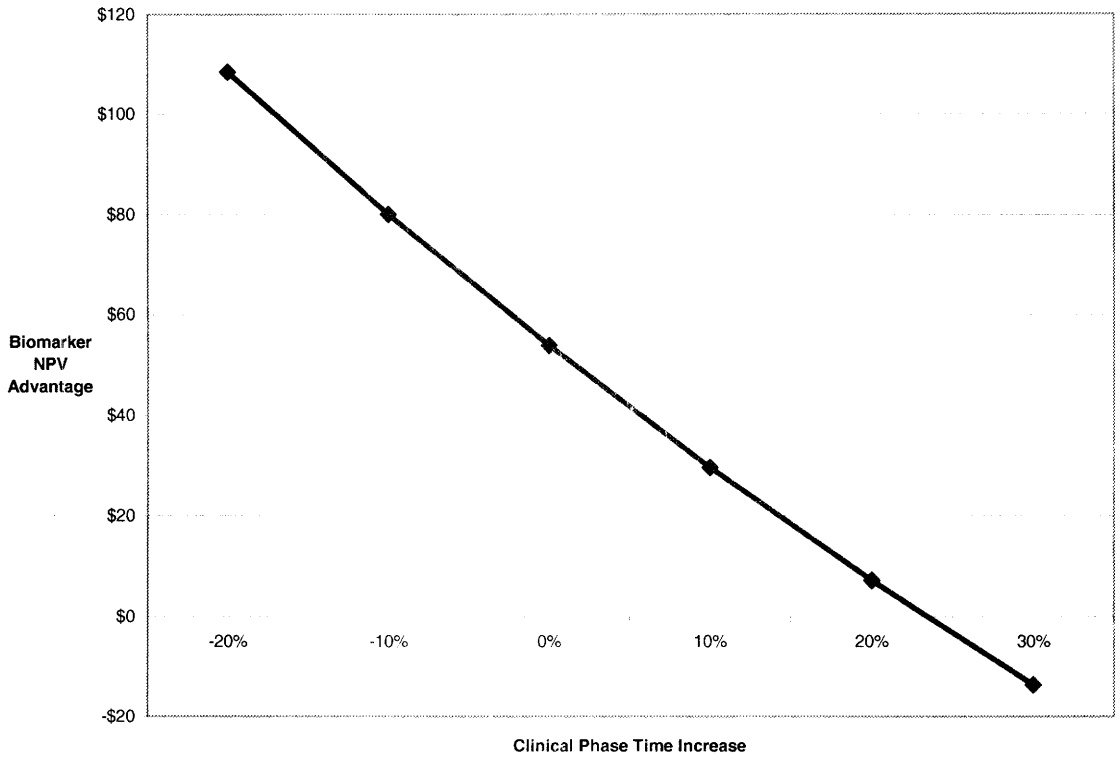
Figure 8 - Sensitivity to Increases in Clinical Phase Time and Cost
(Efficacy Biomarker with 60% Stratum Revenues and 25% Biomarker Success)



This NPV reduction is mainly due to the longer time to revenues and shorter exclusivity period following peak in revenues. Under the assumption that companion diagnostics require increased statistical power in order to allow retrospective stratification, a delay in the marketing of the drug and a similar delay in peak revenues are assumed to occur. These delays shorten the exclusivity time post peak revenues (under the assumption that patent applications deadlines and lifetimes remain unchanged) and hence reduce the peak revenues valuation.

As is evident from Figure 9 - Clinical Phase Time Impact, the relationship between clinical phase time increases and biomarker NPV advantage is essentially linear. Every one percent of phase time increase results in an approximately $2.5M reduction in biomarker NPV advantage.

Figure 9 - Clinical Phase Time Impact
(25% Efficacy Biomarker Success and 60% Stratum Revenues)



Validation

In order to gain further support for my principal hypothesis and to validate the results of the model, I conduct a series of interviews with officials from academia, the U.S. Food and Drug Administration (FDA) and industry. The interview summaries can be found in Appendix 4 - Interviews.

