博士論文（要約）

個別化医療開発における企業の能力

Corporate Capability for Personalized Medicine Development

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論文の内容の要旨

個別化医療開発における企業の能力 (Corporate Capability for Personalized Medicine Development)

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1.　はじめに

個別化医療とは、治療を行う前にバイオマーカーを調べることで、患者一人一人にあった治療方法・医薬品を提供することを可能にする医療モデルである。薬物治療において個別化医療を実現させるには、医薬品の効果予測や安全性予測等を目的としたバイオマーカーを特定できる検査薬、いわゆるコンパニオン診断薬（Companion Diagnostics; CoDx）が必要不可欠である。このことから、個別化医療の開発において、医薬品とCoDxの同時開発は一つの重要な成功要因であり、その開発における企業の能力を正確に把握することは、製薬企業および診断薬企業にとって、戦略やポートフォリオマネジメントを考える上で、大変重要である。個別化医療の開発における成功要因として、バイオマーカーの早期発見や製薬企業と診断薬企業の早期連携等が、先行研究において挙げられた[1]。しかしながら、これらを実施する上で必要な企業の能力については、先行研究において、明確に定義された上で評価が行われたことがない。したがって、本研究では以下に示す二つの研究の実施を通じて、製薬企業と診断薬企業における個別化医療の開発力の実態を評価できる分析枠組みを新たに構築することを目的とした。

2.　Study 1：製薬会社における個別化医療医薬品の開発力の評価[3]

＜背景と目的＞　製薬企業における医薬品開発に焦点を当てた場合、医薬品と CoDx の同時開発におけるプロセスの細分化については、先行研究において議論されてきた[2] [4]。また、医薬品と CoDx の同時開発を実現させる方法として、製薬企業にとっては、社外診断薬企業と提携する方法と社内診断薬部門と提携する方法が存在するが、同時開発プロセスの複雑さを指摘し、診断部門の内製化が有利であるとの提言が先行研究においてなされてきた[5]。しかしながら、製薬企業の個別化医療医薬品の開発力（personalized medicine development capability; PMD capability）の構成要素を定義した上で、それらと PMD capability との関連性について定量的に議論された研究は、これまで報告されたことがない。そこで、Study 1 では、一つの研究モデルを構築し、製薬企業における PMD capability と関連する構成要素間の因果関係について定量的に評価することとした。

＜方法＞　最初に、PMD capability に影響及ぼすと考えられる三つの構成要素として、new product development capability（NPD capability）、capability of CoDx co-development with external parties（external CoDxD capability）、capability of CoDx co-development with internal organization（internal CoDxD capability）があると定義した。次に、PMD capability と各構成要素間の因果関係について 6 つの仮説を立て、それらを Structural Equation Modeling（SEM）分析を用いて検証すべくそれぞれの因子に観測変数を設定し、一つの研究モデルを構築した（Figure 1）。

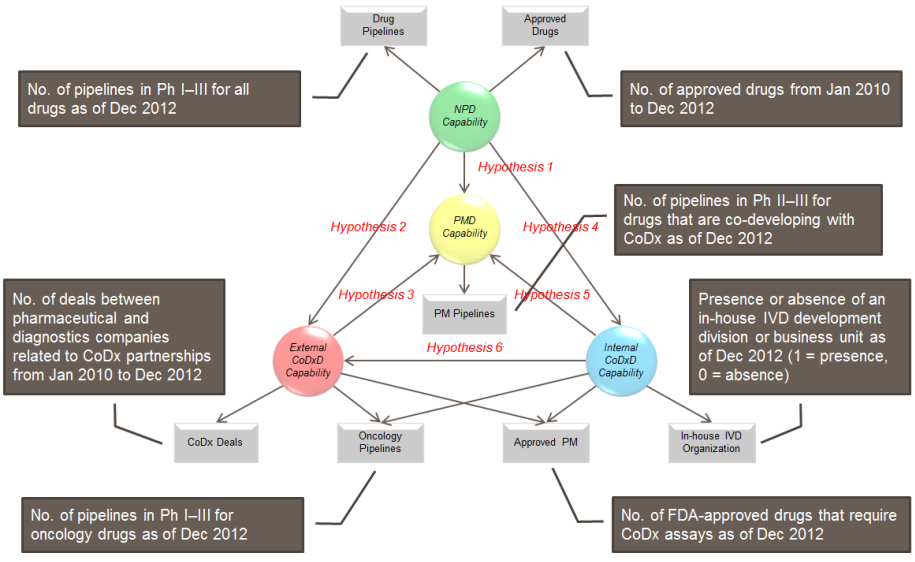
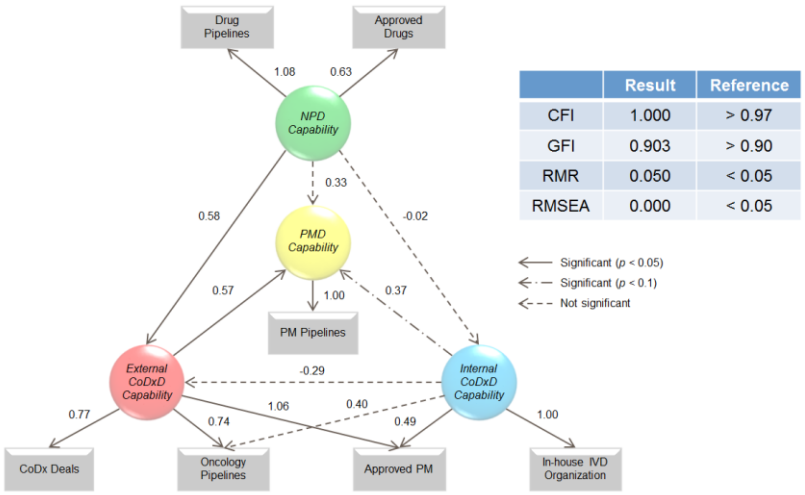


Figure 1. PMD Capability Model

＜結果と考察＞　研究の対象サンプルは、個別化医療医薬品の開発に投資実績のある 15 社の製薬会社に限定した。得られたデータと構築された研究モデルに基づき SEM 分析を行ったところ、Figure 2 に示す結果が得られた。モデルの適合度を示す四つの指標（CFI、GFI、RMR、RMSEA）はいずれも基準値を超え、構築されたモデルは高い適合度を有していることが検証された。各因子間の関係性については、係数が有意であり、且つ、0.5 以上であった場合に因果関係があると定義した。その結果、各因子間の関係は Figure 3 に示す形で簡易化することができ、PMD capability に影響与えるクリティカルパスは、NPD capability を起点に external CoDxD capability を介していることを見出した。



	Result	Reference
CFI	1.000	> 0.97
GFI	0.903	> 0.90
RMR	0.050	< 0.05
RMSEA	0.000	< 0.05

Figure 2. Outcome from SEM analysis

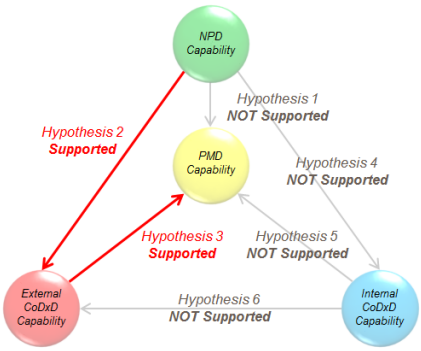


Figure 3. Critical path to PMD capability

この結果については、二点の考察を行った。第一は NPD capability が PMD capability に与える影響についてである。本研究では NPD capability から PMD capability への因果関係として、直接的効果（仮説 1）と、external CoDxD capability あるいは internal CoDxD capability を介した間接的な効果があると仮定（仮説 2～5）したが、分析の結果、external CoDxD capability を介した間接的な効果のみ有していることが見出された。このことは、個別化医療医薬品の開発において、基礎となる NPD capability が高いことは必要条件ではあったが、十分条件ではなかったことが確認された。すなわち、NPD capability が高い企業全てが個別化医療の開発においてイノベーションが進んでいることではなく、CoDxD capability が高い一部の企業のみ特に PMD capability が高いことが、本研究を通じて定量的な評価によって初めて示唆された。

第二は、external と internal CoDxD capability の PMD capability に与える影響についてである。SEM 分析の結果、PMD capability に与える効果として、社内診断薬部門との連携に頼る internal CoDxD capability よりも社外診断薬企業との連携に頼る external CoDxD capability の方が強い因果関係を有していることが示された。この結果を説明する一つの理由として、CoDx 開発には、バイオマーカーを特定するのに合った柔軟、且つ、コスト効果に優れた多種多様なプラットフォームが必要とされていると考えられる。すなわち、社内に診断薬部門を有していても、これら全ての CoDx 開発に伴う技術をカバーすることは困難であり、内部化連携の可否にかかわらず、当該医薬品にとっての最適な CoDx 同時開発ができるよう、優れた external CoDxD capability を有している必要があると、本研究の結果から示唆された。

3.　Study 2：診断薬会社における CoDx の開発力の評価[6]

＜背景と目的＞　Study 1 では製薬企業における PMD capability と各構成要素間の因果関係については定量的に評価できたものの、医薬品と CoDx の同時開発に伴う、診断薬企業における CoDx の開発力の分析は依然不明確のままである。CoDx 開発に関しては、開発プロセスの分解について議論されたものは多く存在するが[4] [7]、それに必要な診断薬企業の能力について定義・評価された研究は、これまで報告されたことがない。そこで、Study 2 では、CoDx 開発における診断薬企業の knowledge management capability を細分化し、その上で、現在の実態を評価することを目的にした。

＜方法＞　企業における knowledge management を分析する際、多くの研究において、ステージを exploration と exploitation に、knowledge ソースを internal と external に細分化して議論してきた[8] [9]。これらは一般論としては有用であるが、CoDx 開発においては、Rajan ら(2012)が指摘するように、knowledge が biomarker knowledge、platform knowledge、diagnostic kit knowledge の三つの要素から構成されていること[10]、そして、それらを統合する必要があることから、一般論では説明することが不十分であると考えられる。そこで、本研究では既存のフレームワークに加え、三つの構成要素を表現するために knowledge exploration ステージを biomarker、platform、diagnostic kit に細分化し、更に、それらを統合し製薬企業と共に CoDx knowledge として発展させる中間段階を knowledge expansion ステージとして追加し、CoDx 開発に必要な knowledge management capability として、Table 1 に示すような形で一つの新しいフレームワークとして提示した。次に、二つの事例研究の実施を通じて、本フレームワークの分解能の妥当性を確認し、そして、CoDx 開発に伴って診断薬企業が利用している能力とその知識ソースの実態を分析することとした。

Table 1. CoDx knowledge framework

	Knowledge Exploration			Knowledge Expansion	Knowledge Exploitation
Internal	***BM Inventive Capacity*** Firm's ability to internally explore biomarker knowledge.	***PF Inventive Capacity*** Firm's ability to internally explore platform knowledge.	***DK Inventive Capacity*** Firm's ability to internally explore diagnostic kit knowledge.	***Integration Capacity*** Firm's ability to internally integrate explored knowledge and to demonstrate analytical validation, clinical validation, and clinical utility of integrated knowledge.	***Commercialization Capacity*** Firm's ability to internally apply the validated CoDx knowledge to commercialize diagnostic products and associated instrumentation as CoDx.
External	***BM Absorptive Capacity*** Firm's ability to explore and acquire external biomarker knowledge from other companies.	***PF Absorptive Capacity*** Firm's ability to explore and acquire external platform knowledge from other companies.	***DK Absorptive Capacity*** Firm's ability to explore and acquire external diagnostic kit knowledge from other companies.	***Outsourcing Capacity*** Firm's ability to outsource expanding functions to other companies.	***Licensing Capacity*** Firm's ability to exploit knowledge by transferring their validated CoDx knowledge to other companies.

