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The Information Pharms Race and Competitive Dynamics of Precision Medicine

Insights from Game Theory

Ernst R. Berndt and Mark R. Trusheim

4.1 Introduction to Precision Medicines

Over the last decade advances in our understanding of the human genome, and biology more generally, have facilitated the development and commercialization of therapies that, when combined with some form of biomarker diagnostic, are able to identify subpopulations of patients that are likely to respond differentially to the therapy—either positively or negatively. This combination of biomarker and therapy has been given a variety of names—for example, personalized medicine, precision medicine, tailored medicine, and stratified medicine (Trusheim, Berndt, and Douglas 2007; Hu et al. 2013; Trusheim et al. 2011). The majority of these medicines identify multiperson subpopulations. Truly personalized medicines extract and harvest human tissues, expose them to external treatment, and then infuse or inject them back into the patient. The Food and Drug Administration (FDA) recently approved a new gene therapy, CTL019 (tisagenlecleucel) CAR-T cell therapy developed by Novartis for B-cell acute lymphoblastic leukemia (ALL)—a truly personalized medicine (Novartis 2017). Prior to

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that, the only FDA-approved personalized medicines were Provenge from Dendreon (recently again independent, Dendreon 2017; Reuters 2017) and a variety of cord blood transplant products (FDA 2017a).

Regardless of what one calls it, the combination of a therapy and a companion diagnostic (CDx) relies critically on the ability ex ante to distinguish treatment responders from nonresponders. The precision medicine opportunity arises because many drugs prove efficacious for only some who take them. For example, clinical remission rates for tumor necrosis factor alpha (TNFα) inhibitors in autoimmune diseases such as Crohn's disease and ulcerative colitis are approximately 25–40 percent (FDA 2015). For many oncology therapeutics perhaps only 20–30 percent respond and have their life expectancy (months of overall survival) increased (Helwick 2014). Companion diagnostics have been used in oncology since at least the 1990s when trastuzumab (Herceptin) was launched with a companion diagnostic for HER2 overexpression (FDA 2017b). Since then, many precision medicines have been introduced not only into oncology, but also into fields such as infectious disease (sofosbuvir [Sovaldi] and HCV genotypes 1–4), respiratory disease (omalizumab [Xolair] and IgE levels for both patient selection and dosing), and neurodegenerative disease (natalizumab [Tysabri]) and John Cunningham virus ([JCV], testing, FDA 2017b; Hu et al. 2013).

The question of whether initially to pursue a precision medicine approach versus a classic "all comers" drug development and commercialization approach is an important choice. Scientific, regulatory, commercial, and ethical considerations all influence the relative attractiveness of the precision medicine options a firm faces for any individual product (Trusheim, Berndt, and Douglas 2007; Trusheim et al. 2013).

Via professional-society-created treatment guidelines, providers, and payers through utilization management protocols also affect the positioning of a product in the treatment regimen, and so, the competition it might face. For example, some insurers require patients on biologics for ulcerative colitis to begin with (less costly) subcutaneous injections, and only upon failure approve infusion therapy. Such first-line treatments are typically older and less expensive treatments that are effective for some, but not all, patients. Balancing the savings to payers with potential harm to patients (through adverse events or avoidable disease progression) is a tension with any treatment regimen considering both financial and clinical factors. Globally optimizing the utility generated for patients by these guidelines and regimens, as well as the economic outcomes for drug developers, medical providers, payers, and their funders, involve a complex discussion beyond the scope of this chapter.

The diagnostic used to identify the subpopulation for a precision medicine could in theory be crafted by the drug developer or independently by a diagnostic firm. In practice, at least to date, all FDA-approved precision medicines have been created by drug developers who also directed the diagnostic

development as a coordinated product. The reasons for this are both regulatory and economic, as discussed in a prior paper (Trusheim et al. 2013). Here we begin our analysis at the point at which a firm with precision medicine options controls both the therapeutic and the diagnostic and expects a single, well-defined position for the combination product within the treatment regimen. Specifically, the drug development firm is concerned with successfully competing with its combination medicine product within the market niche against other medicines of the same class, whether or not they are combination diagnostic-therapeutic products or only therapeutic agents.

Like drugs, however, no diagnostic is perfect. The performance of a diagnostic is quantified by metrics such as sensitivity (the portion of true positives that are diagnosed as such) and specificity (the portion of true negatives that receive a negative diagnostic result). For example, the HER2 test used to qualify breast cancer patients for receiving trastuzumab (Herceptin) was shown to be approximately 89 percent sensitive and only 83 percent specific. The reported performance also indicated that a patient testing positive had a far from perfect 39 percent (two out of five) chance of responding to trastuzumab—the positive predictive value of the companion diagnostic (Ainsworth et al. 2005; Birner et al. 2001).

4.2 Precision Medicine Often Results in Oligopolies

Companion diagnostics inherently reduce the size of the potentially treated population by identifying subpopulations. In practice, precision medicine indications often possess relatively small numbers of patients. For scientific feasibility reasons, already small indications such as cancer have seen the most precision medicine products, and so become even more fragmented (Hu et al. 2013; Trusheim and Berndt 2012). This combination of small patient populations and high mortality conditions has resulted in precision medicines emerging as high-priced "niche busters" rather than broadly prescribed "block busters" such as blood pressure medicines.

One might expect small markets to attract few entrants. In fact, this is largely the case. A study of oncology products (both approved and in development) showed that the number of competitors with products for precision medicine drug targets is generally under five, with one or two exceptions such as HER2- and estimated glomerular filtration rate (eGFR)-targeted therapies (Trusheim and Berndt 2015). Precision medicines to date generally involve a small number of interdependent differentiated product oligopolists, each having some market power. This brings us to game theory.

4.3 Game Theory Useful in Oligopolistic Situations

In markets with a small number of firms producing slightly differentiated products, one firm's pricing, output, and quality decisions affect all other

firms' similar decisions, and vice versa. In a cooperative game, players (firms) can negotiate binding contracts that allow them to plan joint strategies. In many countries, cooperative games are prohibited by law and enforced by antitrust or anticombines authorities. We will not discuss such games here. Rather, we will focus on noncooperative games in which the negotiation and enforcement of binding contracts are not possible, yet players can anticipate, observe, and react to others' behaviors.

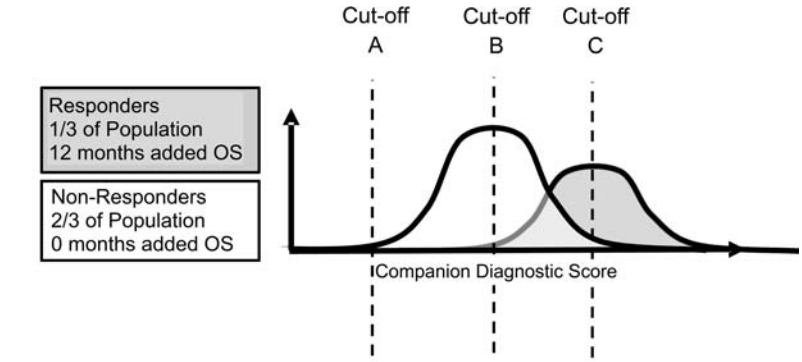
An example of a noncooperative game is a situation in which two competing firms take each other's likely behavior into account when independently setting prices or making research and development (R&D) decisions. A strategy is a rule or plan of action for playing the game to maximize the payoff. If firms solely seek profits, an optimal strategy for a player is the one that maximizes their expected profit (or net present value). In addition to assuming profit maximization as a firm's only objective, game theorists typically assume players are rational. In game theory this means that firms think through the consequences of their actions, with each one asking, "Since our competitors are rational and act to maximize their own expected profits, what will they do and how should we take their likely behavior into account when making our decisions?" (Pindyck and Rubinfeld 2013).

4.4 Plan of Chapter

Game theory has useful insights for traditional drug development in cases where emerging drug classes contain few products. Here we introduce the additional complications that arise when firms choose to use a companion diagnostic to stratify patients into subpopulations. We will focus here on markets for precision medicines that frequently include game theory situations. We are not game theorists. Our goal here is to provide examples of precision medicine market developments that illustrate a variety of classic games and variations, beginning with the iconic prisoners' dilemma game induced by the choices of companion diagnostic cutoff values. But before we begin discussing each of the games, we briefly describe the key features of precision medicine that underpin the game theoretic approach.