From these interviews it is clear that some incentives do in fact exist for industry to use predictive biomarkers in drug development. Both payers and the FDA are requiring developers to improve efficacy and safety as a condition for financial returns, whether it is through regulatory approval or reimbursement. And indeed, many firms, e.g. AstraZeneca (Waltham MA), and Millenium Pharmaceuticals (Cambridge MA) are already employing predictive stratifying biomarkers as project salvage options in an attempt to reduce failures and possibly shrink phase III trials. An interesting observation from an interview with Millenium Pharmaceuticals is that non-response biomarkers may be more useful and valuable than response biomarkers. This is particularly evident in oncology where the efficacy bar is low and toxicity is high, and where it is difficult to exclude such patients unless it is almost certain that they will not respond.

In addition, competitive pressures, for example, Tarceva (Genetech CA) in the case of AstraZeneca's Iressa and from CellGene's Revlimid in the case of Millenimum's Velcade, also point out the possible risks that can arise with the lack of any clinically stratifying biomarker.

Diagnostic companies appear to have incentives to develop post-market predictive safety biomarkers for approved treatments (e.g. Genomas, CT[2]). Another diagnostic business model is the development of predictive markers for treatment monitoring (e.g. Veridex NJ and Immincon PA[3]).

A refreshing view of stratified medicine as a transitional step on the road to reclassification of disease came up in my interviews with Merrimack Pharmaceuticals (Cambridge, MA) and AstraZeneca (Waltham, MA). Instead of viewing a predictive

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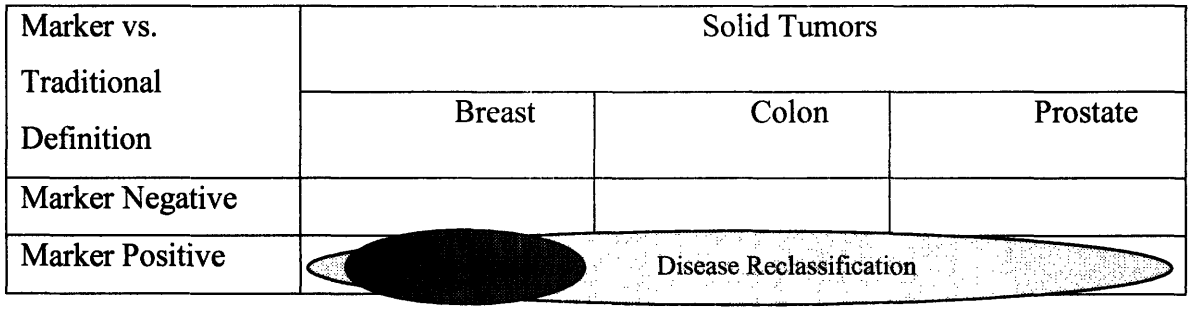
[2] PhyzioType™ system for DNA based adverse events prediction
[3] CellSearch™ system for monitoring response to chemotherapy based on circulating tumor cells

biomarker as market limiting, they view it as market defining as illustrated in the following diagram. The disease space of solid tumors is traditionally divided by tissue of origin. A solid tumor medicine has traditionally been required to focus on one tissue of origin as an indication. Stratified medicine adds a molecular dimension based on which it further divides a traditionally defined disease space into responding and non-responding strata or marker positive and marker negative strata. The result is better medicine for a smaller market. Disease reclassification goes further by using the molecular dimension instead of traditional classifications such as site of origin and solid vs. hematological. The result is better medicine for a molecularly defined condition across many different traditionally defined diseases.

Figure 10 - Stratification vs. Reclassification



As illustrated in Figure 10, while the stratified medicine approach is using a biomarker to segment a predefined space, reclassification is using the same biomarker to define a new space across traditional boundaries.

Discussion and Implications

In general, the results of this study are supportive of the hypothesis that predictive biomarkers can generate economic value by reducing failure rates in drug development. However, the threshold conditions that are required for justifying a biomarker are quite high, especially for efficacy biomarkers, as described in Table 1 - Efficacy Biomarker Breakeven NPV. Moreover, the relationship between both stratum revenues as a share of full market revenues and biomarker NPV advantage appears to be essentially linear as does the relationship between biomarker success probability and biomarker NPV advantage. Every one percent in biomarker success probability translates into approximately $2.4M in biomarker NPV advantage while every one percent of stratum revenues translates into $0.775M. Consequently, around the intersection of 60% stratum revenues and 25% biomarker success probability, the balancing trade-off is around one percent of biomarker success for every three percent of stratum revenues.