BM: biomarker, PF: platform, DK: diagnostic kit

＜結果と考察＞　一つ目の事例研究として、BRAF V600 変異の有無を特定することを目的に、それぞれ Roche Diagnostics 社と bioMérieux 社によって開発・市販された、Cobas® 4800 BRAF V600 mutation test と THxID™ BRAF kit をサンプルとし、本研究のフレームワークの分解能の妥当性について検証した。その結果、Table 2 に示すように、いずれの場合においても、本フレームワークを用いることより、CoDx 開発に用いられたそれぞれの診断薬企業の能力を明確化し、且つ、二つの事例間の差分についても比較することも可能にした。

Table 2. Application of the CoDx knowledge framework to the cases of Cobas® 4800 BRAF V600 mutation test and THxID™ BRAF kit

- Cobas® 4800 BRAF V600 mutation test

	Knowledge Exploration			Knowledge Expansion	Knowledge Exploitation
Internal	***BM Inventive Capacity***	***PF Inventive Capacity*** Roche Dx internally explored that the cobas 4800 system is appropriate to detect BRAF mutation	***DK Inventive Capacity*** Roche Dx built a diagnostic kit for exploratory use to detect the BRAF mutation	***Integration Capacity*** Roche Dx transitioned the diagnostic kit to the Cobas 4800 platform to validate the test as CoDx	***Commercialization Capacity*** Roche Dx submitted a PMA for Cobas® 4800 BRAF V600 mutation test to the US FDA
External	***BM Absorptive Capacity*** Roche Dx acquired from Plexxikon that BRAF can be a potential biomarker to predict vemurafenib efficacy	***PF Absorptive Capacity***	***DK Absorptive Capacity***	***Outsourcing Capacity***	***Licensing Capacity***

Knowledge source: *Internal; Roche Dx* | *Plexxikon*

- THxID™ BRAF kit

	Knowledge Exploration			Knowledge Expansion	Knowledge Exploitation
Internal	***BM Inventive Capacity***	***PF Inventive Capacity***	***DK Inventive Capacity*** bMx built a diagnostic kit for detecting the BRAF mutation	***Integration Capacity*** bMx transitioned the diagnostic kit to the ABI 7500 Fast Dx system to validate the test as CoDx	***Commercialization Capacity*** bMx submitted a PMA for THxID™ BRAF kit to the US FDA
External	***BM Absorptive Capacity*** bMx acquired from GSK that BRAF can be a potential biomarker to predict dabrafenib efficacy	***PF Absorptive Capacity*** bMx externally explored that the ABI 7500 Fast Dx system is appropriate to detect BRAF mutation	***DK Absorptive Capacity***	***Outsourcing Capacity***	***Licensing Capacity***

Knowledge source: *Internal; bMx* | *GSK* | *Life Technology*

Roche Dx: Roche Diagnostics, bMx: bioMérieux,
BM: biomarker, PF: platform, DK: diagnostic kit, PMA: Premarket Approval Application

二つ目の事例研究は、過去 10 年間に FDA により承認された全 CoDx サンプルとして、CoDx 開発に用いた企業の能力の傾向について分析した（Table 3）。その結果、biomarker knowledge exploration においては、全ての事例において、BM absorptive capacity を利用していることが示された。すなわち、Biomarker knowledge については、殆どが製薬会社によって生みだされ、診断薬会社はそれを自社に吸収し CoDx 開発に利用していることが示唆された。一方で、platform と diagnostic kit の knowledge exploration においては internal な能力を利用して knowledge を探索していることが主流であるものの、そのバラツキが大きいことが示された。これに対する考察としては、Study 1 と同様、CoDx 開発には最先端な技術が必要とされ、一社のみでは必要な knowledge 全てをカバーできない実態を反映しているものと考えられる。最後に、knowledge expansion と exploitation においては、全ての事例において、internal な能力を利用して、knowledge を発展・活用していることが示された。これは、knowledge expansion 段階と knowledge exploitation 段階は、CoDx 開発における診断薬企業の中核的能力であり、他社へ外注・ライセンシングすることなく、自社内で実施していることを示唆していると考えられる。

Table 3. Cumulative total number of capacities used by diagnostic firms to develop CoDx

	Knowledge Exploration			Knowledge Expansion	Knowledge Exploitation
Internal	*BM Inventive Capacity* **0**	*PF Inventive Capacity* **7**	*DK Inventive Capacity* **9**	*Integration Capacity* **10**	*Commercialization Capacity* **10**
External	*BM Absorptive Capacity* **10**	*PF Absorptive Capacity* **3**	*DK Absorptive Capacity* **1**	*Outsourcing Capacity* **0**	*Licensing Capacity* **0**

4. 結論

本研究では、個別化医療開発における企業の能力について明確化すべく、二つの研究を実施した。Study 1 では製薬企業に着眼点を置き、NPD capability を起点に external CoDxD capability を介するルートが PMD capability に影響与えるクリティカルパスであることを定量的に検証し、現状においては、診断部門の内製化よりも社外診断薬企業との連携の方が、個別化医療医薬品の開発において有効であることが示唆された。次に、Study 2 においては診断薬企業に着眼点を置き、CoDx 開発に必要な診断薬企業の能力を評価するツールとして分析フレームワークを新たに構築し、その能力を知識の源泉という観点から内外に区分し、三段階のステージに分解して観測した。その結果、診断薬企業の中核的な能力として内部化される部分と技術の進展が早く外部に知識ソースを依存する傾向が高い部分に区分できることを見出した。また、この二つの研究結果を併せて考察することにより、製薬企業の external CoDxD capability と診断薬企業の BM absorptive capacity は、医薬品と CoDx の同時開発に伴う製薬企業と診断薬企業間の連携に重要な役割を果たしていることが示唆された。更には、CoDx 開発には最先端な技術を必要とすることから、現状、一社のみでは全ての必要技術を賄うことが困難であることもこの研究結果から示唆された。

以上のことから、本研究は製薬企業と診断薬企業の両方面から個別化医療開発の企業の能力を評価できる枠組みを初めて構築し、その妥当性・有用性を検証した。このことにより、両産業における企業の個別化医療の開発力を評価することを可能にし、且つ、その傾向をモニタリングすることができることから、企業戦略の立案やポートフォリオマネジメント上も有用であると考えられる。

5. 参考文献

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Abstract

Personalized medicine is a medical model that aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best based on the patient's unique genetic and environmental profile. In the field of pharmacotherapy, the techniques of utilizing a stratified approach and identifying groups of patients based on certain biologic characteristics or biomarkers using companion diagnostics (CoDx) can potentially be more efficient and effective than traditional approaches, while reducing undesirable drug interactions and side effects.

When evaluating corporate strategies in the pharmaceutical and diagnostic industries, it is essential to precisely understand corporate capability for personalized medicine. Therefore, in this thesis, two studies are conducted to describe corporate capability of personalized medicine development from pharmaceutical and diagnostic firms' points of view, respectively. The outline for this thesis is provided below.

In Chapter 1, the background of personalized medicine and the positioning of this thesis are described.

Subsequently, in Chapter 2, a literature review delineates previous works on corporate capability as related to product development.

In Chapter 3, a model is developed to illustrate the corporate capability of personalized medicine development in the pharmaceutical industry (PMD capability).

Firstly, three key PMD capability influencing factors are defined, including corporate capability for new product development (NPD capability), corporate capability of CoDx co-development with external parties (External CoDxD capability), and corporate capability of CoDx co-development with an internal organization (Internal CoDxD capability). Based on these concepts, a research model is developed. Subsequently, structural equation modeling (SEM) analysis reveals that a good fit of the model is successfully achieved. In this model, results indicate that the critical path contributing to PMD capability runs from NPD capability via External CoDxD capability rather than via Internal CoDxD capability.

Next, Chapter 4 develops a framework to illustrate diagnostic firms' corporate knowledge sourcing and management capability of CoDx development. The purpose of this model is to provide an understanding of corporate capability of personalized medicine development in the diagnostic industry. First, three key knowledge elements necessary for CoDx development are defined. Second, a unique framework is constructed to detail firms' ability to manage this knowledge. Finally, the proposed framework is applied to several CoDx development cases to test its practical utility. In the end, the study results indicate that this framework can improve understanding and track trends in corporate knowledge sourcing and management capability for CoDx development in the diagnostic industry.

Finally, Chapter 5 provides a summary and an integrated conclusion of this thesis.

Contents

List of Abbreviations

ALK	Anaplastic lymphoma kinase
BM	Biomarker
BRAF	B rapidly accelerated fibrosarcoma
CFI	Comparative fit index
CoDx	Companion diagnostics
CRO	Contract research organization
DK	Diagnostic kit
DNA	Deoxyribonucleic acid
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
External CoDxD capability	Pharmaceutical firms' corporate capability of CoDx co-development with external parties
FDA	Federal Drug Administration
FISH	Fluorescence in situ hybridization;
GFI	Goodness-of-fit index
GSK	GlaxoSmithKline
HER2	Human epidermal growth factor receptor 2
IND Application	Investigational New Drug Application
IVD	In vitro diagnostics
Internal CoDxD capability	Pharmaceutical firms' corporate capability of CoDx co-development with internal organization
KRAS	Kirsten rat sarcoma
NDA	New Drug Application
NGS	Next-generation sequencing
NPD capability	Pharmaceutical firms' corporate capability of new product development

NSCLC	Non-small-cell lung cancer
PCR	Polymerase chain reaction
PF	Platform
PMA	Premarket Approval Application
PMD capability	Pharmaceutical firms' corporate capability of personalized medicine development
qPCR	Quantitative PCR
R&D	Research and development
RMR	Root mean square residual
RMSEA	Root mean square error of approximation
SEM	Structural equation modeling

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Chapter 1: Background

1.1. Background of personalized medicine

In recent years, healthcare delivery has changed substantially. Traditional approaches to therapeutics discovery and development are pathology and symptom-based, with the objective of finding a blockbuster drug (drugs with sales exceeding $1 billion USD) that is effective for all patients suffering from a disease or condition (Zhang and Zhang, 2013). However, this paradigm is no longer a viable option for pharmaceutical companies because only a fraction of patients responds to traditional therapies and healthcare spending is under intense pressure (Desiere et al., 2013). For example, 38% of depression patients, 50% of arthritis patients, 40% of asthma patients, and 43% of diabetic patients will not respond to initial treatment (Personalized Medicine Coalition, 2014; Spear et al., 2001) (Figure 1). In addition, the demand for evidence-based therapeutics by regulatory authorities are becoming increasingly pressing for the industry, resulting in the need to adopt a novel and more appropriate paradigm for drug discovery and development (Amir-Aslani and Mangematin, 2010).

This paradigm change is closely associated with an increased interest in the discovery of biomarkers. According to the National Institutes of Health Biomarkers Definitions Working Group, a biomarker is defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ (Biomarkers Definitions Working Group, 2001). Biomarkers can play a crucial role in

understanding patient differences and help the business model of drug discovery to move away from mass-marketed products towards targeted treatments.

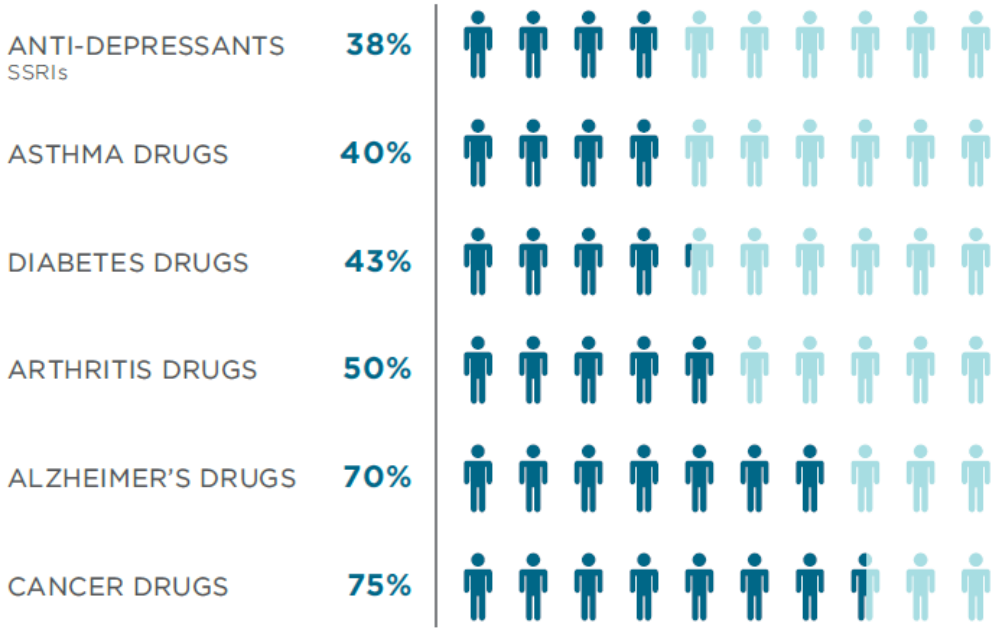


Figure 1. Percentage of the patient population for which a particular drug in a class is ineffective, on average. (source: Personalized Medicine Coalition, 2014)

The first step in this paradigm change is the identification of biomarkers that link disease biology to the therapeutic product in question. This requires an in-depth understanding of the pathways involved in the disease process, detailed characterization of drug targets and identification of biomarkers with a demonstrated relationship with and significance in the disease process, the mode of action of the drug, and the importance of the role played in the relevant patient population (Desiere,

2013). Certainly, this is a trend at the clinical development stage. As shown in Figure 2, the number and rate of clinical trials including biomarker assessments have apparently increased during last decade, implying that many research efforts are currently utilized in this era. Furthermore, to date, the labeling of more than 100 the US Federal Drug Administration (FDA) approved drugs contain information on genomic biomarkers (e.g. gene variants, functional deficiencies, expression changes, chromosomal abnormalities) (FDA, 2014) (Figure 3). Some, but not all, of the labeling include specific actions to be taken based on genetic information.

