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Trends in interorganizational transactions in personalized medicine development

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Personalized medicine is an innovative concept that allows patients with a validated companion diagnosis (CoDx) to receive treatment using the most suitable drug. Currently, a major movement in the pharmaceutical industry involves the integrated use of multiple resources from external sources. To ascertain preferable interorganizational collaborations and their suitable exits, we compared the related transactions in personalized and nonpersonalized cancer drugs. We found that there were significantly more of some alliance deals in personalized medicine, and that market licenses, one of the exits, were well correlated with other alliances only in personalized medicine. Furthermore, four types of collaboration mode were identified, and more active collaborations with external partners were found to lead to more successful outcomes in personalized medicine development.

Introduction

Owing to social challenges, such as improvements in quality of life and an aging worldwide population, the demand for new drugs has been growing rapidly for decades. Although companies and research institutes in the pharmaceutical industry have made great efforts to develop new drugs, their productivity is regrettably stagnant. In particular, launching new therapeutic drugs has become more challenging for pharmaceutical companies since 2010, despite the continuous increase in research and development (R&D) spending [1]. It was estimated that spending on new drug development increased from US$800 million in 2000 to US$2.87 billion in 2013 [2]. Recently, AstraZeneca, a pharmaceutical company in the UK, published an interesting analysis of their drug pipelines and outcomes from 2005 to 2010. They set up five critical frameworks for the decision-making process in R&D: 'right target', 'right tissue', 'right safety', 'right patients', and 'right commercial potential', all of which could heavily affect the success rate of drug development [3,4]. Of particular importance is the concept of 'right patients'; exploring appropriate biomarkers at the early stage of drug development and recruiting patients who are expected to have potential medical efficacy can lead to a much higher rate of successful clinical trials.

Precision drugs or personalized medicine is an innovative therapeutic approach that allows individual patients to be stratified based on their clinical, genetic, and biomarker information by using *in vitro* diagnostic kits (CoDx). CoDx is a diagnostic test used as a companion to a therapeutic drug to determine its applicability to a patient, and includes genetic sequencing, immunohistochemistry (IHC), and fluorescence *in situ* hybridization (FISH). Then clinicians, not only doctors, but also pharmacists and prescribing nurses, can use the most suitable drug to treat the selected group of patients [5]. Consequently, this concept is expected to increase the success rate and reduce the R&D costs of pharmaceutical companies, as previously mentioned. In addition, it will provide the best treatment to patients, increase medical adherence, and reduce the probability of adverse effects and medical wastage, which in turn will also help to reduce the cost of healthcare

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faced by governments [3,6,7]. Despite the many potential benefits described above, few representatives of personalized medicine with CoDx have been approved, and cases of successful implementation remain rare.

The pharmaceutical industry had been taken for granted as a closed business model, where a single company had all the means of following an idea from the R&D stage to the market. However, the idea of open innovation has gained popularity among several industries, including the pharmaceutical industry, since its definition by Chesbrough [8]. There has been a growing trend, even among pharmaceutical companies, to access resources such as ideas, products, and technologies, from academic institutions, small and medium enterprises, or biotech companies [9]. Several previous studies demonstrated a positive correlation between the degree of open innovation by organizations and the growth achieved by them [10,11]. In other studies, experimental analysis and measurement of open innovation in the pharmaceutical industry have been proposed [12,13]. However, there are few studies of the interorganizational relationships for the development of personalized medicine and related advanced medicine.

Haruya and Kano conducted an empirical study using structural equation modeling analysis to identify corporate capabilities that are important for the development of personalized medicine [14]. They found that external CoDx capability was preferable to efficient personalized drug development, which implies that collaboration with external organizations is an important factor for the successful development of personalized medicine. Recently, a research paper was published that analyzed current trends of transactions in personalized medicine development [15]. The authors reported an increase in financing deals for start-ups, which is expected to lead to new patent creation; this suggests that venture capitalists and start-ups are key to further success in this area. Besides private investments, several public funding sites, such as Biomarker consortiums and the Innovative Medicine Initiative, have been established recently. These consortiums enhance collaboration between different organizations, including firms and academic institutes, in the EU and USA [16]. These studies clearly show that collaborating and networking with other organizations are crucial for success in personalized medicine development. However, the characteristics of interorganizational collaborations among the firms and research institutes that launch personalized drugs remain to be addressed.