4.5 Games People Play When Precision Medicine Is Not Precisely Accurate

A firm may choose to develop a companion diagnostic, or not. But when it does, by setting the companion diagnostic cutoff value, developers link science, the clinic, and the marketplace to create a precision medicine. As we shall explain, selecting the cutoff value connects scientific understanding of both therapeutic response and biomarker performance to change the observed efficacy in the selected clinical trial population. This in turn has



RCT Efficacy (Months OS)	4.0	6.7	10.3
Sensitivity	100%	95%	64%
Specificity	0%	64%	95%
PPV (Positive Predictive Value)	33%	56%	86%
Patients Testing Positive	100,000	56,000	24,000

RCT: Randomized Controlled Trial
OS: Overall Survival

Fig. 4.1 Companion diagnostics affect observed efficacy

Notes: In this hypothetical case of an indication with 100,000 total patients, an imperfect companion diagnostic generally scores responders (gray) higher than nonresponders (white), but with overlapping distributions. Cutoff A selects (those to the right of the cutoff) all patients. This is equivalent to an all-comers population with no diagnostic. Cutoff B selects nearly all patients who will respond (95 percent sensitivity) and raises the observed efficacy over 50 percent to 6.7 months by excluding nonresponders. Cutoff C excludes nearly all nonresponders (95 percent specificity), which raises the observed efficacy to 10.3 months survival. See text for computational details.

implications for pricing, especially when price is linked to patient benefit as in "value pricing" regimes.

Figure 4.1 illustrates the mechanics of how companion diagnostics generate the link between biomarker science and clinical efficacy. In the chart, the two curves represent all the patients with the disease who might be treated with the drug. The larger curve to the left represents the patients who will not respond to the therapeutic. The smaller gray-shaded curve to the right represents those patients who will respond. The companion diagnostic test score along the x-axis imperfectly separates the two patient populations with the vertical dashed lines indicating three different possible cutoff values for the test. Those to the right of the dashed cutoff line will be selected for treatment and those to the left will not.

The population overlap from the imperfect biomarker leads to patients with false positive and false negative test results. False positives are those

patients represented by the portion of the larger curve to the right of the vertical cutoff line. False negative patients are those patients represented by the portion of the gray-shaded curve to the left of the cutoff.

To keep the mathematics simple, we assume that 33 percent of the 100,000 patients with this condition respond to treatment and that each responder gains twelve months overall survival compared to standard of care, and that the remaining patients receive zero incremental benefit. We also assume each distribution is standard normal and that the means are separated by two standard deviations. At cutoff A, the clinical trial enrolls all patients to obtain an average clinical benefit of four months overall survival—the weighted average of the one-third of patients who respond with the two-thirds of patients who do not. Cutoff A has 100 percent sensitivity (it selects all patients who might respond), and has 0 percent specificity (it excludes none who will not benefit). Another diagnostic metric, positive predictive value (PPV) reflects the fraction of patients testing positive on the companion diagnostic (CDx+) that actually do respond. More technically, PPV measures the number of true positives as a portion of all those who test positive. The all-comers PPV for cutoff A is 33 percent—the responder prevalence rate in the whole population.

Using cutoff B selects nearly all who respond (95 percent sensitivity, ~31,500 of 33,000), but also includes many who do not. In our assumptions, cutoff B only yields 64 percent specificity so that 24,500 of 67,000 nonresponders test positive (fall to the right of the cutoff B). For an oncology companion diagnostic, this is quite a superior performance. One of the more powerful companion diagnostics known, the KRAS test for detecting likely responders and nonresponders to cetuximab (Erbitux) in colorectal cancer, has an estimated 75 percent sensitivity and 35 percent specificity (Westwood et al. 2014). By enriching for responders, using the companion diagnostic with cutoff B will elevate the observed efficacy in the clinical trial to 6.7 months incremental overall survival (31,500 with twelve months additional survival and 24,500 with zero months additional benefit). This overall survival improvement is about 70 percent greater than if no companion diagnostic were used (2.7 months longer than 4.0 months from using cutoff A). Fifty-six percent of the patients testing positive (CDx+) from using cutoff B would be expected to respond—the positive predictive value. This is 23 percentage points greater than the 33 percent of treated patients responding in an unenriched population. Notably, choosing different cutoff values yields apparently different efficacy outcomes for the same molecule.

Using cutoff C excludes nearly all who do *not* respond (95 percent specificity, ~63,500 of 67,000). This high cutoff also excludes some patients who would benefit from treatment as measured by a lower 64 percent sensitivity (only ~21,000 of the 33,000 potential responders test positive and are eligible for treatment). A clinical trial using cutoff C would be expected to show a mean treatment survival benefit of 10.3 months (21,000 with twelve months

additional survival and 3,500 with zero months additional benefit). This is more than 2.5 times greater than the 4.0 months additional survival expected from a clinical trial not using a companion diagnostic (cutoff A). Also, the cutoff C reported overall survival benefit likely will be 54 percent longer (3.6 months longer than 6.7 months) than that for a trial using cutoff B. The power of the high cutoff C is demonstrated by the resulting high PPV—86 percent of patients testing positive (20,640 of 24,000) would be expected to respond. This is 53 percentage points higher than the 33 percent response rate expected from cutoff A.

Note that the innate drug performance is unchanged in these three scenarios. The differences are driven by the imperfect biomarker creating choices regarding whether to use it at all, and if so employed, what cutoff to choose. This scientific choice underpins the alternative clinical outcomes from the game. Assuming that pricing is at least somewhat proportional to efficacy, the companion diagnostic also sets up the payoffs of the game.

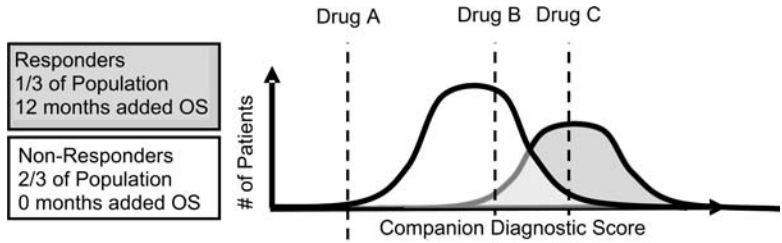
4.5.1 Balanced Clinical Development Impact

A brief digression regarding the incorporation of diagnostic development costs: a precision medicine approach holds the potential for smaller, faster, and less expensive clinical development due to the higher anticipated therapeutic effect owing to companion diagnostic use. However, the approach also requires the development of the diagnostic and its associated risk of failure, more complex patient recruitment, and possibly no savings in trial size due to the potential need to examine negative test result patients and the continuing need to develop an acceptably large patient safety database. For this discussion we assume that these two effects exactly offset each other and so do not affect the games.

4.6 The Diagnostic Cutoff Prisoners' Dilemma: Part 1

The first game-like strategic decision precision medicine developers face is whether to use a companion diagnostic. Figure 4.2 illustrates the base case, iso-payoff game facing developers built on the assumed figure 4.1 case facts. Assuming the companion diagnostic performance and cutoffs as before, plus a price determined by a recent meta-analysis of oncology incremental cost-effectiveness ratios (ICERs) of $138,000 per incremental year of overall survival, developers could choose to have their drug perform as Drug A, Drug B, or Drug C in figure 4.2 (Bae and Mullins 2014). This further assumes that the drug developer faces a small number of other firms advancing drugs that engage the same molecular target, and that they possess essentially identical other characteristics such as adverse event and toxicity profile, dosing form, pharmacokinetics, pharmacodynamics, manufacturing costs, and the like.

In practice, several precision medicines provide examples of this game



RCT Efficacy (Months OS)	4.0	6.7	10.3
Price (ICER	$46,000	$77,00	$119,000
Benefiting Patients	7,250	7,250	7,250
Treated	21,750	13,000	8,400
Payer	$1B	$1B	$1B

RCT: Randomized Controlled Trial
OS: Overall Survival
ICER: Incremental Cost Effectiveness Ratio

Fig. 4.2 Companion diagnostics cutoff game, part 1

Notes: Continuing the figure 4.1 hypothetical case of an indication with 100,000 total patients with an imperfect companion diagnostic, here we illustrate the potential drug prices based on a recent $138,000 ICER oncology benchmark at the three figure 4.1 illustrative companion diagnostic cutoffs. To reach $1 billion of sales, the no cutoff choice (Drug A) must treat 21,750 patients (21.75 percent market share in this 100,000 patient indication). Drug B and Drug C, that each use a companion diagnostic, must treat fewer total patients to achieve the same revenue and the same number of benefiting (responding) patients.

theoretic dilemma. The exciting immuno-oncology therapies that target the PD-1/PD-L1 receptor-ligand complex are one such example. On average 10–20 percent of patients respond to these drugs, with many of those responding experiencing a dramatic remission that endures for over a year. The 10–40 percent of patients who respond to pembrolizumab (Keytruda; Merck & Co.) receive dramatic overall survival increases compared to standard of care (six to ten months median overall survival in non-small cell breast cancer [NSCLC] compared to docetaxel, with 15 percent higher stable, long-term survival—65 percent compared to 50 percent; FDA 2017c). Merck & Co. chose to employ a PD-L1 companion diagnostic assay that was a de minimis fraction of the therapeutic cost. A competing firm, Bristol-Myers Squibb (BMS), developed nivolumab (Opdivo) without a companion diagnostic (FDA 2017b). Initially, the BMS product outperformed the Merck & Co. product in the marketplace, in part, due to easier use from not needing a test (Staton 2016). However, nivolumab subsequently failed a trial in NSCLC, whereas the Merck & Co. product succeeded in a

similar trial partly because the PD-L1 companion diagnostic improved the observed efficacy by enriching the trial with those more likely to respond to pembrolizumab (Pollack 2016).