In addition, the results are very sensitive to increases in clinical phase time due to longer time to revenues and shorter exclusivity period following peak revenues, as described in Figure 8. This sensitivity is perhaps the major significant finding of this study since it points to a strong potential incentive mechanism in the hands of public policy makers that could facilitate a resolution of the aforementioned tension between patient interests and the interests of biopharmaceutical sponsors. Longer exclusivity periods[36 37] for stratified medicines would dramatically change the economics in favor of biomarker adoption. As evident from Figure 9 - Clinical Phase Time Impact, the relationship between clinical phase time increase and biomarker NPV advantage is essentially linear. Every one percent in phase time increase results in approximately $2.5M reduction in biomarker NPV advantage.

One possible policy implication is that the Congress may want to consider a biomarker exclusivity extension provision analogous to the pediatric extension provision whereby branded patent holders gain an extra six months of market exclusivity by conducting efficacy trials on pediatric populations.

In summary, the dynamic trade-offs appear to be that increases in biomarker success probability balance three fold decreases in stratum revenues. However, similar

increases in clinical phase time appear to counter the positive effect of a biomarker on NPV. In other words, the increase in success probability has to be greater than the increase in clinical phase time in order to balance smaller strata revenues.

Two complementary concepts for stratified medicine emerge from the validation interviews. The first is reclassification of disease that is illustrated in Figure 10 - Stratification vs. Reclassification. Disease reclassification goes further than stratified medicine by using the molecular dimension instead of the traditional organ-by-organ classification. The result is superior medicine for a molecularly defined condition across multiple traditionally defined diseases. This is a more attractive model financially but its applicability might well be limited to the pharmacology of oncology.

The second concept is value based reimbursement[38] demonstrated recently by the agreement[39] between J&J (Raritan NJ) and UK's National Institute for Clinical Excellence (NICE) involving Velcade (Millenium Pharmaceuticals, Cambridge MA). According to the agreement J&J will be paid only for responding patients. Such value based reimbursement can be viewed both as an alternative to efficacy biomarkers and also as an incentive mechanism for their development. However, since manufacturing costs tend to be relatively low, even in large molecules, it is my judgment that such models will weigh on the disincentive side of biomarker development since they provide a "salvage" option without the additional investment in a biomarker.

The results of this study should be interpreted in the context of its limitations. These limitations include investigation only of the $1B peak revenues for the empirical medicine. Another factor that I have not taken into account in this study is manufacturing capacity in the case of biologics[40]. Since by FDA regulatory requirements the full manufacturing capacity for a large molecule often has to be available before phase III trials can begin, it may change the results in favor of stratifying biomarkers.

As further research I suggest computing the nested real option value of a biomarker. For example, investment in phase I biomarker buys one an option to invest in a phase II biomarker. Since the value of options is positively correlated both with uncertainty and "time to expiration" it is plausible that the value of early investment in a predictive biomarker, for example, in phase I, can be more fully appreciated through a full real option calculation. In phase I the "time to expiration" is still long and the

uncertainties regarding the value of the "underlying assets", that in this case are the salvage options to stratify in phase II and phase III, are high. I also suggest examining biologics separately, taking into account the investment in manufacturing as part of phase III trials.

Appendix 1 – Data

Table 3 - Data and Estimates

Cost of Capital*
11%

Phase	Biotech Cost ($M)**	Pharma Cost ($M)***	Average Cost ($M)^	Annualized Cost ($M)^^	Present Value^^^
Phase I	$32.28	$17.18	**$24.73**	**$18.66**	($24.32)
Phase II	$37.69	$26.56	**$32.12**	**$13.94**	($26.18)
Phase III	$96.09	$97.52	**$96.80**	**$34.83**	($60.59)

Phase****	Biotech Phase length (mos.)	Pharma Phase length (mos.)	Average Phase length (mos.)^	Average Phase length (years)	Previous Clinical Development (years)
Phase I	19.5	12.3	15.9	**1.3**	0.0
Phase II	29.3	26	27.7	**2.3**	1.3
Phase III	32.9	33.8	33.4	**2.8**	3.6
FDA	16	18.2	17.1	**1.4**	6.4
Total			94.0	**7.8**	7.8