In this study, we explored the characteristics of external transactions in pharmaceutical companies and research institutes that have experience in launching personalized medicine. A comparative study of personalized medicine and nonpersonalized medicine in cancer drugs was carried out to reveal the features specific to external collaborations in personalized medicine development.

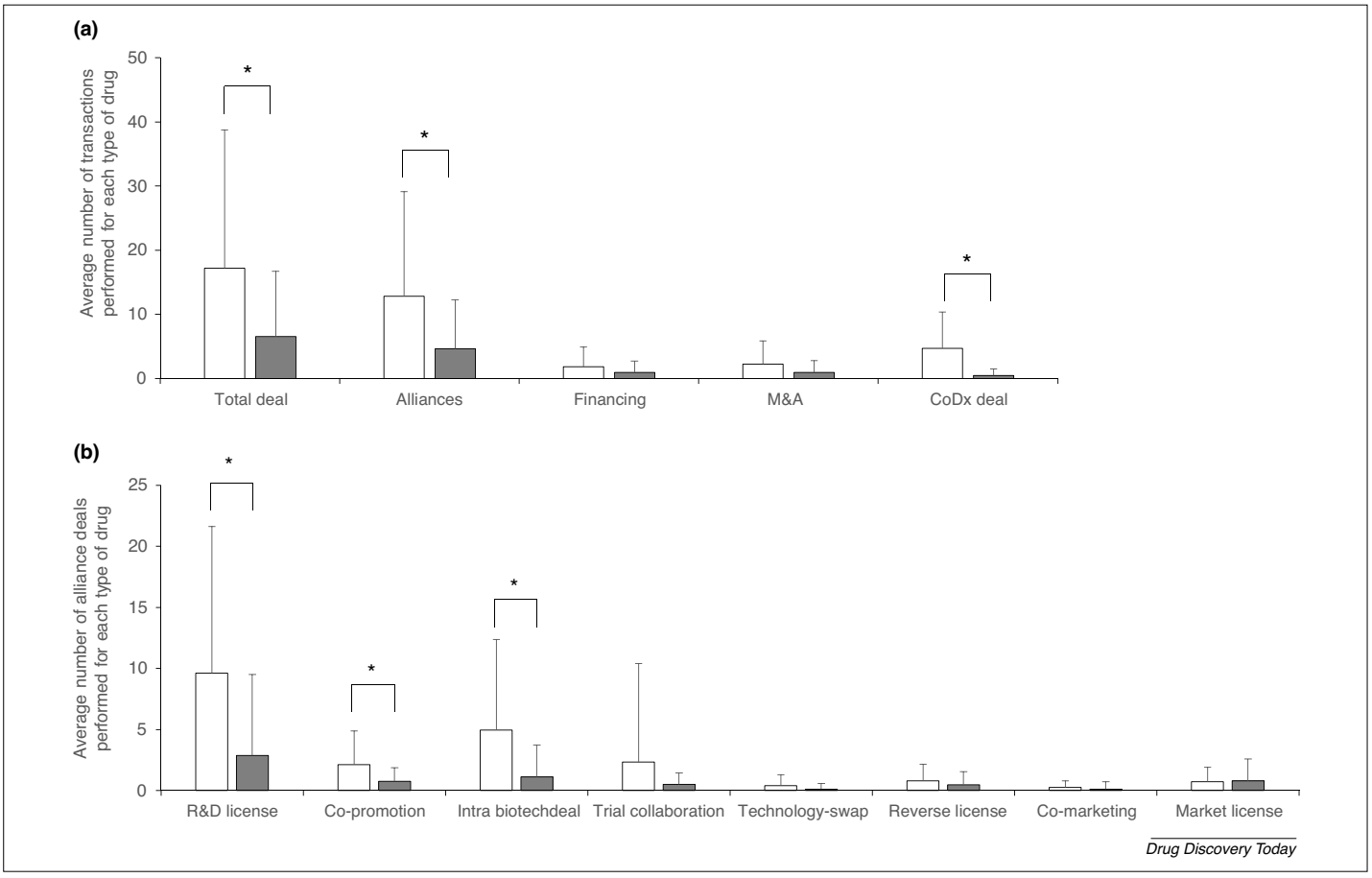

FIGURE 1

Number and types of transactions in launched personalized and nonpersonalized medicine development. (a) Average number of transactions in personalized (unshaded bars) and nonpersonalized (shaded bars) medicine development, including total deal (total number of all deals), alliances, financing, merger and acquisitions (M&A), and CoDx deals are shown. (b) Among Alliances in (a), research and development (R&D) licenses, co-promotion, intra-biotech deal, trial collaboration, technology-swap, reverse license, co-marketing, and market license are shown as the average for each type of drug. *$P < 0.05$.