Other PD-1/PD-L1 immuno-oncology product developers have also faced the choice of whether to use a companion diagnostic test for their products such as atezolizumab (Tecentriq; Roche), avelumab (Bavencio; Pfizer, Merck KGaA), and durvalumab (Imfinzi; AstraZeneca). The firms developing atezolizumab and durvalumab both chose to use a PD-L1 companion diagnostic, but the avelumab developers did not (FDA 2017b). Those that chose to use a companion diagnostic not only chose different cutoff values, but also chose to use distinct diagnostic tests with different performance characteristics. These choices have made it difficult to compare the clinical trial evidence among the products. Simultaneous development of the products hampered the ability to use consistent assays and thus did not provide a common, transparent "game" for the drug developers. But this behavior also demonstrates that one strategy is to change the game through changing the test, not simply changing the cutoff value selection of a common test.

Note that like the classic prisoners' dilemma, each player would prefer a different outcome, but each must choose a strategy to do the best they can given the behaviors of the others. Thus the equilibrium iso-payoffs shown in figure 4.2 suggest a strategy in which higher cutoffs might be preferred by each player.

In most oncology examples, the cost of testing is small compared to the cost of the drug. In cases where this is not true, the cost of testing may outweigh the benefits of enriching the treated population with responders, especially when the treatment works for most, has few side effects, and whose effect is observed immediately, allowing for rapid switching. As an extreme, consider blood pressure medications whose onset of action occurs in hours, if not minutes, and is easily measured with a simple blood pressure cuff. The financial and time delay costs of adding a diagnostic test in such a situation, at least to date, have not been warranted.

4.6.1 Anticipate a Sequential Game

First movers may need to consider fast follower responses. For example, observing that cetuximab (Erbitux) had entered the market with a poor companion diagnostic (eGFR overexpression) that performed not much better than no CDx at all, the developers of panitumumab chose to use KRAS wild-type status to indicate nonresponse, thereby reducing the number of eligible patients by approximately one-third (FDA 2017b). This is similar to selecting the Drug C cutoff in figure 4.2. This provided the panitumumab developers a short-term advantage until the developers of cetuximab could also show that their drug performed similarly with the KRAS marker. Due to relatively sticky prices, the cetuximab developers suffered revenue declines as patients were excluded, but the price could not be raised to reflect the

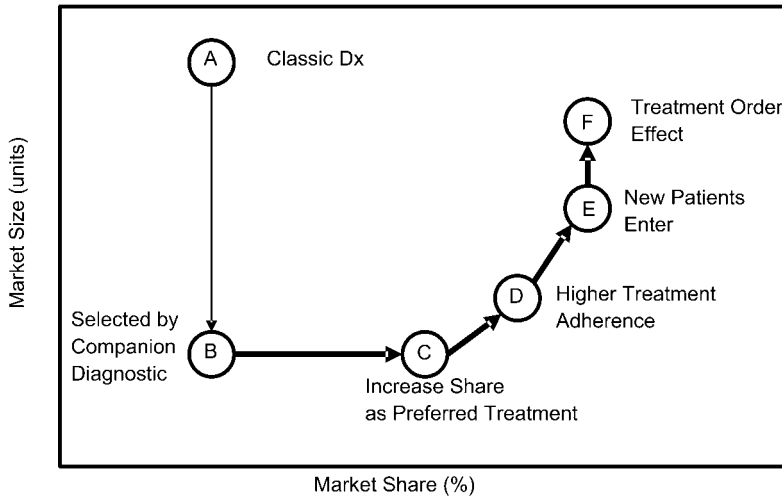


Fig. 4.3 Precision medicine-induced behavior increases the prisoners' dilemma payoff for greater companion diagnostic cutoff value

Notes: The observed therapeutic efficacy increase from selecting a higher cutoff value (figure 4.2, Drug C) can induce multiple behaviors that expand the number of treated patients. After the initial unit volume drop from the diagnostic selection process (A to B), the higher efficacy of the precision medicine usually induces a greater share of the targeted patients than the empirical drug would receive (B to C). Patients who believe this is the best drug for them may adhere more closely and longer to the drug treatment (C to D). Physicians encouraged by the better clinical performance may suggest more aggressive treatment for patients (D to E). Finally, the product with the highest cutoff and efficacy may preferentially deplete the responding patients remaining for other products in its class. This will extend the observed performance gap and increase both share and market size. Multiplied by the higher ICER justifiable price, the revenue for the precision medicine can increase dramatically.

greater efficacy in the enriched patient subpopulation (Carlson 2009). Over time, however, cetuximab garnered increased revenues as more patients and physicians preferred cetuximab over panitumumab for other reasons (in the real world, the assumption of identical other drug properties often does not hold), and annual price increases occurred for both drugs.

This example illustrates that developers must not only consider current players and diagnostics but also anticipate future players, new diagnostics, and their impact on the precision medicine game.

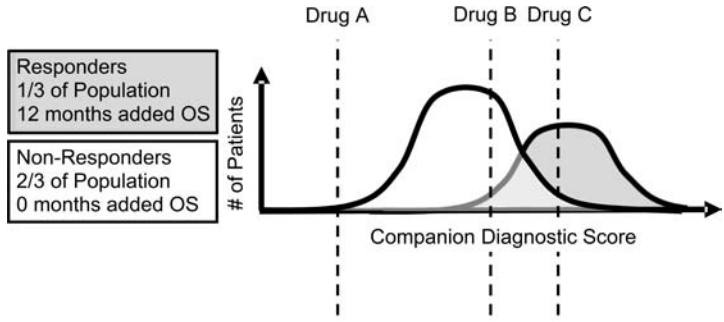
4.6.2 Induced Behavioral Effects

Additional potential benefits not shown in figure 4.2 may result from possible behavior changes induced by a precision medicine entering a market already served by other products. The perturbation from the new entrant will cause dynamic movements toward a new equilibrium (figure 4.3). Although the first step to the new equilibrium reduces patient populations because of diagnostic exclusion, enhanced efficacy/safety increases market share as the

therapy becomes the preferred treatment (figure 4.3 from point A to point B to point C). If the companion diagnostic inspires greater confidence that the therapeutic is the best course for the patient, precision medicines may also benefit from improved patient adherence (C to D). Further market size and market share expansion occurs as underserved patients enter the market encouraged by the greater certainty of outcome should they qualify (D to E). This movement may be less pronounced in high mortality diseases such as oncology, but more so for morbid conditions such as arthritis, HIV, Crohn's disease, or psoriasis. Other factors may also encourage this shift. By providing higher, but not complete, assurance that the therapy will specifically work for them, the test shifts an individual patient's benefit odds and so helps overcome any barriers faced, from fear to inconvenience. A companion diagnostic may also encourage physicians to consider and recommend the therapy by prospectively indicating likely response. Even if the therapy is the only available treatment, a CDx might encourage providers and patients to initiate care. Hence, the diagnostic may not only shift the composition of treatments, but also the overall number of people treated.

4.7 Relaxing the Iso-Payoff Restriction: The Diagnostic Cutoff Prisoners' Dilemma, Part 2

The initial description in figure 4.2 held constant the payoffs as measured by payer cost and product sales for each cutoff selection. In this section, using just the increased market share-induced behavior effect (figure 4.3, B to C), we relax the iso-payoff assumption. In figure 4.4, each strategy leads to a different market share in the selected population. Drug A is hypothesized to now decline to 10 percent market share from 20 percent in the original figure 4.2 case, resulting in it treating 10,000 patients (10 percent of 100,000) and costing $0.5 billion ($46,000 price times 10,000 patients rounded to the nearest $0.1 billion). Drug B is hypothesized to achieve 30 percent market share in its selected population of 56,000 test positive patients. Drug B therefore treats 16,800 patients (30 percent * 56,000) and generates revenues of, or costs payers depending on one's perspective, $1.3 billion (16,800 patients times $77,000 again rounded to nearest $0.1 billion). Drug C is hypothesized to achieve 55 percent market share in its selected population, 25 percentage points above the 30 percent market share hypothesized for Drug B. We calculate this hypothesized market share building upon the hypothesized Drug B 20 percent market share advantage (30 percent vs. 10 percent) over Drug A combined with the Drug B 2.7 months overall survival advantage (6.7 vs. 4.0 months) over Drug A. Drug C achieves a 3.6 month overall survival advantage (10.3 vs. 6.7 months) over Drug B. Extrapolating the same overall survival advantage to market share ratio yields a 26 percent additional Drug C market share, which we round to 55 percent (20 percent Drug B over Drug A market share increase * 3.6/2.7 = 26 percent). With a 55 percent market