Phase*****	Success Probability	Success Probability	Average Success
Phase I	84%	71%	**77%**
Phase II	56%	44%	**50%**
Phase III	64%	69%	**66%**
Total	30%	21%	**26%**

* DiMasi et al. 2003 Table 2
** DiMasi and Grabowski 2007 Table 1
*** DiMasi et al. 2003 Table 1 and Bureau of Economic Analysis 2007 Table 1.1.4. Price Indexes for Gross Domestic Product
**** DiMasi and Grabowski 2007 Figure 2
***** DiMasi and Grabowski 2007 Figure 1

^ Average is a simple average between biotech and pharma
^^ Anualized cost is average cost divided by length of phase in years
^^^ Present value is the value of the cost as an annuity at the beginning of each phase, discounted to time zero

Appendix 2 – Scenarios

Table 4 - Efficacy Biomarker Outcomes

		Empirical		Stratified:	E1	All the Way	S2	S3
Peak Revenues (M)		$ 1,000		70%	$ 1,000	$ 1,000	$ 700	$ 700
Multiple		5.0			4.9	4.4	4.6	4.4
Cost of capital		11%			11%	11%	11%	11%
TTM (years)		7.8			8.1	9.1	8.6	9.1
Time to Peak (years)		5.0			5.0	5.0	5.0	5.0
Exclusivity years left (years)		7.0			6.7	5.7	6.3	5.7
Revenues PV		$ 1,310			$ 1,241	$ 999	$ 788	$ 699
Outcome PVs		**Empirical**			**Stratum Increase**			
Phase 1 Cost PV		$ (24)			$ (29)	$ (29)	$ (29)	$ (29)
Phase 2 Cost PV		$ (26)			$ (26)	$ (30)	$ (30)	$ (30)
Phase 3 Cost PV		$ (61)			$ (61)	$ (66)	$ (61)	$ (66)
Outcome PV		$ 1,199			$ 1,125	$ 875	$ 669	$ 575

E1 - success with failed validation of biomarker in clinical phase I
S2 - success with stratification in clinical phase II
S3 - success with stratification in clinical phase III
All the way - success with no stratification
TTM - Time to Market

Table 5 - Efficacy Biomarker NPV

Outcomes		**Empirical**		**Stratified**			**NPV Advantage to Stratify**
	Probabilities	Cumulative	PV Outcome	Probabilities	Cumulative	PV Outcome	
Phase 1 Fail	23%	23%	$ (24)	23%	22.7%	$ (29)	
Phase 1 Success no biomarker				52%			
Phase 1 Success biomarker				25%			
Phase 2 Fail E1	50%	38%	$ (51)	30%	15.7%	$ (55)	
Phase 2 Success E1				50%			
Phase 2 Fail B1				25%	6.3%	$ (59)	
Phase 2 Success Stratum B1				25%			
Phase 2 Success full B1				50%			
Phase 3 Fail E1 E2	34%	13%	$ (111)	34%	8.9%	$ (116)	
Phase 3 Success E1 E2	66%	26%	$ 1,199	66%	17.5%	$ 1,125	
Phase 3 Fail B1 E2				9%	1.1%	$ (124)	
Phase 3 Success B1 E2				66%	8.3%	$ 875	
Phase 3 Stratum Success B1 E2				25%	3.1%	$ 575	17.89
Phase 3 Fail B1 S2				34%	2.1%	$ (119)	
Phase3 Stratum Success B1 S2				66%	4.1%	$ 669	
Net Present Value		100.00%	$ 270		89.66%	$ 281	$ 12

E1 - after failure to identify a valid biomarker in clinical phase I
E2 - after success in the full population in clinical phase II
B1 - after successful identification of a valid biomarker in clinical phase I
S2 - after stratification in clinical phase II