Transaction analysis of personalized medicines and nonpersonalized cancer medicines

We gathered data about the patents, organizations, and transactions related to on-market personalized medicines and compared them with those of nonpersonalized medicine according to published research frameworks [12,17,18]. To standardize the terminology, 'personalized medicine' was used in place of 'precision drug,' 'personalized drug' and 'CoDx' [*in vitro* diagnosis (IVD)] hereafter, because these terms have the same basic meaning. Given that cancer therapeutics is the main area of focus for personalized medicine development [19,20], we extracted 23 personalized cancer drugs from the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Personalized Medicine Coalition (www.personalizedmedicinecoalition.org/) websites. We also gathered information for 24 nonpersonalized cancer drugs from FDA Approved Drugs in Oncology Center Watch (www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/12/oncology). The detailed information about each drug is listed in Tables S1 and S2 in the supplemental information online. Note that the average year of drugs being on the market (2008 versus 2009, respectively) and ratio of biologics:small molecular drugs (26% versus 29%, respectively) between the personalized and nonpersonalized medicines were normalized and, thus, are similar. We then performed a database search using the transaction database (strategic transactions/deals; www.Pharmamedtechbi.com/deals) to examine the type and number of transactions performed in each on-market personalized and nonpersonalized medicine described in Tables S1 and S2 in the supplemental information online. Both the brand name and generic name of each drug were used for keyword searches; and data were used for analysis after excluding overlaps between them. We checked the summaries of each deal one by one to ensure that each category of transactions were relevant.

In the database, we found the followings deal types: (i) merger and acquisition (M&A): buyout, divestiture, spinout, full acquisition, partial acquisition, and reverse acquisition; (ii) alliance: co-marketing, co-promotion, intrabiotech deal, joint venture, manufacturing or supply partnership, marketing licensing, product-technology swap, product purchase, R&D licensing, reverse licensing, deals related to CoDx, and trial collaboration; (iii) financing: convertible debt, follow-on public offering (FOPO), initial public offering (IPO), private investment in public biotech, private placement, special purpose financing vehicle, and spin-off (note that public funding was not included).

In addition, we searched the number of basic patents and developers for each drug by engaging the patent database (patent lens; www.lens.org/lens/structured-search) and pharmaceutical database (EvaluatePharma; www.evaluategroup.com/public/EvaluatePharma-Overview.aspx). All the data regarding drugs, transactions, patents, and developers were obtained from 1991 to 2016. The data obtained were subjected to quantitative analyses. Descriptive statistics were obtained, and correlation and multi-linear regression analyses were carried out to see whether there was a significant trend in their interactions. For the statistical analysis, IBM SPSS Statistics ver. 22 was used.

The bar chart of transactions relating to personalized drugs and non-personalized drugs is shown in Fig. 1. The major transactions in Fig. 1 are described as the number of all deals (total deals), alliances, financing, and M&A. The alliances include R&D licenses, market licenses, co-promotion, intra-biotech deals, trial collaboration, technology swapping, reverse licensing, and co-marketing. Note that there are some overlaps in the components of alliance deals. Among those, the total numbers of deals, alliance, R&D license, co-promotion, and intra-biotech deal were significantly higher ($P < 0.05$ using Student's t-test) than those with nonpersonalized medicine development.