RCT Efficacy (Months OS)	4.0	6.7	10.3
Price (ICER Based)	$46,000	$77,000	$119,000
Patients Testing Positive	100,000	56,000	24,000
Market Share in Selected	10%	30%	55%
Patients Treated	10,000	16,800	13,200
Product Revenue (Payer Cost)	$0.5B	$1.3B	$1.6B
Total (100%) Market	$4.6B	$4.4B	$2.9B

ICER: Incremental Cost Effectiveness Ratio
OS: Overall Survival

Fig. 4.4 Companion diagnostics cutoff game, part 2: varying financial payoffs based on cutoff selection

Notes: Continuing the figure 4.1 hypothetical case of an indication with 100,000 total patients with an imperfect companion diagnostic, here we illustrate the potential drug revenue (payer cost) payoffs based on varying the market share in the selected population due to the induced behavior effect of perceived better efficacy (figure 4.3, B to C). Market shares in each selected population are hypothesized as 10 percent for Drug A, 30 percent for Drug B, and 55 percent for Drug C. These shares of the respective test positive patient pools times the ICER-based price create expected payer costs (developer revenue) that increases with the higher cutoff values. This creates a firm and social prisoners' dilemma because the high cutoff excludes patients who might benefit and with ICER-based pricing if 100 percent of eligible patients were treated, cutoff B would generate both the most patient benefit and the most firm revenues ($4.4 billion revenue for 31,500 benefiting patients versus $2.9 billion revenue and 20,700 benefiting patients for 100 percent market share at the highest cutoff).

share, Drug C then generates $1.6 billion in revenue (or payer cost, depending on one's perspective) by treating 13,200 patients (55 percent * 24,000 CDx+ patients) at a price per patient of $119,000.

Figure 4.4 illustrates the resulting prisoners' dilemma for both the firms and society. For illustrative purposes, we assume that an individual firm wishes to maximize its firm profits by maximizing revenues. The high Drug C cutoff and corresponding payoff maximizes the individual firm's revenues, and so profits, if it is the only firm to so choose. If all firms move to this high cutoff, however, the overall collection of firms (assuming that 100 percent of patients would then receive treatment) will only receive $2.9 billion in rev-

enue with many potential responding patients not qualifying for treatment (those responders to the left of the Drug C cutoff in figure 4.4).

Society would most benefit by treating the largest number of responders while minimizing the treatment of nonresponders. Given the imperfect companion diagnostic, this approximately corresponds to the Drug B cutoff, which selects 95 percent of responders. The collection of firms also would be better off if the middle cutoff were selected. The Drug B cutoff would result in total market revenues (if 100 percent of those 56,000 testing positive were treated) of $4.4 billion with 31,500 of 33,000 (95 percent) potential responders benefiting. The middle cutoff also avoids potential adverse events and nondrug treatment costs for the 42,500 nonresponders who would test negative and avoid ineffective treatment. Note that acting in their own interests, firms end up at C, whereas as a group they would prefer to be at B—thus the prisoners' dilemma.

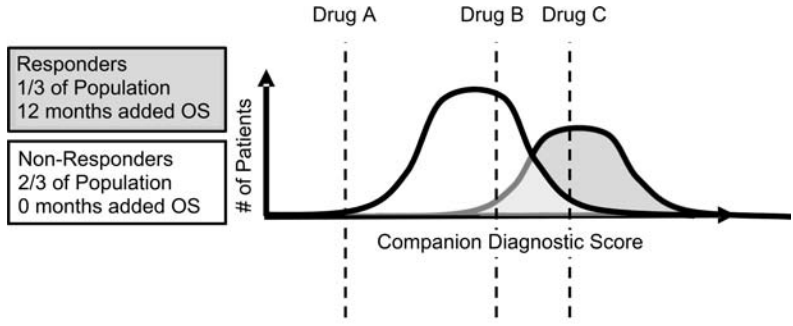
4.7.1 Loser Losses Increased by Responder Depletion

There might be additional market growth beyond that from the induced behavioral effects in the previous section (B to E in figure 4.3). In clinical practice, Firm A might find it difficult to market and compete versus Firm B due to the difference in expected patient overall survival from the use of the companion diagnostic. From a public health perspective, an ordered market with selection bias in which more patients choose Drug B with the companion diagnostic could make the realized benefits from Drug A even lower. Since both work on the same biological target, initial use of Drug B may result in a residual Drug A patient subpopulation that is responder depleted. Thus, rather than being used in an all-comers population with 33 percent responders, Drug A may be relegated to treating a residual all-comers population with lower proportion of responders if Drug B achieves higher levels of market share among its companion diagnostic positive population (see figure 4.5).

If such therapeutic ordering occurs, real-world payer studies may therefore report Drug A efficacy substantially below the already lower average benefit observed in Drug A clinical trials, whereas Drug B real-world studies would align with its original clinical trial observation.

4.8 Game Theory Suggested Strategy under Sequential Responder Depletion

The induced behavior phenomena seen in figure 4.3, along with the responder depletion effect just discussed, transform a simple one period game theoretic dilemma into a sequential one. Facing such a game, what strategy should a rational, game theory oligopolist adopt? While not game theorist specialists, we suggest that the optimal strategy is not clear. If one believes in efficacy proportional pricing (aka "value pricing"), we suggest



RCT Efficacy (Months OS)	0.4 (4.0 prior)	4.0 (6.7 prior)	10.3
Price (ICER Based)	$46,000	$77,000	$119,000
Benefiting Patients	1,500	10,800	20,700
Treated Patients	44,000	32,000	24,000
Payer Cost	$2B	$2.4B	$2.9B

ICER: Incremental Cost Effectiveness Ratio
OS: Overall Survival

Fig. 4.5 Responder depletion effect increases incentive to select higher cutoff

Notes: If patients are first treated with Drug C, the pool of patients remaining for Drug B that test positive have fewer responders. The population that remains is not similar to the clinical trial, but to the population between the Drug B and Drug C cutoffs. In the real world this step-therapy depletion effect would be expected to reduce the observed overall survival benefit for Drug B to 4.0 months from 6.7 previously, and for Drug A to lower the overall survival (OS) benefit to less than half a month from the clinical trial result of four months.

that the optimal initial strategy may be to select a high biomarker cutoff to set an initial high price and protect against subsequent players selecting an even higher cutoff that would suggest that their product could make a superiority claim. Trastuzumab (Herceptin) effectively pursued this strategy with an initially high overexpression cutoff of 3+ on the HER2 test. Over time, this cutoff has been lowered, at least unofficially, to include more potential responding patients. Cetuximab (Erbitux) is an example where not pursuing this strategy had negative results, at least for a period. Thus empirical support exists for the proposed initial high cutoff strategy, illustrating the prisoners' dilemma outcome.

This strategy is defeated, however, if one or more of the above assumptions do not hold. The immuno-oncology checkpoint inhibitors provide an example demonstrating the real-world risk. Bristol-Myers Squibb chose cutoff A (no PD-L1 companion diagnostic) for nivolumab (Opdivo), while Merck & Co. instead chose to use a companion diagnostic for its highly similar pembrolizumab (Keytruda). Companion diagnostics for checkpoint

inhibitors are more cumbersome than other precision medicine genetic tests. Oncologists have preferred the ease and speed of choosing nivolumab over testing and waiting for pembrolizumab, as evidenced by Bristol-Myers Squibb's product's sales being double that of the Merck & Co product. However, in the sequential game where Merck & Co. has now received positive non-small cell cancer first-line treatment clinical trial results, while Bristol-Myers Squibb has not, the dynamic may now be changing. But in the initial game theoretic round, not using precision medicine proved the superior choice for Bristol-Myers Squibb. It appears that many physicians (and their patients) preferred not to order and wait for the companion diagnostic test result when they could prescribe a drug from the same class without waiting. It is not clear this resulted in a patient optimal treatment outcome if the PD-L1 test could have allowed some patients to avoid the cost and the wasted time, with resulting disease progression, of noneffective treatment.

4.9 Variations of the Precision Medicine Prisoners' Dilemma

Precision medicine science creates additional variants of the prisoners' dilemma game beyond that created by companion diagnostic enrichment. Here we describe two variants: precision medicine treatment dosing rules and stopping criteria.

4.9.1 The Dosing Game

The FDA lists many drugs that have pharmacogenomic biomarkers (genetic tests) to indicate metabolism issues that can change the effective dose for either efficacy enhancement or adverse event avoidance. These biomarkers mostly involve liver enzyme mutations (CYP gene family and others; FDA [2017d]). For example, mutations in the CYP2D6 gene in the cytochrome P450 family have been associated with metabolism differences for drugs as varied as the tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) and cardiovascular drugs such as beta blockers and antiarrhythmics (Gardiner and Begg 2006). Mutations in another member of the gene family, CYP2C9, affect the metabolism of proton pump inhibitors, benzodiazepines, barbiturates, and also the tricyclic antidepressants. Some mutations accelerate drug metabolism, requiring increased dosing strength to maintain therapeutic levels in the blood. Other mutations slow drug metabolism, requiring lower dosing strength to avoid effectively overdosing patients. If their dose strengths were adjusted, patients would see their beneficial responses rise and adverse events fall. The effect on drug revenues is more ambiguous because in some instances, assuming revenues are proportional to dosing strength, drug consumption would be increased, and so sales. In other instances, drug consumption would be lowered with drug revenues falling accordingly. In addition, as with companion diag-

nostics, improved dosing may induce second-order behaviors. In this case, patient adherence may increase with concomitant increases in total drug usage and sales over time.