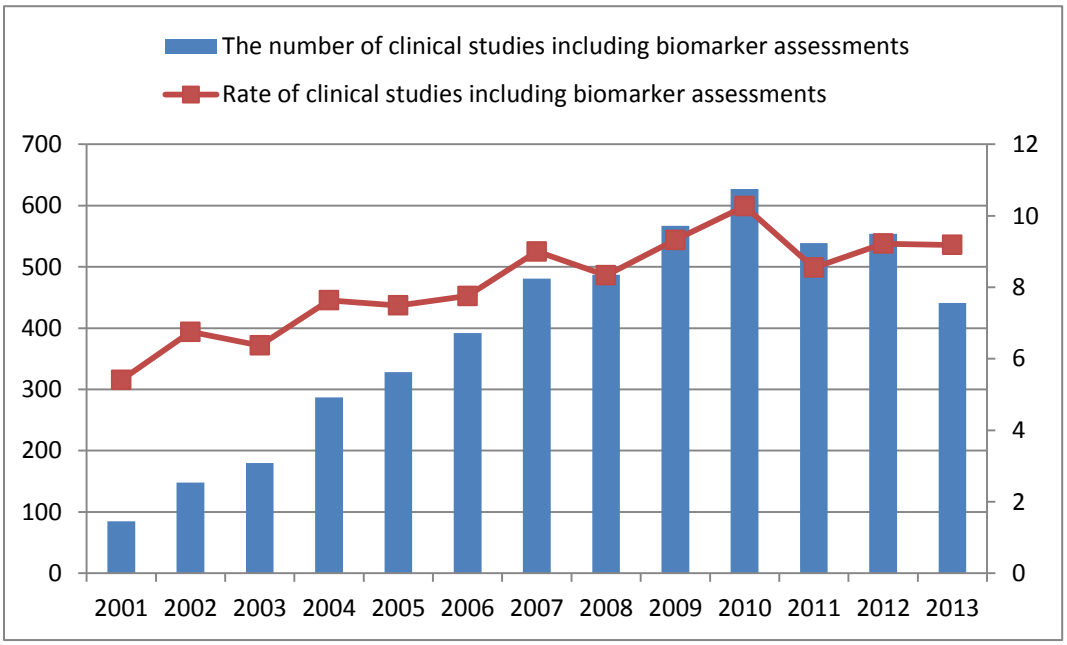


Figure 2. The number and rate of clinical studies including biomarker assessments (source: analyzed based on data in ClinicalTrials.gov. See Appendix 1 for details.)

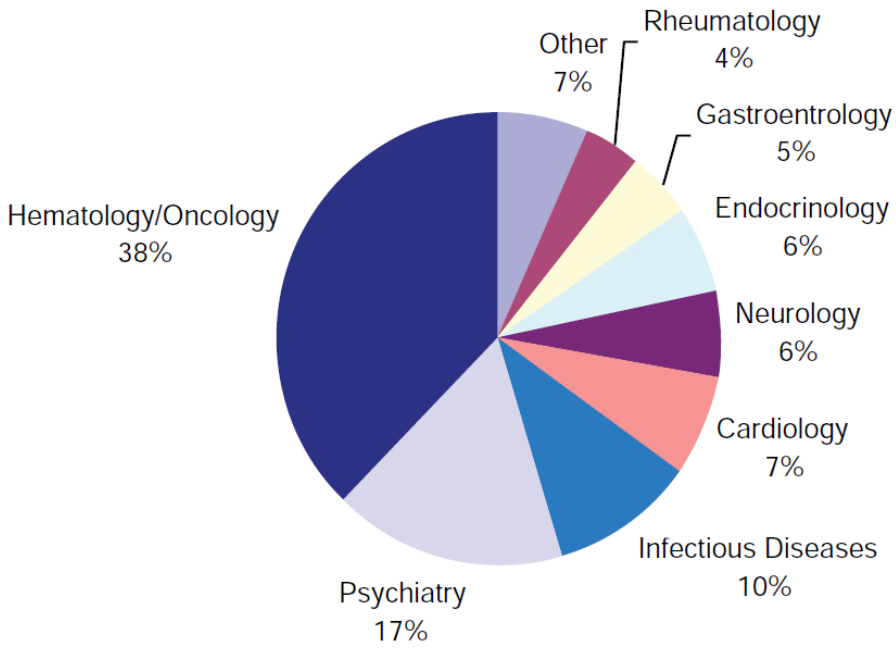


Figure 3. Pharmacogenomic biomarker information in drug labeling (source: FDA, 2014)

1.2. Concept of personalized medicine

Personalized medicine is a medical model that is aligned with the existing paradigm change. In the late 1990s, the term 'personalized medicine' was first introduced by Langreth and Waldholz (Jørgensen, 2009; Langreth and Waldholz, 1999). Subsequently, scientific advantages have made it possible to diagnose and treat a rapidly growing number of diseases much earlier and with greater precision than ever before. These developments have vastly expanded physicians' power to customize

therapy, maximizing drug treatment effectiveness and minimizing side effects (Aspinal and Hamermesh, 2007).

Currently, personalized medicine is widely defined as a tailored approach to patient treatment, based on the molecular analysis of genes, proteins, and metabolites (Davis et al., 2009). It aims to achieve optimal medical outcomes by helping physicians and patients choose the disease management approaches likely to work best based on the detection of the patient's unique genetic and environmental profile (Amir-Aslani and Mangematin, 2010; Marshall, 1998; McClellan et al., 2013; Ong et al., 2012; Tutton, 2012).

In the field of pharmacotherapy, the techniques of utilizing a stratified approach and identifying groups of patients based on certain biologic characteristics or biomarkers, as detected by companion diagnostic (CoDx) tests, have the potential to be more efficient and effective than the traditional approaches, while reducing undesirable drug interactions and side effects (Figure 4). Recent advances in understanding of the disease pathophysiology, drug activity, and biomarkers involved in these approaches have resulted in a focus on tailoring treatment for specific patient subgroups based on their genetic makeup or other differentiating features (Desiere et al., 2013).

In addition, this trend has led to a recent rise in academic and practitioner interest in personalized medicine development. As shown in Figure 5, the increase in the number of publications about personalized medicine has shown an exponential growth since the Langreth and Waldholz's first article was published in 1999 (Jørgensen,

2011). The growth rate has been significant, especially within the past few years. Additional evidence of a growing interest in personalized medicine is detailed in Table 1 (FDA, 2011; Moore et al., 2012; Personalized Medicine Coalition, 2006; 2011; PricewaterhouseCoopers, 2009; Tufts Center for the Study of Drug Development, 2010; 2011).

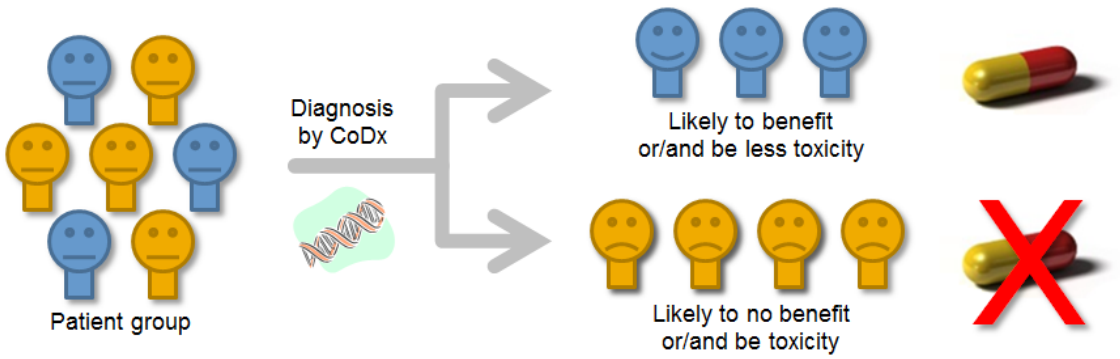


Figure 4. Concept of personalized medicine (source: Haruya, original)

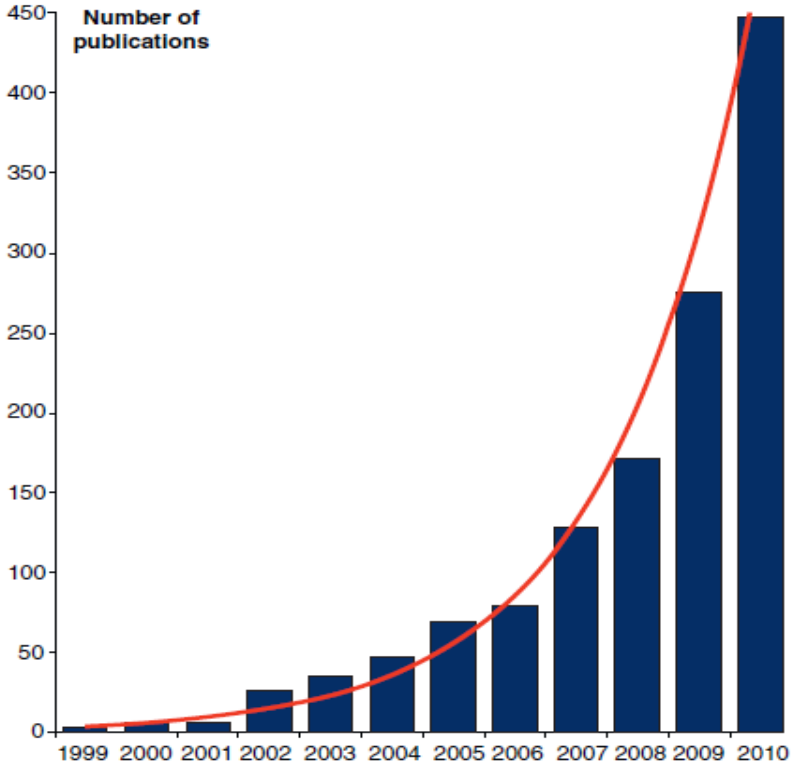


Figure 5. Number of articles per year from 1999 to 2010 that included the term 'personalized medicine' (source: Jørgensen, 2011)

Table 1. Statistics demonstrating growing scientific, medical and economic interests in personalized medicine (source: Moore, 2012)

Example	Statistic
Number of prominent examples of personalized medicine drugs, treatments and diagnostics products available in 2006	13
Number of prominent examples of personalized medicine drugs, treatments and diagnostics products available in 2011	72
Percentage of marketed drugs with a CoDx in 2011	1%
Percentage of marketed drugs that inform or recommend genetic testing for optimal treatment	10%
Number of pharmacogenomic biomarkers that are included on US-FDA approved drug labels	33
Portion of all treatments in late clinical development that rely on biomarker data	30%
Portion of all treatments in early clinical development that rely on biomarker data	50%
Portion of all treatments in preclinical development that rely on biomarker data	60%
Amount of all biopharmaceutical companies surveyed that require all compounds in development to have a biomarker in 2011	30%
Percentage increase in personalized medicine investment by industry over the last 5 years	75%
Estimated personalized market size in 2009	$225–232 billion USD
Estimated personalized market size in 2015	$344–452 billion USD
Estimated molecular diagnostics market size in 2009	$3 billion USD
Estimated molecular diagnostics market size in 2015	$7 billion USD

1.3. Opportunities in personalized medicine development

1.3.1. Market trends in personalized medicine

While still in the very early stages, personalized medicine is steadily emerging as the new healthcare paradigm (Figure 6). According to PricewaterhouseCoopers' estimates, the total US market for personalized medicine was estimated at $232 billion USD in 2009 and is projected to grow 11% annually, nearly doubling in size by 2015 to a total of $452 billion USD (PricewaterhouseCoopers, 2009). The core segment of this market, which is comprised primarily of diagnostic tests and targeted therapies, is estimated at $24 billion USD and is expected to grow by 10% annually to $42 billion USD by 2015.