TABLE 1

Correlation analysis of transactions, developers, patents, and licenses in personalized and nonpersonalized medicine development[a]

	1	2	3	4	5	6	7	8	9
Personalized medicine									
1. Total deals	1.00								
2. Basic patents	*0.41**	1.00							
3. Developers	0.55*	0.77*	1.00						
4. Alliances	0.98**	*0.40**	0.50*	1.00					
5. R&D licenses	0.90**	0.52*	0.65*	0.84**	1.00				
6. Market licenses	**0.85****	0.46*	0.42*	**0.88****	0.66*	1.00			
7. Financings	**0.87****	**0.42***	0.68*	**0.80****	**0.87****	0.62*	1.00		
8. M&A	0.84**	*0.34*	0.50*	0.75*	0.91**	0.63*	**0.81****	1.00	
9. CoDx deals	0.62*	0.66*	0.43*	0.60*	0.73*	0.60*	0.49*	0.60*	1.00
Nonpersonalized medicine									
1. Total deals	1.00								
2. Basic patents	0.48*	1.00							
3. Developers	0.66*	0.82**	1.00						
4. Alliances	0.98**	*0.35*	0.60*	1.00					
5. R&D licenses	0.96**	0.41*	0.62*	0.95**	1.00				
6. Market licenses	**0.50***	*0.10*	*0.25*	**0.54***	0.29	1.00			
7. Financings	**0.58***	**0.80****	0.59*	**0.45***	**0.56***	*–0.02*	1.00		
8. M&A	0.88**	0.42*	0.62*	0.83**	0.79*	0.49*	**0.42***	1.00	
9. CoDx deals	0.76*	0.61*	0.66*	0.70*	0.86**	*–0.08*	0.75*	0.58*	1.00

Coefficients with values 0.4–0.8 are shown by * and those with values >0.8 are shown by **. Header numbers indicate the following variables: 1. Total deals; 2. Basic patents; 3. Developers; 4. Alliances; 5. R&D licenses; 6. Market licenses; 7. Financings; 8. M&A; and 9. CoDx deals, respectively.

[a] Entries in italic indicate values with no significance ($P > 0.05$), entries in standard font indicate significant values ($P < 0.05$), entries in bold indicate significant differences ($P < 0.05$) between coefficients of personalized medicine and nonpersonalized medicine.

Next, we performed a correlational analysis of personalized medicine and nonpersonalized medicine by comparing several variables with one another (Table 1). The details of descriptive statistics of variables (total number of deals, number of basic patents, developers, alliance deals, R&D license deals, market license deals, financing, and M&As for analysis) used in the analysis are shown in Table 2. We checked the relevance of each coefficient by performing the significant test, and found almost all the data were statistically significant ($P < 0.05$). In addition, we examined whether the differences in coefficients between personalized and nonpersonalized medicine were statistically significant (Table 1). The personalized medicine and each type of transaction (alliance deals, R&D license deals, market license deals, financing, and M&A) were positively and strongly correlated to each other, which was similar to those of nonpersonalized medicine. However, the coefficient of market licenses and financing towards other alliances in nonpersonalized medicine development were significantly lower than those in personalized medicine (Table 1). Therefore, we examined which factors were explanatory variables for market license by using multiple linear regression analysis with stepwise methodology (Table 3). The data set of Table 2 was used for variables. In personalized medicine development, the number of market licenses could be explained by the number of alliances deals with a 74% power of explanation ($R^2 = 0.74$). A significant regression equation was found [F (1,21) = 56.0, $P < 0.000$] and the participant's predicted 'market licenses' in personalized medicine = $-0.092 + 0.858 \times$ (alliance), where 'alliance' is measured in numbers (Table 3). By contrast, less of the variance in the number of market licenses in nonpersonalized medicine could be explained by other variables ($R^2 = 0.29$) (Table 3). Accordingly, our data suggested that more active alliances towards external partners could lead to successful outcomes for the number of market licenses in personalized medicine development, whereas this trend was not evident in nonpersonalized medicine development.

TABLE 2

Descriptive statistics of deals, developers, patents, and licenses in personalized medicine and nonpersonalized medicine development

Statistic	Average	Standard deviation
Personalized medicine		
1. Total deals	17.2	21.6
2. Basic patents	111.9	111.2
3. Developers	6.9	5.4
4. Alliances	12.8	16.4
5. R&D licenses	9.6	12.0
6. Market licenses	0.7	1.2
7. Financings	1.8	3.0
8. M&A	2.3	3.6
Non-personalized medicine		
1. Total deals	6.5	10.3
2. Basic patents	104.7	109.5
3. Developers	7.0	4.1
4. Alliances	4.6	7.8
5. R&D licenses	2.9	6.8
6. Market licenses	0.8	1.8
7. Financings	1.0	1.8
8. M&A	1.0	1.9

TABLE 3

Multiple linear regression analysis of market licenses in personalized and nonpersonalized medicine development[a]