Developers thus face a variation of the prisoners' dilemma involving coordination complications. Should they invest in elucidating the gene mutation effects and promoting the dosing changes in the hopes of improving patient care, gaining competitive advantage and increasing sales? Will competitors match their investments and so eliminate any preferential revenue payoff but raise costs for all? Or should the developer save the genetic discovery investment and hope others do as well? This game has an added feature: in clinical practice to date, physicians rarely test for these genetic mutations or use the test results to adjust their prescribed dosing. Unless physician practices change, the dosing game remains substantially moot. Or put another way, the genetic investment costs far outweigh the potential increased payoff—making the clearly dominant strategy to do nothing.

4.9.2 The Stopping Game

Precision medicine and diagnostic tests can indicate not just when a patient should begin a treatment, but also when a patient would be best off to terminate a treatment. At least two subvarieties of the stopping game have occurred. One suggests via a diagnostic that a therapy is not providing the expected benefit and so should be stopped. An example is the serum M test for gauging the effectiveness of Johnson & Johnson's Janssen bortezomib (Velcade) after six weeks of treatment for multiple myeloma (National Institute for Health and Care Excellence 2007).

The second stopping test subvariety indicates when it is appropriate to halt a chronic therapy, at least for a time. Another, new therapy for multiple myeloma from Johnson & Johnson's Janssen called daratumumab (Darzalex)/clonoSEQ is proving so effective that a new term is emerging, "minimal residual disease," to indicate such dramatic remission that no cancer cells or their detritus can be detected (Adaptive Biotechnologies 2017). So-called liquid biopsies using next generation RNA and DNA sequencing tools on blood samples are being used to detect unique cancer cell signatures. When no signature is detected after general remission, the patient is declared to harbor minimal residual disease. Current studies are now ongoing to determine if chronic adjuvant therapeutic treatment can also be halted and then resumed only as necessary as indicated by a liquid biopsy conducted as a routine monitoring test.

Deciding whether to sponsor the trials for such a stopping rule creates a game theoretic dilemma for the drug company. Under a successful trial, drug revenues from chronic treatment decrease but could be offset by increases from patients preferring the treatment due to the high implied efficacy making stopping a possibility. Patients may also prefer the treatment owing to the possible savings and avoided adverse event risk from stopping. Like the

companion diagnostic enrichment game, the payoffs may change as drug competitors facing the same choice do or do not also seek stopping rule tests.[1]

4.10 Prisoners' Dilemma, Part 3: Including the Payer

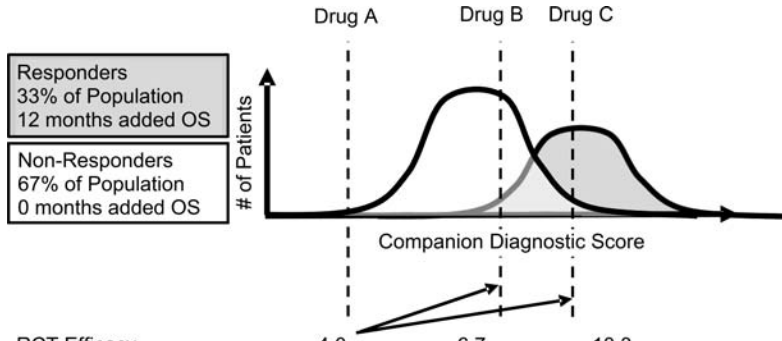
The classic prisoners' dilemma focuses on the prisoners' payoffs, but usually ignores the jailor's desired information payoff from one or more prisoners and society's preference for seeing justice served. Including the payer perspective as another player but with a different objective—to minimize the product revenue (i.e., minimize payer's costs) rather than maximize it—changes the rules of the game and introduces new payoffs for the payer.

As Cortez demonstrated when he burned his ships, changing the rules can dramatically change payoffs and thus the player behaviors (Ross 2016). In the case of Cortez, it removed the payoff of returning home for the conquistadors and so focused them on searching for gold in the New World—Cortez's preferred payoff. Introducing the payer as player not only transforms the payoffs, but also moves the form of the game toward a Bertrand competition—the payer's preferred game.

A savvy payer might recognize that Drugs A, B, and C in the above example are essentially identical, but their developers use different companion diagnostic cutoffs to create the (misleading) perception of differentiated products. Faced with the table in figure 4.2, such a savvy payer may decide to play to optimize his or her own payoffs (minimize costs), rather than passively fund the drug company payoffs.

Specifically, the payer might choose to use the cutoff from Drug C (the high cutoff) but require the use of Drug A (or negotiate discounts with Firms B and C to match Drug A pricing). Such a strategy would save the payer 60 percent compared to purchasing Drug C as per figure 4.2 ($46,000 * 8,400 patients = ~$0.4 billion). Because the Drug C cutoff excludes many who might benefit from treatment, the payer may choose the cutoff from Drug B and still reduce costs by 40 percent. The effective cost per QALY correspondingly falls to $81,000 from the $138,000 reference used in these examples. This 40 percent price reduction from Drug B's price to Drug A's price saves the payer $0.4 billion of the $1.0 billion initial illustration, and $1.7 billion compared to the $4.4 billion amount the payer would expend at the

1. The stopping rule presents a second game to the patient at the time when the stopping criteria have been met. Should the patient actually choose to halt therapy with the risk of more rapid cancer recurrence and benefit of no more drug cost, associated doctor visits, and adverse events? Or should the patient continue treatment to keep the cancer at bay? The evidence supporting the stopping rule will likely be limited, which will add uncertainty regarding the payoffs in this game in which the patient literally bets his or her life. This raises issues of whether these stopping-rule tests are strategic complements or strategic substitutes. For discussion, see Tirole (1988, 205–08).



RCT Efficacy (Months OS)	4.0	6.7	10.3
Price (ICER Based)	$46,000	$46,000	$46,000
Benefiting Patients	7,250	7,250	7,250
Treated Patients	21,750	13,000	8,400
Original Payer Cost	$1B	$1B	$1B
Revised Payer Cost	$1B	$0.6B	$0.4B
Savings	0%	40%	60%

Fig. 4.6 Companion diagnostics cutoff game, part 3: adding the payer as player

Notes: Recognizing the fundamental equivalence of the three drugs differentiated by their companion diagnostic strategies, a savvy payer may switch Drug A for Drug B or Drug C. Alternatively, the payer may negotiate the lower price for Drug B or Drug C. The savings could reach 60 percent in this example.

ICER-justified Drug B price to treat 100 percent of companion diagnostic-selected population (see figure 4.6). Such payer actions would, of course, reduce incentives for developers to pursue precision medicines in the future, if in the end, they still only receive the all-comers nonstratified price.

This has a strong resemblance to finitely repeated prisoners' dilemmas in which backward induction causes all players to undercut from the first round onward (Pindyck and Rubinfeld 2013, 499–500). Moreover, note that the payer has effectively changed the rules of the game to transform a precision medicine prisoners' dilemma game into a Bertrand competition for undifferentiated products. In practice, if not theory, the rules of a game can be changed capriciously. We now consider Bertrand competition games within the context of precision medicines.

4.11 A Precision Medicine Bertrand Competition

Generic, small-molecule drugs are certified by the FDA to be fully interchangeable and undifferentiated from each other and from the original branded product. In such an environment, payers and manufacturers engage in Bertrand competition, with the winning bidder (the lowest price bidder)

potentially supplying the entire market. This competitive bidding process among undifferentiated products results in the price approaching marginal cost, since each bidder realizes bidding a price above marginal costs risks being underbid by a competitor. When products are highly substitutable but not identical, payers may still possess significant pricing power that they may exercise in Bertrand competition-like behaviors (Berndt, McGuire, and Newhouse 2011). For example, the Centers for Disease Control and Prevention (CDC) used to have winner-take-all bidding for vaccines that successfully lowered prices to the lowest marginal cost of the lowest cost manufacturer, driving all others out of the market and leaving the market vulnerable to supply shortages from manufacturing shutdowns (Danzon, Pereira, and Tejwani 2005). In the face of this Bertrand competition result, the CDC altered its bidding process by allowing individual states to run bidding competitions with evaluation criteria beyond lowest price. The number of vaccine manufacturers has since rebounded to restore both competition and supply security (Berndt, Denoncourt, and Warner 2009).