While the market for personalized medicine diagnostics and therapeutics shows great potential, the biggest opportunities exist beyond these core products and services, particularly in less traditional, more consumer-oriented areas. The nutrition and wellness market, including retail health, complementary and alternative medicine, nutraceuticals and organic care, and health clubs and spas, is estimated at $196 billion USD and projected to grow by 7% annually to $292 billion USD by 2015. The personalized medical care segment of the market, including telemedicine, electronic medical records, and disease management services, is estimated to be between $4 billion USD and $12 billion USD and could grow tenfold to over $100 billion USD by 2015. This segment largely consists of a range of healthcare players, as well as information technology companies that are starting to enter the space.

Such robust market size and growth potential will continue to attract many new players and require the development of new business models. Specifically, a wide variety of organizations that successfully market directly to consumers are entering this space, including consumer products, food and beverage, leisure and retail companies, as well as more traditional health companies.

There are other products and services related to the field of personalized medicine, such as genetically modified food and stem cell products. The growth of these newly emerging submarkets is difficult to predict.

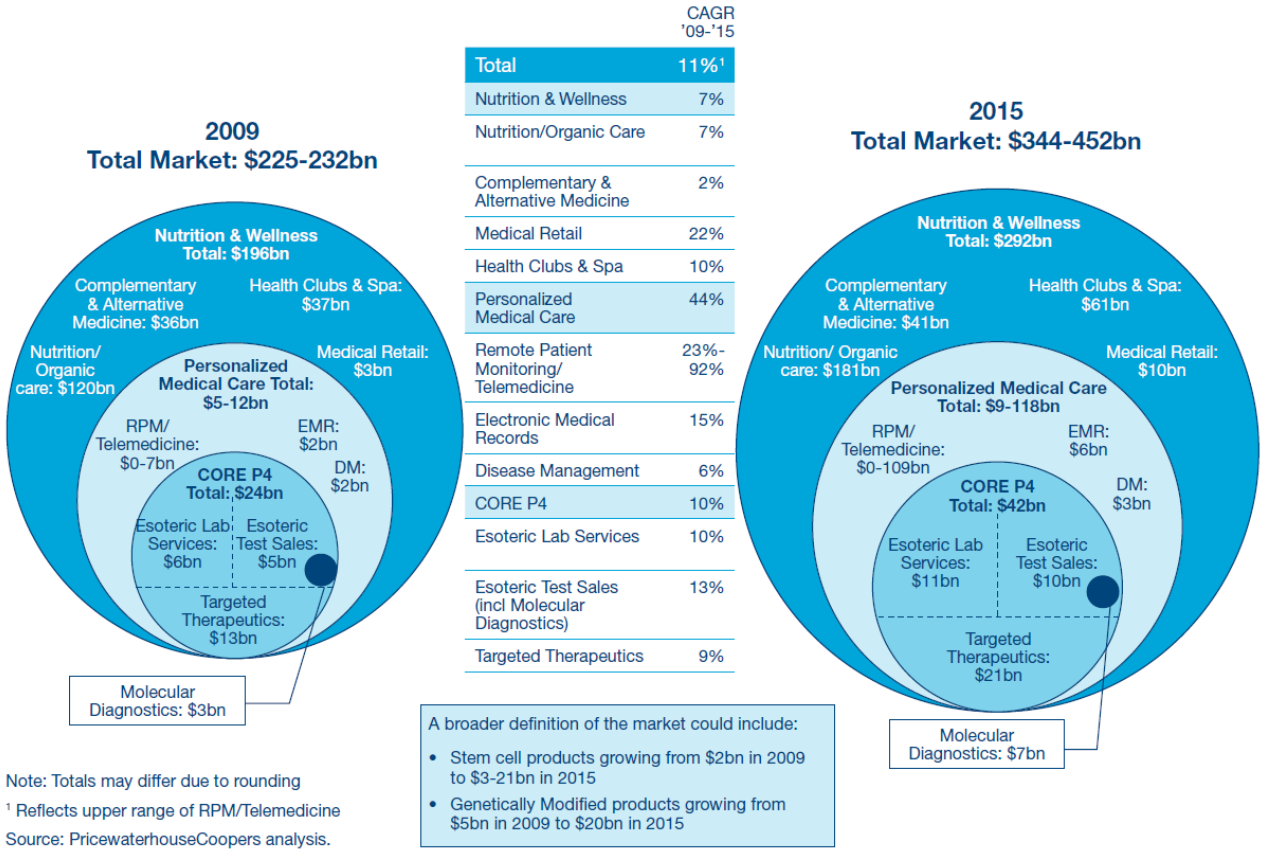


Figure 6. Personalized medicine market size in 2009 and 2015 (source: PricewaterhouseCoopers, 2009)

1.3.2. Benefits of personalized medicine for each player

The personalized medicine approach is clearly focused on patient benefits. However, there are other key stakeholders in the healthcare environment that may also benefit from the development and availability of personalized medicine, including physicians, regulatory agencies, pharmaceutical companies, diagnostic companies, society, and other healthcare providers (Aspinall et al., 2007; Blair, 2010; Desiere et al., 2013; Love et al., 212; Parkinson and Ziegler, 2009). According to PricewaterhouseCoopers, key challenges, key opportunities, and key barriers for each player can be summarized as shown in Table 2 (PricewaterhouseCoopers, 2009).

Since it can increase economic benefits, personalized medicine development would be especially important to pharmaceutical businesses (Figure 7) (Chugai Pharmaceutical, 2011). In particular, the largest economic benefit for pharmaceutical firms' incorporation of personalized medicine may be decreased study periods and patient numbers in clinical studies. For instance, in the pivotal phase III study of Trastuzumab, patients with human epidermal growth factor receptor 2 (HER2)-positive tumours were eligible, and 469 patients were enrolled. However, if the study was not conducted with a preselection of patients with HER2 overexpression, a much larger trial (8050 patients may be needed if the sample size was calculated based on untargeted design) would have been needed in order to detect the same observed survival gain (Slamon et al., 2001; Winther and Jørgensen, 2010).

Table 2. Key challenges, key opportunities, and key barriers in personalized medicine for each player (source: PricewaterhouseCooper, 2009)

Player	Key Challenges	Key Opportunities	Key Barriers
Pharmaceutical, biotechnology, and medical device companies	✓ Moving from general to specific treatments, and from disease treatment to prevention	✓ Reducing time, cost, size, and failure rate of clinical trials ✓ Capitalizing on preferential use of and premium pricing for drugs of proven effectiveness ✓ Reducing the number of drugs recalled as the result of safety concerns	✓ Changing research funding models and drug approval regulations ✓ Addressing pricing and reimbursement ✓ Identifying appropriate incentives for innovation ✓ Addressing changing revenue streams (i.e., shift from blockbuster model to smaller, targeted markets) ✓ Navigating the cultural shift required to work with diagnostics companies to match drugs with CoDx ✓ Developing the ability to share R&D information both internally and with external collaborators ✓ Recognizing the need to share 'precompetitive data' to avoid redundant research

Player	Key Challenges	Key Opportunities	Key Barriers
Diagnostic companies	✓ Developing and validating new diagnostics to enable personalized medicine	✓ Capitalizing on a growing market driven in part by new, value-based reimbursement policies ✓ Creating new partnerships with pharmaceutical companies ✓ Capitalizing on new distribution models to create new businesses	✓ Addressing joint CoDx/drug approval processes/ regulations, including the daunting cost of traditional randomized controlled trials ✓ Addressing pricing and reimbursement practices ✓ Determining if, when, and how to partner with drug companies ✓ Identifying and mobilizing resources needed to educate physicians about diagnostic tests ✓ Developing improved decision support tools to assist physicians to take action based on test results

Player	Key Challenges	Key Opportunities	Key Barriers
Technology companies (including medical device manufacturers)	✓ Developing new business models to capitalize on the value of data ✓ Developing/embracing new technologies for measurement and visualization	✓ Facilitating new, data-driven healthcare models ✓ Facilitating new data mining models to make sense of vast quantities of data ✓ Developing new product offerings ✓ Creating new partnerships	✓ Developing common data standards ✓ Accelerating medicine/IT convergence ✓ Understanding and influencing emerging regulatory standards ✓ Protecting privacy and preventing genetic discrimination ✓ Securing regulatory approval of combination devices ✓ Overcoming a lack of domain knowledge of the healthcare space
Other non-healthcare companies (e.g., consumer products, food, beauty/ cosmetics)	✓ Adapting to a new focus on wellness and the rise of consumerism ✓ Developing effective strategies to broaden the definition of what is considered ‘health’ ✓ Addressing consumer demands for higher quality foods and products that contribute to healthfulness	✓ Developing new products ✓ Tapping new markets ✓ Engaging in more precise customer segmentation	✓ Educating the public about the multitude of available wellness options ✓ Influencing and understanding emerging regulations ✓ Developing better consumer metrics ✓ Overcoming a lack of domain knowledge of the healthcare space

Player	Key Challenges	Key Opportunities	Key Barriers
Health systems, AMCs, and other providers	✓ Providing cutting edge care while controlling healthcare delivery costs ✓ Receiving reimbursement for providing wellness and prevention services ✓ Operationalizing a consumer-oriented business model	✓ Developing new models of care ✓ Increasing revenues ✓ Improving quality/outcomes	✓ Adapting to the 'unbundling' of the hospital and non-traditional competitors ✓ Making operational changes ✓ Correcting misalignment of incentives ✓ Managing consumer/patient expectations for costly and potentially unnecessary diagnostic tests
Government and private payers	✓ Embracing innovation ✓ Controlling healthcare reimbursement costs while improving healthcare outcomes to increase value per dollar spent	✓ Influencing new reimbursement models ✓ Identifying risk more precisely while delivering improved quality	✓ Realigning provider incentives ✓ Collecting and disseminating outcome data

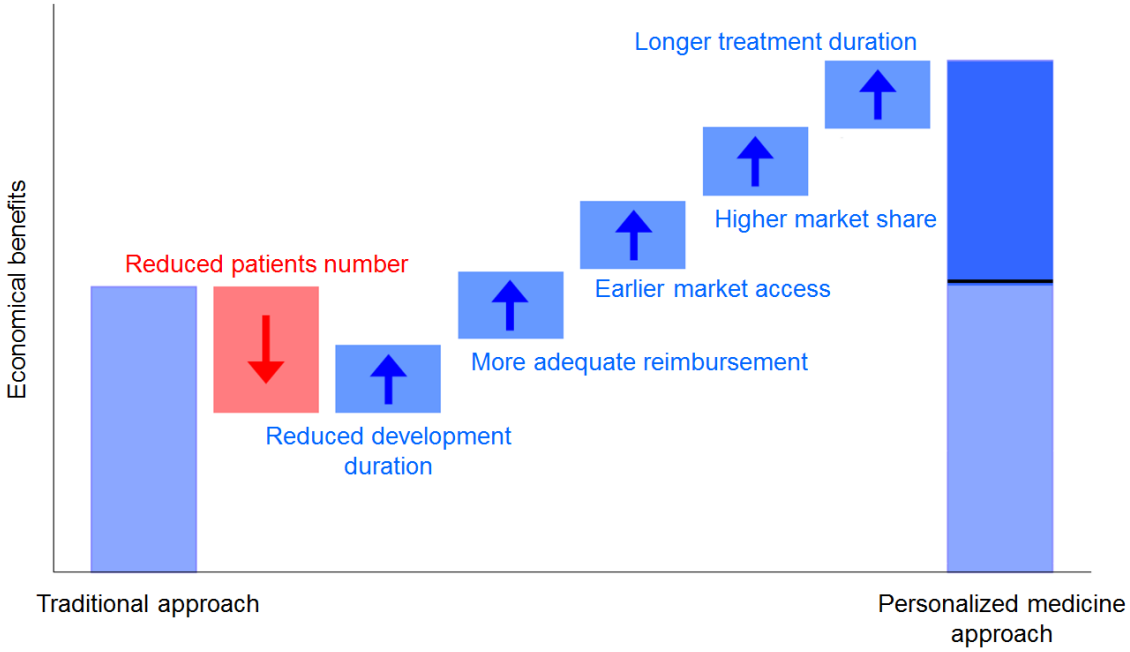


Figure 7. Economical benefits of personalized medicine approach (source: modified based on Chugai Pharmaceutical's presentation material, 2011)

1.4. Personalized medicine development

1.4.1. Regulatory requirements for CoDx

In approaches to personalized medicine, CoDx have emerged as crucial tools for identifying patient sub-segments for drug treatment (Love et al., 2012; Papadopoulos et al., 2006; Singer and Watkins, 2012).