	Variables						
	B	***SE***	**B**	***t***	***P***	**Tolerance**	**VIF**
Personalized medicine[b]							
Constant	−0.091	0.156	–	−0.579	0.569	–	–
Alliances	0.066	0.009	0.858	7.485	0.000	1.00	1.00
Nonpersonalized medicine[c]							
Constant	0.219	0.391	–	0.582	0.858	–	–
Alliances	0.126	0.043	0.540	2.938	0.008	1.00	1.00

[a] *B*, unstandardized coefficient; SE, standard error; B, standardized coefficient; VIF, the variance inflation factor.
[b] $R = 0.86$, $R^2 = 0.74$, $F_{(1,21)} = 56.0$, $P < 0.000$.
[c] $R = 0.54$, $R^2 = 0.29$, $F_{(1,22)} = 8.6$, $P = 0.008$.

Longitudinal transaction analysis of launched personalized medicine as case study

To obtain more detailed attributes of transactions in each launched drug, we performed a longitudinal transaction analysis of several on-market personalized medicines using text data of the transactions as a case study (Table 4). A text summary of each transaction for each drug was categorized into R&D license, market license, co-promotion or trial collaboration, deal related to CoDx (CoDx deal), deals for combination therapy or seeking additional indication (combo/additional indication), deal with clinical trial, financing, and M&A, and paneled on a yearly basis (Table 4).

Each personalized drug could be categorized into four groups: Type 1, co-development of CoDx before launched (Erbitux, Zellbora, Tafinlar, Midostaurin, Tagrisso, Xalkori, and Lynparza); Type 2, co-development/funding for R&D of drugs before launched (Tarceva, Idhifa, Mekinist, Venetoclax, Vectibix, Rubraca, and Kadcyla); Type 3, co-development of CoDx after launched (Gleevec, Herceptin, and Iressa); and Type 4, trial collaboration of combination therapy with other drugs after launched (Keytruda). In the case of Erbitux [a monoclonal antibody therapeutic against epidermal growth factor receptor (EGFR) for the treatment of metastatic colorectal cancer and others], Imcolne (originator) started co-promotion with Merck and Bristol-Myers Squibb (BMS) for the development of drugs and co-developed CoDx kit with Dako in advance before launching the drug. They kept collaborating with other diagnostic and pharmaceutical companies and successfully launched several CoDx kits and expanded its indication. As for the Type 2 group, Tarceva was initially co-developed with Roche group and fundraised from several private offerings for clinical development. After the launch, the originator, OSI pharma, aggressively collaborated with diagnostic and biotech companies to try the combination therapy, and to develop companion diagnosis kits. In the case

TABLE 4

Longitudinal transaction analysis as a case study[a]

Factor	Year of deal																		
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Type 1: co-development of CoDx before launched (Erbitux, Zelboraf, Tafinlar, Midostaurin, Tagrisso, Xalkori, Lynparza, Revlimid); drug name, Erbitux; originator: Imclone																			
Launched																			
R&D license																			
Market license																			
Co-promotion/trial collaboration																			
CoDx deal																			
Combo/additional indication																			
Deals with clinical trial																			
Financing																			
M&A																			
Type 2: co-development/funding of drug development before launched (Tarceva, Idhifa, Mekinist, Venetoclax. Vectibix, Rubraca, Kadcyla) ; drug name, Tarcev;, originator, OSI pharma																			
Launched																			
R&D license																			
Market license																			
Co-promotion/trial collaboration																			
CoDx deal																			
Combo/additional indication																			
including with clinical trial																			
Financing																			
M&A																			
Type 3: co-development of CoDx after launched (Gleevec, Herceptin, Rituxan and Iressa); drug name, Gleevec; originator, Novartis																			
Launched																			
R&D license																			
Market license																			
Co-promotion/trial collaboration																			
CoDx deal																			
Combo/additional indication																			
Deals with clinical trial																			
Financing																			
M&A																			
Type 4: trial collaboration of combination therapy with other drugs after launched (Keytruda) : drug name, Keytruda; originator: Merck																			
Launched																			
R&D license																			
Market license																			
Co-promotion/trial collaboration																			
CoDx deal																			
Combo/ additional indication																			
Deals with clinical trial																			
Financing																			
M&A																			