Precision medicines can also experience situations very similar to Bertrand competition. The new generation of hepatitis C treatments are precision medicines. Hepatitis C infections are classified into six major genotypes or strains creatively named 1 through 6. Perhaps the most famous hepatitis C treatments are sofosbuvir (Sovaldi) and the fixed-dose combination of ledipasvir-sofosbuvir (Harvoni) from Gilead Pharmaceuticals. Sovaldi essentially cures patients with genotypes 1 through 4 when combined with other supporting drugs, while Harvoni was initially approved as a sole treatment for patients with genotypes 1 or 4 (FDA 2017b). Harvoni has subsequently been approved to also treat patients with hepatitis C genotypes 5 and 6. Thus, to select the appropriate treatment the patient must first have their infection genetically identified with an immunoassay blood test that detects the genotype-specific antibodies the patient's body produces to combat the virus (Centers for Disease Control 2013). Sovaldi was the first drug launched in its new class of chemistry that both attacks the unique hepatitis C NS5B protein (critical for its machinery of replicating inside the human cell) and that efficiently penetrates the host human cell (FDA 2017b).

Sovaldi was launched in December 2013 with a list price of $84,000 per patient course of treatment (Pollack 2013). This pricing received widespread publicity and incurred considerable criticism from payers and those who sympathized with them. Harvoni launched soon after with a list price of $94,500 for its one tablet a day, twelve-week treatment course. Gilead justified these prices based on the value to the health care system for avoiding the expensive liver transplants and other care that advanced hepatitis C patients incur, and by Harvoni being priced at rough parity per cure obtained compared to earlier generations of hepatitis C treatments (Pollack 2013).

Gilead only had the market to itself for one year. In early December 2014, AbbVie received approval for Viekira Pak, which combined three drugs to

cure those patients with the most prevalent hepatitis C genotype, genotype 1. By Christmas, Express Scripts (at the time the largest pharmacy benefits manager in the United States) announced that its National Preferred Formulary would exclude Gilead's Sovaldi and exclusively offer AbbVie's Viekira Pak, for which it claimed it had received at a large discount (Humer 2014).

Since then, in August 2017 AbbVie has launched a new drug, Mavyret, that cures in only eight weeks rather than the ten to fourteen weeks required of the prior drugs and at a list price of $26,400. The National Acquisition Center makes available the federal government pharmaceutical purchasing cost in the four major programs of the Federal Service System (FSS) and the so-called Big 4 (DoD, VA, Public Health Service, and Coast Guard) prices. The lowest shown prices of Sovaldi, Harvoni, Viekira Pak, and Mavyret at the end of August 2017 extrapolated for a full treatment course are $49,860, $56,700, $60,153, and $29,235, respectively (US Department of Veterans Affairs). The gradual decline to something closer to the Bertrand competition marginal cost continues with price discounts and rebates, some of which are government mandated.

4.12 Defending against a Bertrand Competition: Biologics

A game with payers included can be transformed into a Bertrand competition as discussed above for small molecules, but in large molecule biologics competition may be limited by the entry-deterring science of proving similarity and interchangeability. To date, to protect patient safety, the FDA has certified some biologics to be biosimilar but not interchangeable, thereby not fully enabling Bertrand competition (Berndt and Trusheim 2015). In Europe, biologics have been successfully defending their franchises for nearly a decade (Berndt and Trusheim 2015). Janssen's Remicade is successfully defending its brand position in the United States against biosimilars such as Inflectra from Pfizer (private communication with Aaron Gal of Berstein). Janssen appears to be pursuing a three-pronged strategy of payer negotiations with increased rebates to secure exclusive first-line contracts; volume-based discounts with providers to incentivize stocking; and bundling Remicade with other Johnson & Johnson products to reduce Inflectra's appeal as a standalone discount. Janssen has pursued a discounting approach that leverages its economies of scale and scope and lingering medical concerns that inhibit switching all patients to a biosimilar, thus requiring some continued inclusion of Remicade by providers and payers. In short, sophisticated discounting and continued product differentiation has blunted the price advantage of the Inflectra biosimilar.

Game theory models with learning incorporated can formalize these defense strategies, for example, by incorporating Bayesian learning behavior, but because of their complexity we do not have space to pursue further discussion of them here (Fudenberg and Tirole 1991).

4.13 The Emerging Multiclass Precision Medicine Game

We have described some of the games that cohorts of precision medicines face within their niches. While each niche is defined by its scientific therapeutic target and the associated biomarkers, the niches may begin to overlap and compete for the same patients. Such a situation is emerging in inflammatory disease where no fewer than five drug classes will be competing for rheumatoid arthritis, Crohn's disease, and psoriasis patients. Each of these drug classes provides significant benefits for as few as 30 percent or as many as 60 percent or maybe even 75 percent of patients. Biomarkers exist or are being explored for many of these drug classes.

Drug developers, payers, and patients face a complex simultaneous game in these multiclass situations. This is built upon, but significantly different from, the multiplayer within product class games we discussed above. Each precision medicine niche will likely be at a different maturity stage. Some will be early in their life cycles, while others will be entering postexclusivity. The games will likely link with the payoffs of the early life-cycle games being influenced and constrained by the payoffs and strategies employed by the later games. Similarly, the late-stage game will be influenced by the new niches, which may threaten them with technological obsolescence.

The five-set Venn diagram in figure 4.7 shows the combinations and competition emerging in these overlapping precision medicine niches. The legend assigns a current or emerging inflammatory drug class to each set,

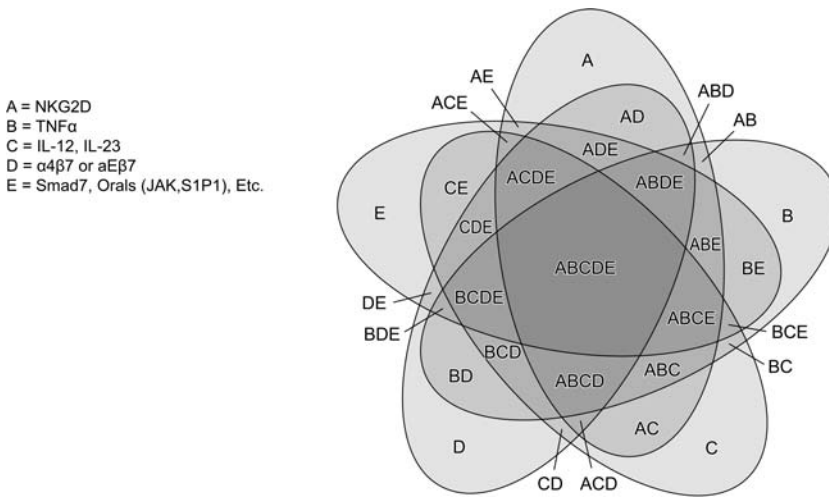


Fig. 4.7 The emerging multiclass game for inflammatory diseases such as rheumatoid arthritis, irritable bowel disease, Crohn's disease, and psoriasis, among others, maybe even cardiovascular

Note: This figure was made in ConceptDraw PRO then rendered in grayscale.

A through E. Each class may provide benefits exclusively to some patients, represented as the pure, nonoverlapping shade of gray at the exposed point of each set. All other products fail for these patients. Most patients, however, will likely respond to two, three, four, or maybe all the drug classes. These are represented by all the overlapping, labeled sections. Note that the schematic shows the logical overlap but does not necessarily show the quantitative actual results. Some small section(s) on the schematic may contain large numbers of patients and vice versa. Also, the schematic does not show the degree to which patients respond more strongly or more weakly to the product classes within a multiclass intersecting area. Navigating the game and determining the optimal strategies for the players is beyond the scope of this chapter and will, of course, depend upon the specific payoffs as determined by the performance of the products and patient value inherent to these indications. The developers, payers, providers, and patients in this inflammatory disease space nonetheless are facing this complex game, whether they fully comprehend its complexity or not. We suggest that game theory can provide multiple insights to guide the clever, rational player.

Oncology faces a similar explosion of product classes for an individual cancer type with the even more complex possibility of including drug combinations to increase efficacy for some molecularly defined patient subpopulations. Oncology has maintained stronger differentiation of each molecular subtype as a distinct market limited to a particular cohort of precision medicines. For example, the HER2-positive breast cancer treatment remains distinct from other precision medicines and classic medicines. This keeps the prisoners' dilemma game focused among Roche and its competitors GlaxoSmithKline and Puma Biotechnology. Roche has two products in the game—trastuzumab (Herceptin) and trastuzumab emtansine (Kadcyla; T-DM1 that adds a cytotoxic chemotherapeutic to the trastuzumab antibody for double action). The other players compete with differently targeted precision medicines that are also approved for HER2-positive breast cancer patients. GlaxoSmithKline markets lapatinib (Tykerb) and Puma Biotechnology offers neratinib (Nerlynx).

This multiclass game will be accentuated by the decisions of guideline development groups or payer utilization management bodies to suggest the order of treatment given complete diagnostic profiling and even the order of testing if complete panels are infeasible or perceived as not cost effective. The resultant effective step-therapy could improve or harm the speed of patient access to the most appropriate treatment. In such an environment, the false positive and false negative rates (Type 1 and Type 2 errors) of the diagnostic will impact the optimal testing and treatment order.