Table 6 - Safety Biomarker Outcomes

		Empirical		Stratified:	S1	All the Way	S2	S3
Peak Revenues (M)		$ 1,000		70%	$ 700	$ 1,000	$ 700	$ 700
Multiple		5.0			4.9	4.4	4.6	4.4
Cost of capital		11%			11%	11%	11%	11%
TTM (years)		7.8			8.1	9.1	8.6	9.1
Time to Peak (years)		5.0			5.0	5.0	5.0	5.0
Exclusivity years left (years)		7.0			6.7	5.7	6.3	5.7
Revenues PV		$ 1,310			$ 868	$ 999	$ 788	$ 699
Outcome PVs		**Empirical**			**Stratum Increase**			
Phase 1 Cost PV		$ (24)			$ (29)	$ (29)	$ (29)	$ (29)
Phase 2 Cost PV		$ (26)			$ (26)	$ (30)	$ (30)	$ (30)
Phase 3 Cost PV		$ (61)			$ (61)	$ (66)	$ (61)	$ (66)
Outcome PV		**$ 1,199**			**$ 753**	**$ 875**	**$ 669**	**$ 575**

S1 - success with stratification in clinical phase I
S2 - success with stratification in clinical phase II
S3 - success with stratification in clinical phase III
All the way - success with no stratification
TTM - Time to Market

Table 7 - Safety Biomarker NPV

Outcomes		**Empirical**		**Stratified**			**NPV Advantage to Stratify**
	Probabilities	Cumulative	PV Outcome	Probabilities	Cumulative	PV Outcome	
Phase 1 Fail	23%	23%	$ (24)	-2.4%	-2%	$ (29)	
Phase 1 Success				77.4%			
Phase1 Success stratified				25%			
Phase 2 Fail S1	50%	38%	$ (51)	49.8%	12%	$ (55)	
Phase 2 Success S1				50.3%			
Phase 2 Fail E1				25.3%	20%	$ (59)	
Phase 2 Success Stratum				25.0%			
Phase 2 Success full				49.8%			
Phase 3 Fail S1	34%	13%	$ (111)	33.7%	4%	$ (116)	
Phase 3 Success S1	66%	26%	$ 1,199	66.4%	8%	$ 753	
Phase 3 Fail E1 E2				8.7%	3.3%	$ (124)	
Phase 3 Success E1 E2				66.4%	26%	$ 875	
Phase 3 Stratum Success E1 E2				25.0%	10%	$ 575	
Phase 3 Fail E1 S2				33.7%	6.5%	$ (119)	
Phase 3 Stratum Success E1 S2				66.4%	13%	$ 669	
Net Present Value		100.00%	**$ 270**		100.00%	**$ 393**	**$ 123**

S1 - after stratification in clinical phase I
S2 - after stratification in clinical phase II
E1 - after success in the full population in clinical phase I
E2 - after success in the full population in clinical phase II

Appendix 3 – Validation Questionnaire

What is your view of "stratified medicine"? How does it tie into your strategy?

What are the drivers and incentives for "stratified medicine"?

What are the inhibitors, disincentives and alternatives?

What was the "case" biomarker?

When was the biomarker discovered? At what stage of the drug development?

What was the biomarker business case? Efficacy, safety, perceived success probability?

Appendix 4 - Interviews

FDA

Dr. Federico Goodsaid, Genomics Group, Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Conference Call, May 18 2007

1) Toxicity biomarker development can be justified even post marketing in order to prevent Vioxx like cases.
2) Reduced revenues may be a negative incentive for developing efficacy biomarkers but not for toxicity biomarkers.
3) The FDA has taken over biomarker qualification.
4) Firms must increase power of clinical trials in order to validate biomarker as well as the treatment.

Academia

Dr. Stacy Melanson, Clinical Laboratory, Brigham and Women's Hospital, Boston MA, May 16 2007

Identified two drug metabolism efficacy/toxicity/dosing biomarkers: Warfarin and Cyclophosphomide.

Dr. Jon Aster, Associate Professor, Department of Pathology, Harvard Medical School, Boston MA, May 17

Sees intellectual property issues as the main challenge that inhibits the development of new biomarkers.

Dr. Raju Kucherlapati, Scientific Director of Harvard Partners Center for Genetics and Genomics, Paul C. Cabot Professor of Genetics, Harvard Medical School, Boston MA, June 20 2007

The question is interesting but the model is wrong. Hedging with biomarkers is impossible because it is retrospective. At best it can generate hypotheses for repeat trials.