[a]Time course of each type of transactions (R&D license, market license, co-promotion/trial collaboration, deals related to CoDx (CoDx deal), deals for combination therapy or additional indication (combo/additional indication), deals with clinical trial, financing, and M&A are tiled in blue in four types of case: Erbitux as a representative of Type 1 (co-development of CoDx before launch); Tarceva as a representative of Type 2 (co-development/funding of drug development before launch); Gleevec as a representative of type 3 (co-development of CoDx after launch); and Keytruda as a representative of Type 4 (trial collaboration of combination therapy with other drugs after launch). Yellow shading indicates drug-launch events. Number of deals are indicated as 1∼4 (light blue), 5∼9 (mid blue), and ∼10 (dark blue).

of Gleevec (Type 3), Novartis started collaborations with other biotech or pharmaceutical companies to seek combination therapy and CoDx development after they launched the drug. The Keytruda case (Type 4) is unique because they started co-promotion with other pharmaceutical companies just for combination therapy and expansion of its indication.

Discussion

For the successful development of personalized medicine, selective biomarkers have to be identified and applied for patients' stratification during the early stage of development, where there are many uncertainties in R&D. By contrast, initiating biomarker discovery during the late stage of drug development provokes the problem of biomarker lag, where the beneficial opportunities of personalized medicine are eventually lost. To circumvent this dilemma, co-development of therapeutics and companion diagnoses in vertical-integrated organization would be an effective method for strategic management [21,22]. However, exploring resources from outside the organization and

cooperating with each other while maintaining in-house expertise is another effective strategy for development of personalized medicine [14,23].

In this study, we analyzed genuine transaction data from personalized and nonpersonalized cancer medicine development and compared them with each other to address what type of collaboration mode would be suitable for personalized medicine development. As shown in Fig. 1, we found that a significantly higher number of alliance deals, including R&D licensing, co-promotion, intra biotech deals, and CoDx deals, have been carried out in personalized medicine development compared with nonpersonalized medicine. This indicates that external collaborations are more preferable in personalized medicine development than in nonpersonalized medicine, and the aforementioned deals are the characteristic transactions.

These results prompted us to explore whether these active transactions could lead to outcomes for these companies. For start-ups or small-sized companies, the outcome can be translated as the number of patents, cooperative partnerships, initial public offering (IPO), and M&A, whereas for medium-sized and mega pharmaceutical companies, it can viewed in terms of the number of pipelines, market licenses, number of launched drugs, and sales [24,25].

Considering the above definitions, the number of basic patents, market licenses, M&A, and financing deals, including IPO, can serve as indicators of successful outcome within the variables obtained in this study. When we carried out a correlational analysis among these variables, and compared personalized and nonpersonalized medicine, we could not find any clear differences among them regarding the basic patents and M&A. By contrast, as shown in Table 1, market licenses and financing were more positively correlated with other transactions in personalized medicine, but not in nonpersonalized medicine. It is interesting to note that market licenses are considered as one of the successful outcomes of R&D, and those licenses include launching the product itself or allocating them to other countries during the later-stage of development. Financing deals are also a good indicator of exits of small and medium enterprises. Furthermore, our multiple linear regression analysis in Table 3 showed that market licenses can be explained by alliance deals with $R^2 > 0.7$ in personalized medicine development, but not in nonpersonalized medicine.

The case study of longitudinal transaction analysis gave us more direct implications for this industry. We found that most drugs or CoDx kits were co-developed with other companies or institutes before their launch, especially in biotech companies, indicating that collaborating with others is effective for better outcomes (Table 4). Imclone (type 1) and OSI pharma (type 2), both mid-sized biotech companies, received financings from several venture capitalists and were eventually acquired by big pharma (Eli Lilly and Astellas Pharma, respectively), which were other typical outcomes. The drugs in Type 3 (Herceptin, Gleevec, and Iressa) were launched around 2000, when the ideas of companion diagnosis and personalized medicine were not well established. Even during that era, co-development of CoDx with external collaborators was observed (Table 4).

Concluding remarks

Our study supports the view that, in personalized medicine development, more active transactions with external organizations lead to more exits compared with pursuing all the processes in closed organizations. Therefore, a multidisciplinary approach by collaborating with other specialties is preferable for the co-development of therapeutics and their CoDx. For future study, it would be interesting to analyze the sales of drugs or number of pipelines as additional predictors of successful outcomes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drudis.2018.09.022.

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