4.14 The Phased Precision Medicine Game

We have explored a series of precision medicine examples and the game situations they exemplify. These examples also suggest that cohorts of preci-

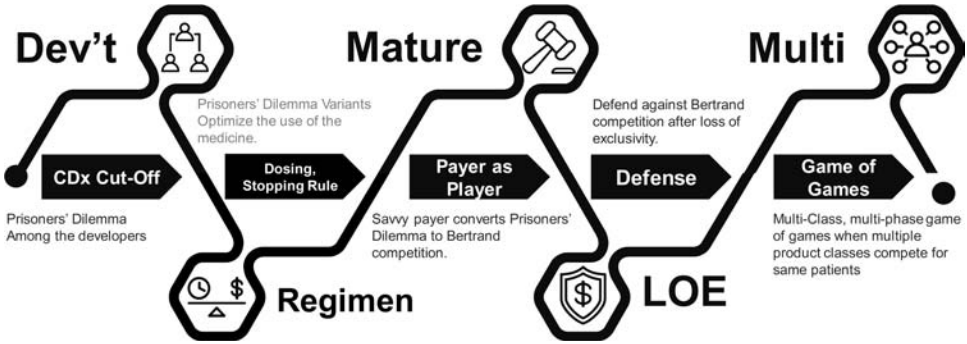


Fig. 4.8 The phased precision medicine life-cycle game

Notes: The games can be arrayed across the life cycle of a therapeutic. While not guaranteed to occur for all precision medicines, a developer might choose to prepare for the sequential, connected games that the individual specific cases suggest might occur.

sion medicines that share niches might present a series of linked games over their life cycles (figure 4.8).

In the process of a precision medicine cohort emerging, drug developers face the first game theoretic dilemma as they make decisions regarding their clinical trial programs and prepare for regulatory submissions. It is likely they engage in the companion diagnostics core game but may also consider the dosing or stopping rule variants, or even a combination of the three.

After market authorization occurs along with the entrance of multiple near-substitute precision medicines, the payers may enter the game and attempt to change it into a Bertrand competition. This has been illustrated in the hepatitis C market. Payers may learn to develop their own scientific insights to mix diagnostics with therapies, as we suggested in the prisoners' dilemma, part 3.

If the branded therapeutic does not succumb to a Bertrand competition prior to legal loss of exclusivity, it then faces the "defense" game. The branded therapeutic firm may attempt to deter entry through increasing legal costs of its competitors or by demonstrating a prior ability to combat franchise erosion as traditional biologics products in the United States have been demonstrating against biosimilars. Traditional small-molecule brands have also demonstrated some ability to delay, but less ability to defeat, generic competition. Precision medicine remains too young to have similar examples. But simply because it has not yet occurred does not mean that the defense game will be avoided when exclusivity ends for precision medicine products.

Participants in precision medicine markets can expect a series of games and opportunities to apply game theory for each market. Participants will need to discern, however, which game applies to each cohort or niche at a given time. Participants will also need strategies that link across games as payoffs from the prior games may influence later games, and so reputational

effects may evolve. In any case, the preparation for later games will begin even as the initial games unfold.

4.15 Conclusion

In this chapter we have described how precision medicines create situations that bear some semblance to game theory constructs such as the prisoners' dilemma and Bertrand competition. We are not game theorists, yet we recognize that the textbook examples of the prisoners' dilemma are typically a one-time static game, whereas what we have described here is more dynamic in nature. But the resulting Nash equilibrium outcomes are similar. In particular, outcome equilibria emerge in which players each prefer a different outcome but must choose a strategy to do the best they can assuming the anticipated rational behaviors of the others. The examples we have discussed usually involve drug developers in competition with each other. We have also described situations in which other stakeholders join the game or face their own unique game. For instance, when payers joined the prisoners' dilemma game, they transformed it into a Bertrand competition-like game. Another prisoners' dilemma-like game occurs when patients face their own distinct decision in the stopping rule variant. When patients join the drug developer companion diagnostic prisoners' dilemma, their induced behaviors typically alter the payoffs for the primary drug developer players.

We also observe that the games may predictably array themselves across the life cycle of each precision medicine indication niche. These arrayed games may remain independent or may become linked into a sequentially evolving metagame. This might be an area for additional fruitful theoretical research immediately and for future empirical studies as the precision medicine niches mature. Techniques similar to those that Brekke and Kuhn (2006), building on the work of Grossman and Shapiro (1984) two decades earlier, applied to study the impact of advertisements on patient choices may also help us understand the impact of companion diagnostics, perceived quality, and reputation on treatment selection.

Finally, we hypothesize that some precision medicine areas such as inflammatory diseases are becoming complex simultaneous multigames in which separate drug cohorts in distinct precision medicine niches compete with other cohorts for patients as well as within their own cohort. This intertemporal multigame is further complicated by cohorts being in different life-cycle stages even as the cohorts compete across niches. Some cohorts may be young and just emerging into the market, while others are established and still others may be entering the mature loss of exclusivity game. By stretching the classic game frameworks, this multigame might be a particularly exciting, albeit challenging, area for future research.

One dynamic we have not considered here concerns implications of the existence of a small number of producers with market power in therapeutic

classes for competition and antitrust policy, particularly when those producers are multiproduct firms with market power for each product. As shown in, among others, Tirole (1988, 70), a multiproduct firm selling two products each having market exclusivity will set prices for both products greater (lower) than prices set by two standalone firms each selling a single product with market exclusivity, provided the two products are substitutes (complements). An example of complementarity in the present context occurs when a single firm has monopoly power in selling both the therapeutic and its companion diagnostic. In such a case, vertical integration eliminates double marginalization (Pindyck and Rubinfeld 2013, 442–43) and results in both the companion diagnostic and the therapeutic having lower prices than if the two products were each sold by standalone, nonvertically integrated firms. In such cases, other things equal, public policy that encourages vertical integration may result in both consumers' and producers' surplus being greater than in the no-integration case. However, one can also envisage situations in which, for example, two patent-protected precision cancer medicines are substitutes. In such a case, the oncology division of a single firm selling both exclusivity-protected products could exploit its market power and charge higher prices for both oncology treatments than if they were sold by separate firms. Thus competition and antitrust public policies may need to focus on determining and weighing substitutability versus complementarity relationships, thereby confronting multiproduct market power issues that were prominent in the Microsoft litigation early in the first decade of the twenty-first century. Such antitrust scrutiny will likely be even more complex and challenging as an increasing number of precision medicines are composed of combination therapies, with at least some of the components having market exclusivity. Thus, in addition to developers playing the prisoners' dilemma to differentiate their products, even as payers attempt to transform that game into Bertrand competition, both payers and developers will need to be cognizant of developments in competition and antitrust public policy.

Precision medicines have been a moderately successful pharmaceutical category since their introduction in the late 1990s. Rapidly increasing molecular understanding of disease and the falling cost of genetic testing due to next generation sequencing technologies have swollen the precision medicine product pipeline in many therapeutic areas. Whether these precision medicines can achieve sustainable commercial success and payer acceptance remains to be seen. The underlying science may support virtually unlimited differentiation with few precision medicines directly competing for each patient subpopulation. Precision medicines may be natural oligopolies or even natural monopolies in the case of biologics, cellular, or gene therapies for which scientific identity and clinical interchangeability is difficult to demonstrate. The resulting seller power may be mitigated as payers also consolidate in the United States to create oligopsonistic buyers. European and Asian countries are already dominated by single payer, government

monopsonistic health care systems. Game theory-based analyses would seem to be increasingly relevant in such concentrated markets, particularly to inform potential policy changes by governments that will have incentives to alter rules for their economic buying interests that may not consider the impact on translating these same governments' public research investments into public health-enhancing therapies.

In such a context, the credibility of evidence sources will play a critical role, again raising enduring issues of the optimal societal roles for public and private sectors in creating, disseminating, and pricing information. Those players that learn the most rapidly and apply that learning the most asymmetrically will be advantaged in this ongoing information pharms race.

References

Adaptive Biotechnologies. 2017. "Adaptive Biotechnologies Announces a Collaboration with Janssen Biotech, Inc. to Use the ClonoSEQ® Assay to Measure Minimal Residual Disease in Ongoing and Future DARZALEX® Multiple Myeloma Trials." Press Release, July 21. Accessed Aug. 27, 2017. http://www.adaptivebiotech.com/news/adaptive-biotechnologies-announces-collaboration-janssen-biotech-inc-use-clonoseq%C2%AE-assay.

Ainsworth R., J. M. S. Bartlett, J. J. Going, E. A. Mallon, A. Forsyth, J. Richmond, W. Angerson, A. Watters, and B. Dunne. 2005. "IHC for Her2 with CBE356 Antibody Is a More Accurate Predictor of Her2 Gene Amplification by FISH than HercepTest™ in Breast Carcinoma." *Journal of Clinical Pathology* 58:1086–90.

Bae, Y. H., and C. D. Mullins. 2014. "Do Value Thresholds for Oncology Drugs Differ from Nononcology Drugs?" *Journal of Managed Care and Specialty Pharmacy* 20 (11): 1086–92.