There are several policy and guidance documents issued from the U.S. FDA (FDA, 2013; Personalized Medicine Coalition, 2014) (Table 3). According to the recent

guidelines issued by the U.S. FDA, it specify that CoDx is essential for the safe and effective use of a corresponding therapeutic product to (i) identify patients most likely to benefit from the therapeutic product, (ii) identify patients likely to be at an increased risk of serious adverse reactions due to treatment with the therapeutic product, (iii) monitor treatment response to the therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness, and (iv) identify patients in the population for whom the therapeutic product has been adequately studied and found to be safe and effective (FDA, 2014).

The U.S. FDA guidelines also specify that a therapeutic product and its corresponding CoDx should be developed contemporaneously, with the clinical performance and clinical significance of the CoDx established using data from the clinical development program of the corresponding therapeutic product (FDA, 2014).

Particularly, according to the labeling regulations for drugs and biological products (FDA, 2014), product labeling must include information about: (i) specific tests necessary for selection or monitoring of patients who need a drug; (ii) dosage modifications for special patient populations (e.g., groups defined by genetic characteristics); and (iii) the identity of any laboratory test(s) helpful in following a patient's response or in identifying possible adverse reactions. The labeling regulations identify sections where such discussion is appropriate (e.g., Indications and Usage, Dosage and Administration, Contraindications, Warnings and Precautions, Use in Specific Populations). In addition, labeling *in vitro* diagnostics (IVD) is also required to specify the intended use of the diagnostic device (FDA, 2014). Therefore, a CoDx

that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use.

Table 3. Policy and guidance documents from the U.S. FDA (source: modified based on Personalized Medicine Coalition, 2014)

Year	Policy and guidance documents
2005	Guidance on PG Data Submissions Concept Paper on Drug-Diagnostic Co-Development
2007	Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
2010	Guidance on Qualification Process for Drug Development Tools
2011	E16 Guidance on Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure, and Format of Qualification Submissions
	Guidance on in vitro Companion Diagnostic Devices
2012	Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies
	Guidance on Clinical Trial Designs Employing Enrichment Designs
2013	Guidance on Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
2014	Guidance for industry and Food and Drug Administration staff – In vitro companion diagnostic devices.

1.4.2. Drug-CoDx combinations

Based on this guidance issued by FDA (FDA, 2014), it is clear that drug-CoDx combinations would be one of the key components in personalized medicine development. The history of drug-diagnostic combinations was initiated with the discovery of the estrogen receptor (ER) in the late 1950s (Jensen et al., 1967). Soon after that discovery, a diagnostic assay for the detection of the receptor in tissue was developed in the beginning of the 1960s (Jensen et al., 1967; Winther and Jørgensen, 2010). Subsequently, in the 1970s, a drug was developed by ICI Pharma (today AstraZeneca) for the treatment of breast cancer that was targeted towards ER. This drug was the selective ER modulator tamoxifen (Nolvadex®; AstraZeneca). Based on a phase II study of tamoxifen performed in patients with advanced breast cancer, the investigators concluded that there was a high correlation between treatment response to the drug and a positive test result from the ER assay, suggesting that the ER assay should be used for the selection of patients for treatment with tamoxifen (Lerner, 1976; Winther and Jørgensen, 2010). In fact, the ER assay is still a very important stratification test in breast cancer, and is used for selecting patients for treatment with tamoxifen or aromatase inhibitors, such as anastrozole (Arimidex®; AstraZeneca) and letrozole (Femara®; Novartis).

Over the last decade, a number of drugs have been developed and marketed together with CoDx in order to identify the patients who are most likely to respond to therapy (Table 4) (FDA, 2014). One of the best-known examples is trastuzumab (Herceptin®; Roche/Genentech), the humanized monoclonal antibody directed towards

HER2 and its corresponding CoDx, the immunohistochemical (IHC) assay HercepTest® (Dako). During clinical development, trastuzumab clearly showed an increase in the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. Furthermore, the use of the IHC assay for selecting HER2-positive breast cancer served as a major inspiration for the parallel drug-CoDx co-development model (Slamon et al., 2001; Jørgensen; 2012).

Table 4. Examples of the U.S. FDA approved drugs that require CoDx (source: FDA, 2013)

Drug	Drug Manufactures	CoDx	CoDx Manufacturers
Zelboraf	Roche	Cobas 4800 BRAF V600 Mutation Test	Roche Diagnostics
Tarceba	Roche	Cobas EGFR Mutation Test	Roche Diagnostics
Erbitux	Bristol-Myers Squibb	Dako EGFR PharmDx Kit	Dako
		Therascreen KRAS RGQ PCR Kit	Qiagen
Vectibix	Amgen	Dako EGFR PharmDx Kit	Dako
		Therascreen KRAS RGQ PCR Kit	Qiagen
Gleevec/Glivec	Novartis	DakoCytomation c-Kit PharmDx	Dako
Kadcyla	Roche	HER2 IQFISH PharmDx	Dako
		HercepTest	Dako
Perjeta	Roche	HER2 IQFISH PharmDx	Dako
		HercepTest	Dako
Gilotrif	Boehringer Ingelheim	Therascreen EGFR RGQ PCR Kit	Qiagen
Mekinist	GlaxoSmithKline	THxID BRAF Kit	bioMérieux
Tafinlar	GlaxoSmithKline	THxID BRAF Kit	bioMérieux
Xalkori	Pfizer	VYSIS ALK Break Apart FISH Probe Kit	Abbott

ALK: Anaplastic lymphoma kinase; BRAF: B rapidly accelerated fibrosarcoma; EGFR: Epidermal growth factor receptor; FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor 2; KRAS: Kirsten rat sarcoma

1.4.3. Drug-CoDx co-development

Concomitant development of a drug and its CoDx is considered to be best practice, bringing the drug-CoDx combinations into the market (Figure 8). There are a number of articles describing the ideal process or way of collaborating between pharmaceutical and diagnostic companies for personalized medicine development (Cheng et al., 2012; Desiere et al., 2013; Jørgensen, 2012; Metcalfe, 2010; Moore et al., 2012; Scherf et al., 2010; Simon, 2013; PricewaterhouseCoopers, 2011; Winther and Jørgensen, 2010).

For instance, Jørgensen (2012) suggested that collaborations between pharmaceutical and diagnostics companies for CoDxD begin from an early stage of drug development. Ideally, as the clinical efficacy data generated during phase II must be used to provide an indication of the predictive or selective value of the assay, a CoDx assay should be developed during the preclinical development of the drug, or at least at the beginning of phase I (Jørgensen, 2012).

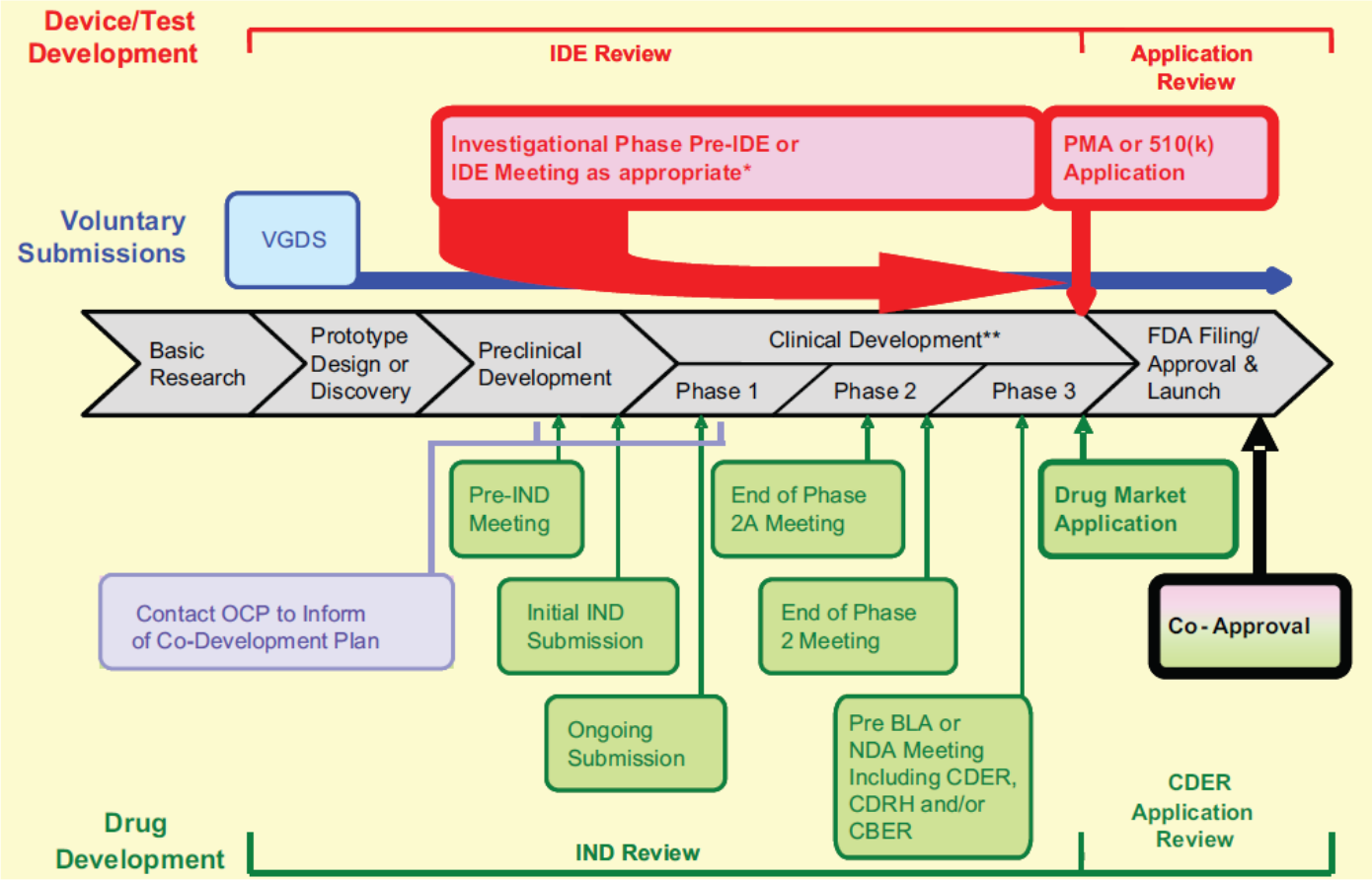


Figure 8. Ideal drug-CoDx co-development process (source: Scherf et al., 2010)

In contrast, according to Simon, the ideal approach to co-development of a drug and CoDx involves three key points (Simon, 2013). First, there is the identification of a predictive biomarker based on an understanding of the mechanism of action of the drug and the role of the drug target in the disease pathophysiology. This biological understanding should be validated and refined during pre-clinical studies and early phase clinical stages. Second, it is necessary to develop an analytically validated test for measurement of that biomarker. In this case, analytically validated means that the test accurately measures what it is supposed to measure, or if there is no gold-standard measurement, that the test is reproducible and robust. Third, there is the use of that test to design and analyze a new clinical trial to evaluate the effectiveness of the drug and how effectiveness relates to the biomarker value.

Furthermore, Winther and Jørgensen (2010) emphasized that clinical study design should be an essential point when considering drug-CoDx co-development (Winther and Jørgensen, 2010). The randomized clinical study has been a crucial factor regarding the change in pharmacotherapy from being more or less empirical to the contemporary substantially more evidence-based approach. For most drugs developed during the last several decades, the standard for documenting safety and efficacy and obtaining regulatory approval has been that at least two independent, randomized, phase III studies show positive results above the current standard treatment. However, despite this approach being a kind of ‘gold standard’ in drug development, the design of the traditional randomized clinical study does not answer the question of the response to a given drug in the individual patient. Thus, extrapolation of the average

study result from the entire patient population could produce negative results (Winther and Jørgensen, 2010; Woodcock, 2007).

With the emergence of new molecular targeted drugs, especially within oncology, it is important to address variability in individual pathophysiology in the drug development process in order to draw the correct conclusions. This can only be accomplished by incorporating molecular diagnostic methods into clinical trial designs. As proposed in the parallel drug-CoDx co-development model, by making CoDx an integrated part of the clinical development process, important information about the molecular pathophysiology will be accessible, and this information should be used to identify patients likely to respond to the targeted drugs tested in clinical trials (Winther and Jørgensen, 2010).