Pharma companies already use/hunt biomarkers but they don't use them in the approval process because they have incentives to do just better than the standard of care in order to get approval and full market access.

An exception may be Novartis's anti-HIV drug.

American Society of Clinical Oncologists

Dr. Dan Hayes, Clinical Director, Breast Oncology Program, University of Michigan Comprehensive Cancer Center, Conference Call June 14 2007

1) Biomarkers should go through the same rigorous validation process that drugs go through. So far, too many have been based on studies of convenience (retrospective).
2) At the same time, there has to be a regulatory driven incentive (carrots, not just sticks) for developing biomarkers, such as exclusivity and proper reimbursement.
3) In addition, FDA should require DNA banking in clinical trials since this is one of the missing resources in biomarker "excavation".

Industry

Bob Mulroy, CEO, Merrimack Pharmaceuticals, Cambridge MA, June 18

Bob felt that the research question and the model are highly relevant for the industry and that the sensitivity analysis answers a key question for pharmaceutical companies that have been disappointed with biomarker "fishing expeditions".

Since Merrimack's approach is different than that of the pharmaceutical industry its perspective on the effects of biomarkers and stratification are different. Merrimack is using a disease molecular model as the basis for its identification of both drug target and biomarkers. Hence, the development of biomarker is inherent in the development of the treatment rather than a hedging strategy. One immediate consequence is that there is no question of biomarker validation as a separate question from drug development. If the biomarker is not valid than the disease model is wrong and needs to be corrected. A second immediate consequence is that there is no "stratum success" or "success", but only "stratum success". The third immediate consequence is that Merrimack can reap the benefits of smaller clinical trials and shorter time to market. The largest consequence, however, is that Merrimack sees stratification increasing rather than shrinking its market size. While the industry views stratification within a predefined disease space, Merrimack redefines the disease space at the molecular level and across traditional disease boundaries. For example, its first drug is targeting solid tumors with a specific molecular

signature whether they originate from breast, colon or other tissues. By redefining the indication based on the molecular level Merrimack's first drug is targeting a huge stratum across different empiricalally defined diseases.

Dr. Jeff Hanke, Oncology CSO AstraZeneca, Waltham MA, June 25 2007

Drivers of stratified medicine:

1) There is a push from payers towards stratification through the need to show clinically significant improvements over standard of care.
2) It is easier to get approved where there is an incumbent due to FDA policies.
3) Diseases are being reclassified molecularly across traditional definitions and so it is more reclassification than stratification.
4) It is possible to agree upfront with the FDA to stratify retrospectively (but not trivial).

Caveats:

1) Retrospective markers that are based on small samples can be misleading (e.g. EGFR mutation).
    a) Don't deny patients based on a retrospective marker. Enrich but don't exclude.
    b) Response doesn't necessarily correlate with survival (e.g. Iressa and EGFR mutation).

Inhibitors:

2) Separate track of approval for the diagnostic.
3) Today there is no motivation to do a stratification trial for Iressa since it would also be relevant for Tarceva. Hence, it is impossible to use the diagnostic as a gate keeper.

The Iressa Case:

1) The data about the EGFR mutation came as a result of the trials and when Phase III was already underway.
2) In a larger sample the mutation was less predictive of survival than other markers and that is why they never tried to stratify based on the EGFR mutation.

Dr. Gualberto Ruano, CEO Genomas, Conference Call June 29 2007

There are incentives for stratified medicine for non-pharmaceutical companies such as Genomas. He sees an opportunity to stratify approved blockbuster drugs, such as

cholesterol lowering drugs, for toxicity. The focus is on toxicity that can be observed fairly quickly in order to shorten clinical trials and consequently, time to market.

Dr. Anthony Boral, Millennium Pharmaceuticals. Conference Call Aug 2 2007

1. Incentives:
    a. Smaller and shorter phase III trials.
    b. Better efficacy, competition.
2. Disincentives:
    a. Linking a pre-clinical biomarker to outcomes proved to be difficult.
    b. Price inflexibility makes post market stratification hard to justify.
3. Conclusion:

Non-response biomarkers may be more valuable than response biomarkers, especially in oncology where the efficacy bar is low and toxicity is high. It is hard to exclude patients unless it is almost certain that they will not respond.

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