Berndt, E. R., R. N. Denoncourt, and A. C. Warner. 2009. *US Markets for Vaccines: Characteristics, Case Studies, and Controversies*. Washington, DC: AEI Press.

Berndt, E. R., T. G. McGuire, and J. P. Newhouse. 2011. "A Primer on the Economics of Prescription Pharmaceutical Pricing in Health Insurance Markets." *Forum for Health Economics & Policy* 14 (2): article 10. November. https://doi.org/10.2202/1558-9544.1301.

Berndt, E. R., and M. R. Trusheim. 2015. "Biosimilar and Biobetter Scenarios for the US and Europe: What Should We Expect?" In *Biobetters: Protein Engineering to Approach the Curative*, edited by Amy Rosenberg and Barthelémy Demeule, 315–60. New York: Springer.

Birner P., G. Oberhuber, J. Stani, C. Reithofer, H. Samonigg, H. Hausmaniger, E. Kubista, W. Kwasny, D. Kandioler-Eckersberger, M. Gnant, and R. Jakesz. 2001. "Evaluation of the United States Food and Drug Administration-Approved Scoring and Test System of HER-2 Protein Expression in Breast Cancer." *Clinical Cancer Research* 7:1669–75.

Brekke, K. R., and M. Kuhn. 2006. "Direct to Consumer Advertising in Pharmaceutical Markets." *Journal of Health Economics* 25 (1): 102–30.

Carlson, B. 2009. "KRAS Testing: Optimizing Cancer Therapy." *Biotechnology Healthcare* 6 (5): 7–9.

Centers for Disease Control (CDC). 2013. "Hepatitis C Information on Testing and

Diagnosis." Publication no. 220411. Accessed Aug. 31, 2017. https://www.cdc.gov/hepatitis/hcv/pdfs/hepctesting-diagnosis.pdf.

Danzon, P. M., N. S. Pereira, and S. S. Tejwani. 2005. "Vaccine Supply: A Cross-National Perspective." *Health Affairs* 24 (3): 706–17.

Dendreon. 2017. "Sanpower Group Closes Acquisition of Dendreon." Press Release, June 29. Accessed Aug. 22, 2017. https://www.businesswire.com/news/home/20170629005592/en/Sanpower-Group-Closes-Acquisition-Dendreon.

Fudenberg, D., and J. Tirole. 1991. *Game Theory*. Cambridge, MA: MIT Press.

Gardiner, S. J., and E. J. Begg. 2006. "Pharmacogenetics, Drug-Metabolizing Enzymes, and Clinical Practice." *Pharmacological Reviews* 58 (3): 521–90.

Grossman, G. M., and C. Shapiro. 1984. "Informative Advertising with Differentiated Products." *Review of Economic Studies* 51 (1): 63–81.

Helwick, C. 2014. "Pathologic Complete Response: Understanding the Subtleties." *The ASCO Post* 5 (16). Oct. 15. Accessed May 4, 2015. http://www.ascopost.com/issues/october-15,-2014/pathologic-complete-response-understanding-the-subtleties.aspx.

Hu, S. X., M. L. Aitken, A. M. Epstein, M. R. Trusheim, and E.t R. Berndt. 2013. "Defining and Quantifying the Use of Personalized Medicines." *Nature Reviews Drug Discovery.* Online version published Nov. 29, 2013. http://www.nature.com/nrd/journal/v12/n12/full/nrd4177.html?WT.ec_id=NRD-201312.

Humer, C. 2014. "Express Scripts to Cover AbbVie Hepatitis C Drug, Drops Gilead Treatment." *Reuters*, Dec. 22. Accessed Aug. 31, 2017. http://www.reuters.com/article/express-scripts-abbvie-hepatitisc-idUSL1N0U50M120141222.

National Institute for Health and Care Excellence (NICE). 2007. "Bortezomib Monotherapy for Relapsed Multiple Myeloma." NICE Technology Appraisal Guidance no. 129. Accessed Aug. 27, 2017. https://www.nice.org.uk/guidance/ta129.

Novartis. 2017. "Novartis CAR-T Cell Therapy CTL019 Unanimously (10–0) Recommended for Approval by FDA Advisory Committee to Treat Pediatric, Young Adult r/r B-cell ALL." Press Release, July 13. Accessed Aug. 22, 2017. https://www.novartis.com/news/media-releases/novartis-car-t-cell-therapy-ctl019-unanimously-10-0-recommended-approval-fda.

Pindyck, R. S., and D. L. Rubinfeld. 2013. "Game Theory and Competitive Strategy." In *Microeconomics*, 8th ed., edited by R. S. Pindyck and D. L. Rubinfeld, 487–528. New York: Prentice Hall.

Pollack, A. 2013. "FDA Approves Pill to Treat Hepatitis C." *New York Times,* page B1, Business Day, Dec. 7. Accessed Aug. 31, 2017. http://www.nytimes.com/2013/12/07/business/fda-approves-pill-to-treat-hepatitis-c.html?mcubz=1.

———. 2016. "Immunotherapy Drug Opdivo Fails Clinical Trial to Expand Use." *New York Times*, Aug. 5. Accessed Aug. 27, 2017. https://www.nytimes.com/2016/08/06/business/lung-cancer-drug-opdivo-fails-clinical-trial-to-expand-use.html?mcubz=1.

Reuters Staff. 2017. "BRIEF-Valeant Pharmaceuticals Completes Sale of Dendreon to Sanpower Group." June 29. Accessed Aug. 22, 2017. http://www.reuters.com/article/brief-valeant-pharmaceuticals-completes-idUSFWN1JQ07C.

Ross, D. 2016. "Game Theory." In *The Stanford Encyclopedia of Philosophy Archive*, Winter 2016 ed., edited by Edward N. Zalta. https://plato.stanford.edu/archives/win2016/entries/game-theory/.

Staton, T. 2016. "Bristol-Myers' Opdivo Far Outpaced Merck's Keytruda Again in Q2. What Gives?" *FiercePharma*, Aug. 1. Accessed Aug. 27, 2017. http://www.fiercepharma.com/marketing/bristol-myers-opdivo-far-outpaced-merck-s-keytruda-again-q2-what-gives.

Tirole, J. 1988. *The Theory of Industrial Organization*. Cambridge, MA: MIT Press.
Trusheim, M. R., M. J. Austin, C. Raucsh, and E. R. Berndt. 2013. "Uncertain Prognosis for High-Quality Diagnostics: Clinical Challenges, Economic Barriers and Needed Reforms." *Pharmacogenomics* 14 (3): 325–34.
Trusheim, M. R., and E. R. Berndt. 2012. "The Segmentation of Therapeutic Populations in Oncology." *Health Management, Policy and Innovation* 1 (1): 19–34.
———. 2015. "The Clinical Benefits, Ethics, and Economics of Stratified Medicine and Companion Diagnostics." *Drug Discovery Today* 20 (12): 1439–50.
Trusheim, M. R., E. R. Berndt, and F. L. Douglas. 2007. "Stratified Medicine: Strategic and Economic Implications of Combining Drugs and Clinical Biomarkers." *Nature Reviews Drug Discovery* 6 (4): 287–93.
Trusheim, M. R., B. Burgess, S. X. Hu, T. Long, S. D. Averbuch, A. A. Flynn, A. Lieftucht, et al. 2011. "Quantifying Factors for the Success of Stratified Medicine." *Nature Reviews Drug Discovery* 10 (11): 817.
US Department of Veterans Affairs. National Acquisition Center (CCST) Pharmaceutical Catalogue Search. Accessed Aug. 31, 2017. https://www.va.gov/nac/Pharma/List.
US Food and Drug Administration (FDA). 2015. Remicade (Infliximab) Label, Revised: January 2015. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/.
———. 2017a. Cellular & Gene Therapy Products-Marketed Products. Page updated Aug. 11, 2017. Accessed Aug. 22, 2017. https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/default.htm.
———. 2017b. FDA Online Label Repository. http://labels.fda.gov/.
———. 2017c. Keytruda Label. FDA Online Label Repository. http://labels.fda.gov/.
———. 2017d. Table of Pharmacogenomic Biomarkers in Drug Labeling. Accessed Aug. 27, 2017. https://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.
Westwood, M., T. van Asselt, B. Ramaekers, P. Whiting, M. Joore, N. Armstrong, C. Noake, J. Ross, J. Severens, and J. Kleijen. 2014. "KRAS Mutation Testing for the Prediction of Response to Treatment with Cetuximab in Addition to Chemotherapy." Health Technology Assessment, no. 18.62. Chapter 3, Table 8, "Accuracy of KRAS Mutation Testing for the Prediction of Response to Treatment with Cetuximab in Addition to Chemotherapy." Southampton (UK), NIHR Journals Library. October. https://www.ncbi.nlm.nih.gov/books/NBK262659/; https://www.ncbi.nlm.nih.gov/books/NBK262667/#s3-2.