1.4.4. Details of CoDx development process

The aim of CoDx is to measure if a patient is likely to positively respond to a specific drug in a reliable and robust setting (FDA, 2014). Hence, the development of CoDx is dependent on the selection of a relevant and valid biomarker as well as patient outcome data that reflect the efficacy of the medical drug (Papadopoulos et al., 2006; Phillips et al., 2006; Scherf et al., 2010; Metcalfe, 2010).

Figure 9 shows the stages of CoDx development that correspond to the clinical phases of drug development (FDA, 2005; Jørgensen, 2012; Metcalfe, 2010; Scherf et al., 2010; Winther and Jørgensen, 2010). Taken together, this process demonstrates the

need for close collaboration between pharmaceutical and diagnostic organizations to simultaneously develop drugs and CoDx. In this thesis, the processes of drug and CoDx development are defined including the steps indicated in Figure 9. Regarding CoDx development, diagnostic firms need to follow the steps described below.

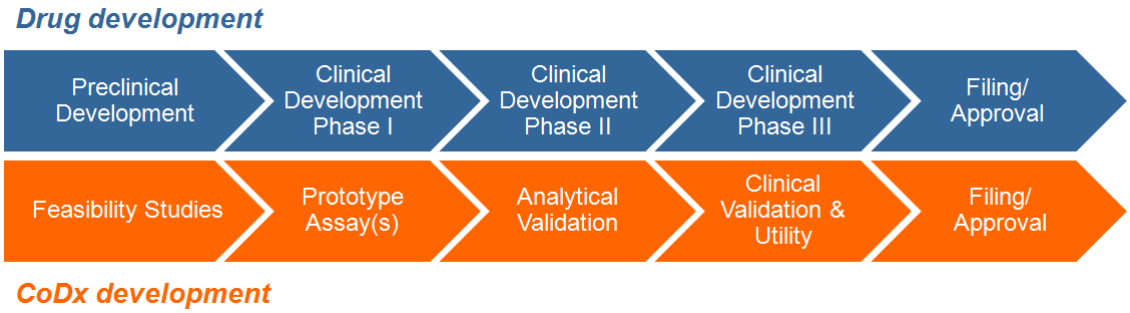


Figure 9. Process for drug-CoDx co-development (source: Winther and Jørgensen, 2010)

Feasibility studies are the first step in the CoDx development process and suggest whether or not CoDx development is possible (Phillips et al., 2006; Scherf et al., 2010; Winther and Jørgensen, 2010). This stage also explores the biomarker to be used in the CoDx. The biomarker is a characteristic that measures and evaluates normal biological processes, disease processes, or responses to a therapeutic intervention. As such, biomarkers are applied to identify patients most likely to benefit or to experience an increased risk from a potent drug. After biomarkers are selected for a potent drug, an appropriate platform will also be selected for biomarker detection. Many platforms are currently available for biomarker detection (Table 5), and selecting the correct one(s)

is crucial to the successful CoDx and drug development (Love et al., 2012). Significant factors for the selection of an appropriate assay platform include the biomarker type (e.g., genetic, genomic, protein), sample type (e.g., serum, tissue-based, urine), where the test will be used (e.g., point-of-care test or a test performed by a specialist laboratory), how to achieve the highest level of reliability, and the test's required sensitivity and specificity of (Desiere et al., 2013; Papadopoulos et al., 2006). The wrong platform can potentially be detrimental to patient care and an obstacle to the successful uptake of the diagnostic test and the drug.

Further, a feasibility assay/kit system is developed as a prototype. During this stage, activities related to the design of assay specifications are typically performed, including definitions of assay sensitivity, specificity, interpretation system, and clinical indications. CoDx exploratory clinical trial testing provides information concerning assay performance in the clinical setting and the correlation between patient response and assay results (Winther and Jørgensen, 2010).

Table 5. Examples of biomarkers, platforms/technologies, and CoDx (source: Fridlyand et al., 2013)

Biomarker	Platform or technology	Examples of CoDx	Challenges
Mutation(s)	Sequencing	No current examples	Test results depend on the percentage of cells with mutations (i.e., there is a lower detection limit); may measure non-specific exons
Mutation(s)	qPCR	Cobas 4800 BRAF V600 Mutation Test	Test results depend on the percentage of mutant sequences, adequate specimen integrity, and sufficient DNA detection
Protein expression	Immunohistochemistry staining	Dako HercepTest	Generally, semi-quantitative and non-automated evaluation; test results can depend on pre-analytical tissue processing factors
Gene expression	Quantitative real-time PCR	No current examples	Manual macrodissection may be necessary for samples with low tumor cell content
DNA copy number	FISH or chromogenic *in situ* hybridization	HER2 FISH pharmDx Kit	Relatively complex assay technology and interpretation
Fusion protein product	FISH	Vysis ALK Break Apart FISH Probe Kit	Relatively complex assay technology and interpretation
Gene signature	Next-generation sequencing	No current examples	Complex assay technology and interpretation

ALK: Anaplastic lymphoma kinase; BRAF: B rapidly accelerated fibrosarcoma; FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor 2; NGS: Next-generation sequencing

In the next stage, the prototype assay is refined to comply with design specifications and to demonstrate analytical validation. Once the biomarker in question has been adequately de-risked through the qualification process, it can be developed on a commercial IVD platform. The costs per marker of this step are usually high in relation to the development of the prototype and this development work will not be undertaken unless there is a high likelihood that the resulting novel IVD assay will attain regulatory approval and demonstrate sufficient clinical utility to warrant broad commercial uptake (Metcalfe, 2010). During this stage, areas of focus include preparation of assay control material and final optimization and characterization of the full assay. Verification studies of the assay include testing of: accuracy; sensitivity; specificity; robustness (tolerance); precision (intra-assay run, inter-assay run, inter-lot variability, inter-reader variability, inter-instrumentation variability, and inter-laboratory variability); and reproducibility (internal and external evaluation) (Jørgensen, 2012; Metcalfe, 2010; Scherf et al., 2010; Winther and Jørgensen, 2010).

Finally, clinical validation and utility are confirmed by demonstrating how the test information facilitates superior decision-making relating to the treatment. Typically, this is accomplished by further refinement of the patient's condition/disease characterization beyond that possible using the current standard of care (Rifai et al., 2006; Simon, 2013; Winther and Jørgensen, 2010).

This process is completed by the submission of all requested data to the relevant regulatory authorities, concurrent with the drug regulatory submission. Following regulatory approval, the assay becomes the commercialized CoDx product containing

all reagents, including positive and negative control materials (if required), and pre-diluted analytes (e.g., antibody/probe).

1.5. Partnerships in Drug-CoDx co-development

Outsourcing options for pharmaceutical companies are widely available and commonly utilized in the traditional drug development and approval process (Moore, 2012). One of the common choices is contract research organizations (CROs), which provide efficient, cost-effective solutions to conducting clinical research. Specifically, CROs can offer assistance with drug development, preclinical research, clinical research, and clinical trial management. In addition, their focus and expertise is on operational efficiency and clinical trial support for pharmaceuticals. Thus, CROs offer a complete solution for large drug companies developing traditional therapeutics.

However, in drug-CoDx co-development, to develop a CoDx for their own product, pharmaceutical companies must find a diagnostic partner that specializes in the development and manufacturing of diagnostic tests and equipment. There are two options for pharmaceutical companies to access to CoDx co-development: external partnerships or in-house cooperation (Figure 10) (PricewaterhouseCoopers, 2009, 2011).

Since most companies do not have sufficient in-house CoDx development capability, external partnerships are the main route used by pharmaceutical firms, and include licensing-in and fee-for-service collaboration. Indeed, the rising numbers of CoDx partnerships between pharmaceutical and diagnostic companies during 2009–2010 imply that a larger number of pharmaceutical companies are seriously considering the need for biomarker and diagnostic programs to accompany their drug development efforts (Figure 11).

In contrast, in-house cooperation tends only be available to pharmaceutical companies with both a pharmaceutical and an *in vitro* diagnostics (IVD) development organization.

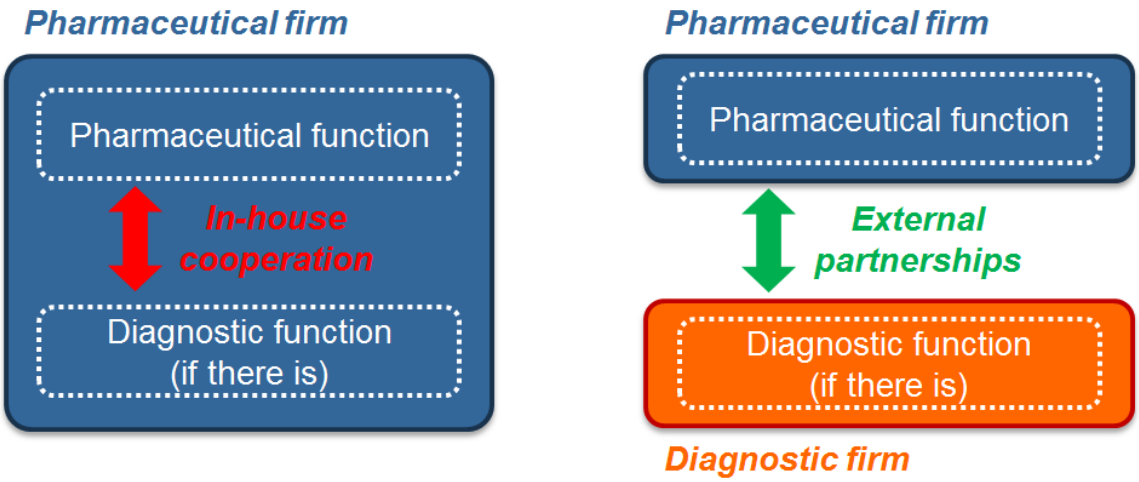


Figure 10. Options for pharmaceutical firms to access CoDx co-development: In-house cooperation or external partnerships (source: Haruya, original)

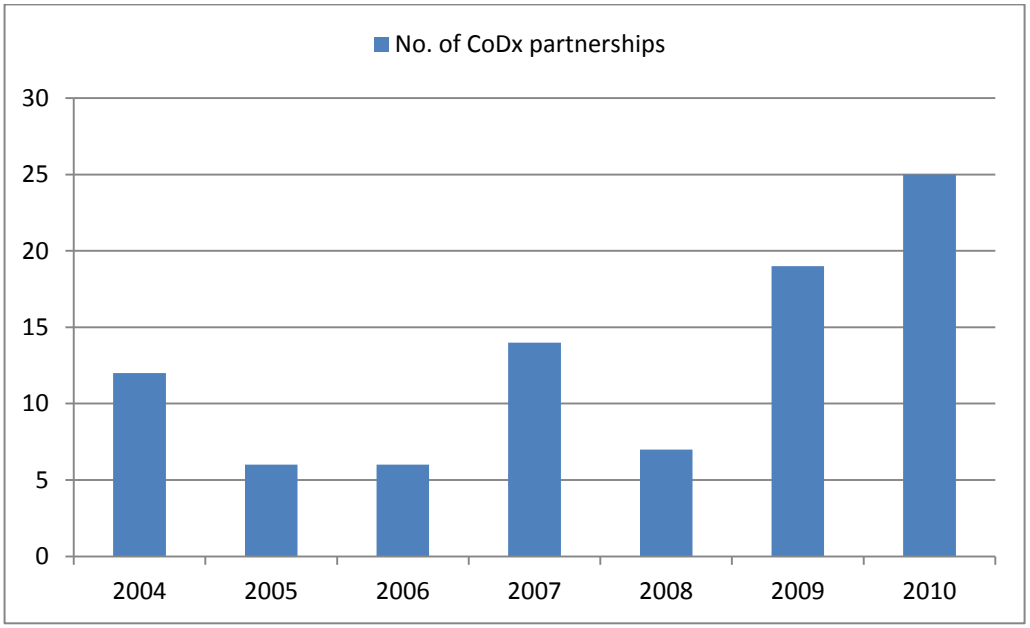


Figure 11. Number of CoDx partnerships between pharmaceutical and diagnostic companies (source: PricewaterhouseCoopers, 2011)

1.6. Arguments on the way of collaboration for drug-CoDx co-development

There are some previous studies that argued the way of collaboration for drug-CoDx co-development. For instance, Moore et al. (2012) indicated that there are several potential barriers to the current co-development process: a relatively low probability of success after a scientific discovery, navigating various development objectives for different drugs, targeting appropriate markets and users, lack of clear regulatory and policy guidance, and partnership challenges between research and diagnostic cultures (Moore et al., 2012). Consequently, they pointed out that there

should be as few partners as possible in the co-development process to avoid conflict and inefficiency. Therefore, from a pharmaceutical firm's point of view, using in-house cooperation to co-develop the drug and its CoDx could be considered as a better option than partnerships with external diagnostic firms.

The case of vemurafenib (Zelboraf™) and its CoDx (Cobas® 4800 BRAF V600 mutation test) is one example of in-house cooperation. The Cobas® 4800 BRAF V600 mutation test is an IVD device developed by Roche Diagnostics as a CoDx to select melanoma patients with tumors carrying the B rapidly accelerated fibrosarcoma (BRAF) V600E mutation and who are treated with vemurafenib. Vemurafenib is a first-class selective inhibitor of oncogenic BRAF kinase, identified by Plexxikon and developed by Roche (Cheng et al., 2012; Roche Molecular Systems, 2011). In this case, Cheng et al. (2012) pointed out that the key success factors in the development process for vemurafenib were early identification of the BRAF V600E biomarker, early development of the diagnostic test, and close collaboration between the pharmaceutical and diagnostic development teams (Cheng et al., 2012). This focused and integrated process resulted in the first personalized medicine for the treatment of metastatic melanoma less than five years after the Investigational New Drug (IND) Application, a remarkably short time (Cheng et al., 2012; Roche, 2011).

A contrasting case is that of crizotinib (Xalkori®) and its CoDx (VYSIS® ALK Break Apart FISH Probe Kit), where co-development occurred through a partnership between Pfizer and Abbott Laboratories. VYSIS® ALK Break Apart FISH Probe Kit is an IVD device developed by Abbott Laboratories to select non-small-cell lung cancer

(NSCLC) patients containing Anaplastic lymphoma kinase (ALK) rearrangements for treatment with crizotinib, which is an ALK inhibitor developed by Pfizer (Choi et al., 2010; Gerber et al., 2010; Kwak et al., 2010). According to interviews with executives at Pfizer and Abbott Laboratories, it seems that some strategic problems arose during this co-development (Rockoff, 2011). Specifically, early on, Pfizer researchers hesitated to give Abbott Laboratories some of its valuable tumor tissue with the ALK genetic abnormality, while Pfizer fretted that Abbott Laboratories did not appear to update them on test development progress.

Based on the above observations, having a diagnostics organization within one corporate group seems to be an advantage for effective drug-CoDx co-development because it can remove potential some issues around sharing the overall value of the drug-diagnostic combination and synchronization.

However, as suggested by the disclosed CoDx development relevant deals, even in the case of pharmaceutical companies with internal diagnostic organizations, the route to access CoDx co-development has not been exclusively internal (PricewaterhouseCoopers, 2009, 2011). That is, regardless of whether or not a pharmaceutical firm has an internal IVD organization, it recently appears that a rising number of CoDx partnerships between pharmaceutical and diagnostics companies have been established (PricewaterhouseCoopers, 2009, 2011). This implies that having strong capability to build external partnerships would be more important for effective drug-CoDx co-development.

1.7. Corporate capability in personalized medicine development

There are a number of articles that describe the ideal process or way pharmaceutical and diagnostic companies collaborate for personalized medicine development (Cheng et al., 2012; Desiere et al., 2013; Jørgensen, 2012; Metcalfe, 2010; Moore et al., 2012; Scherf et al., 2010; Simon, 2013; PricewaterhouseCoopers, 2011; Winther and Jørgensen, 2010). The major topic in these articles can be categorized as the process-orientation approach, which consists of structuring management according to the flow of organizational activities (Walter and Götze, 2009).

The implementation of process-oriented concepts is associated with productivity gains in organizations, and many academic and consulting publications have explained how different approaches provide improvements, primarily in terms of costs, quality and lead-time levels (Walter and Götze, 2009). In addition, these concepts have largely been implemented at operational levels, and 'process improvement' and 'process reengineering' could be considered the main approaches to this topic (Davenport, 1993; Hammer and Champy, 1993; Harrington, 1991). While the importance of these optimizations cannot be denied, it should be recognized that they are fundamentally related to tactical and operational management aspects.

In order to precisely understand strategic management, it is necessary to clarify corporate capability. However, to our knowledge, no study has clearly defined the level of personalized medicine development capability pharmaceutical and diagnostic

firms should have or how it can be managed in business practice. Additionally, since there has been a paradigm change from traditional drug development to personalized medicine, this is especially important in the pharmaceutical and diagnostic industries. Therefore, when analyzing the corporate capability of personalized medicine development in the pharmaceutical and diagnostic industries, it would be important to clarify differences in corporate capability between personalized medicine development and traditional drug development and to illustrate the corporate capability of mutual interactions between pharmaceutical and diagnostic companies.

In order to define and illustrate such corporate capability of personalized medicine development, in next chapter, a literature review will be conducted to better understand the preceding discussion of corporate capability in product development.

Chapter 2: Literature Review

2.1. Process and corporate capability

Process is usually defined in the context of an 'input-output' transformation (Harrington, 1991). Thus, a process might be considered an 'action' performed using resources and capabilities (Amit and Schoemarker, 1993). Such an action is the result of some skill the firm possesses. Therefore, a process may be seen as the application of a capability.

In contrast, to be capable of some thing is to have a reliable capacity to bring that thing about as a result of intended action (Dosi et al., 2000). Capabilities fill the gap between intention and outcome, in such a way that the outcome bears a definite resemblance to what was intended. Within the literature, a general equivalence between 'competency' and 'capability' is often assumed (Dosi et al., 2000; 2008; Teece et al., 1997; Trejo et al., 2002; Ulrich and Smallwood, 2006; Vincent, 2008). Dosi et al. (2000) indicated that 'capability' should be a quite large-scale unit of analysis that has a recognizable purpose expressed in terms of the significant outcomes it is supposed to enable. Furthermore, it is significantly shaped by conscious decisions both in its development and deployment (Dosi et al., 2000).

Based on this background, Walter and Götze (2009) proposed two assumptions: (i) a process represents the ordered application of resources and capabilities to provide some expected result (i.e., a process is a transformation performed using specific resources and capabilities), and (ii) each process can be performed because there is a corresponding 'process-related' capability that coordinates and applies the concerning

resources and other skills. Thus, this means that a process-related capability is the ability to execute a given process and can be understood as the capability of a business unit to execute a given process. The same logic should also be applied at the different process sublevels (i.e., sub-process, activity, and task) (Harrington, 1991). In each sublevel, other resources and capabilities are usually necessary to support the coordination of the subsequent lower process levels (Figure 12).

Moreover, in order to manage the integrated use of the process-related capabilities, Walter and Götze (2009) also defined 'main' and 'combined capabilities,' which are capabilities related to the integration and application of bundles of combined and process-related capabilities, respectively. Based on this foundation, Figure 13 shows the net of relationships among different classes of capabilities whereby a core competence involves the integration of different capabilities that: (i) are located at different business units, and (ii) may be of any class (process-related, combined, and/or main). In the case of the represented core competence, one main and three combined capabilities integrate specific bundles of process-related capabilities.

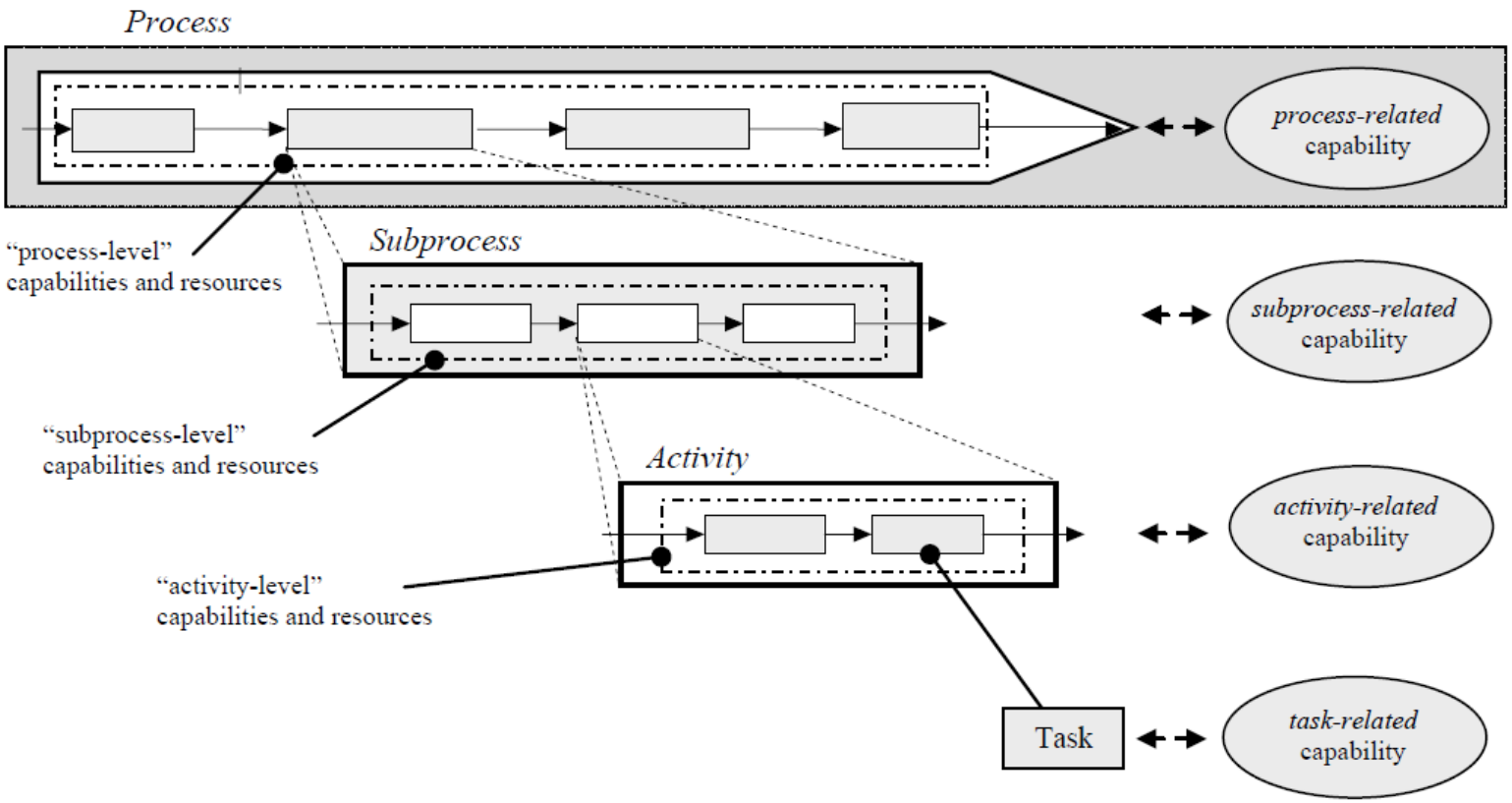


Figure 12. Framework of association between capabilities and processes (source: Walter and Götze, 2009)

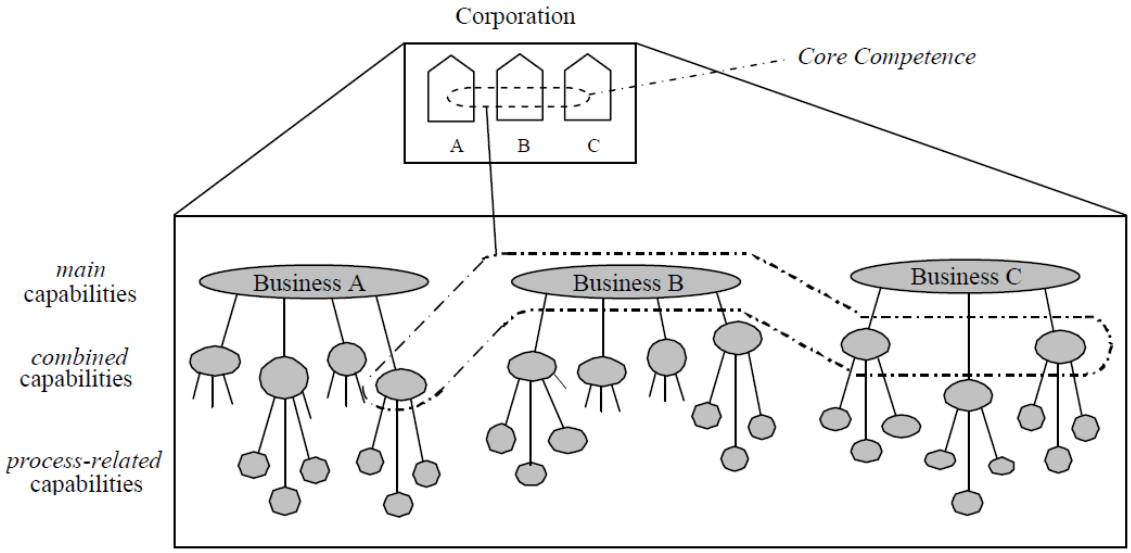


Figure 13. Net of relationships among corporate capabilities (source: Walter and Götze, 2009)

Firms are heterogeneous in that they develop different organizational routines, even if they belong to the same industry and produce similar outputs. These features distinguish 'capability' from 'organizational routines,' as the latter term is used in organizational theory and evolutionary economics (Dosi et al., 2008). Firm-specific operations are based on organizational capabilities that have gradually been accumulated and shaped within firms (Dosi et al., 2000). Therefore, to precisely understand strategic management, it is important to clarify not only process but also process-related capability. Hence, in this thesis, corporate capability is defined as organizational process-related capability that enable firms to effectively deal with organizational problems in a firm-specific way; I aim to understand the corporate

capability of personalized medicine development from the perspective of both pharmaceutical and diagnostic firms.

Thus, to prepare for illustration of these capabilities, a literature review is conducted in Chapter 2 to facilitate an understanding of current research trends in corporate capability.

2.2. Corporate capability for new product development in pharmaceutical firms

Corporate capability of new product development (NPD capability) is a key strategic activity in many firms because new products significantly contribute to sales. Some published articles have described measures for NPD capability in the pharmaceutical industry (Bierly and Chakrabarti, 1996; Deeds et al., 2000).

Deeds et al. (1999) developed a model of new product development, which was tested on a sample of 94 pharmaceutical biotechnology companies (Deeds et al., 2000). In this study, it was hypothesized that NPD capabilities are a function of a firm's scientific, technological, and managerial skills. To test this relationship, they developed several firm-specific measures in an attempt to triangulate the core construct of firm-specific NPD capabilities.

This study's results have some important implications for entrepreneurs/managers of high technology firms. First, entrepreneur/managers need to view the choice of geographic location as an important strategic decision that will influence their firm's access to the skilled technical personnel and knowledge streams. Furthermore, results indicate that choice locations have a significant concentration of similar firms, but the level has not yet reached a point where competition for resources in the local environment offsets any location advantages. In the case of biotechnology, this appears to indicate that prime locations would be expanding areas such as San Diego, Seattle, and Philadelphia rather than the established locations of Silicon Valley and Boston.

Second, as scientific knowledge plays an increasingly important role in a firm's success, the quality of the firm's scientific team is a critical ingredient in new product development capability. However, regarding how to evaluate the quality of scientific personnel, results indicate that there is a strong positive relationship between the impact (as measured by citations) of a team's prior research in the academic community and the productivity of that team in a commercial research laboratory. Therefore, the judgment of a scientific field, captured by citations or perhaps expert judgment, should prove to be a useful tool when evaluating personnel for a firm's research team.

Third, the study presented interesting results in its measurement of CEO experience and the percentage of members of the top management team with a Ph.D. As expected, a CEO's prior experience in managing a commercial research facility enhances a firm's new product development capabilities. However, results for the top

management team variable appear to indicate that overreliance on technical personnel in organization management detracts from the product development process. Taken together, these results seem to imply that while it is important that organization leadership has knowledge of and experience in managing the new product development process, it may be counterproductive to divert the energies of the firm's scientific personnel away from the laboratory and into organization management. Therefore, a high technology venture appears to require leadership that understands and has experience in the new product development process, but is separate and distinct from the scientific team. This type of leadership keeps the scientific team focused on research and development, and out of the boardroom.

In another study, Bierly and Chakrabarti (1996) aimed to better understand strategic management using the dynamic capabilities approach (Bierly and Chakrabarti, 1996). In this study, they focused on two fundamental constructs of dynamic capabilities, technological learning and strategic flexibility, and discerned their influence on organizational performance.

The researchers' main argument was that a firm's strategic flexibility moderates the relationship between technological learning and technological performance as evidenced by new product development. Consequently, their model is based on the synthesis of the traditions of research in strategic and technology management.

Technological learning has been defined in two dimensions: internal and external learning. Additionally, strategic flexibility has been operationalized in financial,

marketing, manufacturing, and technological dimensions. In this study, data from the U.S. ethical pharmaceutical industry from 1977–1991 were used to test the hypotheses.

Although the researchers found support for their basic argument, they observed that the strategic flexibility factors (i.e., Technological learning, strategic flexibility, and new product development) are related with the variables (i.e., research and development commitment, number of patents, measure of 'scientific linkage', and number of strategic alliances) in a more complex way. Furthermore, internal learning involves a different process than learning from external sources. Overall, the robustness of these findings is due to the longitudinal data and objective indicators used in construct measurement.

2.3. Corporate capability for knowledge management in pharmaceutical firms

Many articles describe corporate capability of knowledge management by dividing knowledge management into knowledge exploration and knowledge exploitation (Gilsing and Nooteboom, 2006; He and Wong, 2004; Kane and Alavi, 2007; Lavie and Rosenkopf, 2006; Lichtenthaler and Lichtenthaler, 2009; March, 1991). For instance, March (1991) indicated that exploration includes terms such as search, variation, risk taking, experimentation, play, flexibility, discovery, and innovation. Subsequently,

exploitation includes concepts such as refinement, choice, production, efficiency, selection, implementation, and execution (March, 1991).

In addition, a substantial number of articles have argued about pharmaceutical firms' capability of knowledge management by dividing internal and external knowledge sources (Bierly and Chakrabarti, 1996; Coates and Bals, 213; Graves and Langowits, 1993; Hoang and Rotharmel, 2010; Hughes and Wareham, 2010; Holmqvist, 2004).

Hoang and Rothaermel (2010) distinguished the external and internal experiences of both exploration and exploitation (Hoang and Rothaermel, 2010). Specifically, they hypothesized that alliance exploitation experience has positive effects on research and development (R&D) project performance, while alliance exploration experience has negative effects. They further posited that an internal exploration competence allows firms to more fully leverage their external exploitation experience. In contrast, when firms combine internal exploitation experience with external exploration experience, the negative effects on R&D project performance become more pronounced. To test this integrative model of organizational learning, the researchers leveraged a unique and detailed dataset of 412 R&D biotechnology projects conducted by pharmaceutical companies between 1980 and 2000. Using a competing risk event-history model predicting successful product approval versus project termination, the researchers found that the combination of internal exploration and external exploitation improves R&D outcomes in the pharmaceutical industry, while the combination of internal exploitation and external exploration reduces R&D project performance.

In addition, Bierly and Chakrabarti (1996) conducted a study to identify groups of pharmaceutical firms with similar generic knowledge strategies, determine how these strategies change over time, and compare the groups' profit margins (Bierly and Chakrabarti, 1996). In this study, the knowledge strategies of 21 U.S. pharmaceutical firms were analyzed from 1977 to 1991. Cluster analysis was used to group firms over different time periods based on: (i) balance between internal and external learning, (ii) preference for radical or incremental learning, (iii) learning speed, and (iv) breadth of knowledge base. In terms of results, the researchers found that there are four generic knowledge strategy groups: 'Explorers,' 'Exploiters,' 'Loners,' and 'Innovators.' Subsequently, they reported that the firms in the 'Innovator' and 'Explorer' groups tended to be more profitable than firms in the 'Exploiter' and 'Loner' groups.

2.4. Architecture of product and development process for drug

Some previous studies described knowledge management of product development by considering product architecture (Clark and Baldwin, 1994; Baldwin and Clark 2000; Pisano, 2006; Ulrich, 1995).

According to Baldwin and Clark's definition, when a product or development process has 'modularity,' the elements of its design can be split up and assigned to modules according to a formal architecture or plan (Baldwin and Clark, 2000). For

instance, in the computer industry, firms do not design or make whole computer systems; instead, they design and/or make modules that are parts of larger systems. These modules include hardware components such as computers, microprocessors, and disk drives; software components such as operating systems and application programs; and process components such as fabrication, assembly, systems integration, and testing.

In contrast, according to Pisano (2006), there are three points where pharmaceutical development differs from other high-tech sectors: (i) profound and persistent uncertainty, rooted in the limited knowledge of human biological systems and processes, makes drug development highly risky; (ii) the drug development process cannot be neatly broken into pieces, meaning that the multiple disciplines involved must work in an integrated fashion; and (iii) substantial knowledge from diverse disciplines comprise the pharmaceutical sector is intuitive or tacit, rendering the task of harnessing collective learning especially daunting (Pisano, 2006). Particularly, Pisano pointed out that effectively discovering and developing drugs requires all the pieces to come together and that the drug development process and drug product itself lack 'modularity' (Pisano, 2006). Consequently, it was indicated that integration across diverse scientific, technical, and functional domains is essential for discovering and developing drugs.

It is clear that drug products themselves lack modularity. However, given the number of partnerships in the personalized medicine era, I argue that the process of drug development should have modularity. This could be one point Pisano did not

discuss; therefore, more research efforts need to be devoted to clarifying this when discussing corporate capability of personalized medicine development.

2.5. Architecture of product and development process for CoDx

Rajan et al. (2011) indicated that there are three key components that companies must address to successfully develop a CoDx: biomarkers that are predictive of a therapeutic response; accurate, cost-effective techniques for detecting biomarkers; and suitability of testing materials (Rajan et al., 2011). These three key components will be integrated to build commercialized CoDx product, which implies that CoDx knowledge should be viewed as integrated knowledge consisting of multiple key knowledge elements. Rajan et al. also pointed out that the adoption and commercial success of a CoDx technology require: flexibility in handling clinically relevant body fluids and tissue biopsy samples; cost-effectiveness and scalability in relation to clinical demand; accuracy, reliability and efficient turnaround time; and the ability to multiplex efficiently in light of patient-to-patient heterogeneity and the limited utility of single biomarkers (Rajan et al., 2011). With this background, they concluded that to create an effective CoDx, one of the most important things diagnostic companies need to do is carefully select technologies based on the characteristics of the particular biomarker and on how the diagnostic will be used. To ensure routine, widespread

adoption, Rajan et al. emphasized that diagnostic companies must thoroughly evaluate the pros and cons of the technology and ensure that the key factors of accuracy, reliability, cost effectiveness, turnaround time, and scalability are consistent with clinical demand (Appendix 2).

In contrast, most CoDx products consist of medical devices (including necessary software) and diagnostic kits (Rajan et al., 2011). Therefore, the architecture for both the product itself and its development process should be completely different from that for drug products and their development process. Consequently, this signifies that corporate capability for CoDx development should be illustrated separately from that of drug development. However, although some studies describe the CoDx development process (FDA, 2005; Jørgensen, 2012; Metcalfe, 2010; Scherf et al., 2010; Winther and Jørgensen, 2010), thus far, there is no study that define or illustrate diagnostic firms' corporate capability for CoDx or traditional diagnostics development.

2.6. Research questions

As mentioned in Chapter 1, a number of articles describe the ideal process or collaboration between pharmaceutical and diagnostic companies for personalized medicine development (Cheng et al., 2012; Desiere et al., 2013; Jørgensen, 2012; Metcalfe, 2010; Moore et al., 2012; Scherf et al., 2010; Simon, 2013; PricewaterhouseCoopers, 2011; Winther and Jørgensen, 2010).

For instance, Moore et al. (2012) reported several potential barriers to the current co-development process including: a relatively low probability of success after a scientific discovery, navigating various development objectives for different drugs; targeting appropriate markets and users, a lack of clear regulatory and policy guidance, and partnership challenges between research and diagnostic cultures. Moreover, they indicated that there should be as few partners as possible in the drug-CoDx co-development process to avoid product delays and inefficiency. In addition, Jørgensen (2012) suggested that collaborations between pharmaceutical and diagnostics companies for drug-CoDx co-development begin in an early stage of drug development. Ideally, a CoDx assay should be developed during preclinical drug development (or at least the beginning of phase I) because the clinical efficacy data generated during phase II must be used to provide an indication of the predictive or selective value of the assay (Jørgensen, 2012).

Pertaining to the pharmaceutical industry, these relevant previous works provided some particularly useful insight into drug-CoDx co-development. However, all conclusions reached in these studies were based on qualitative analysis of case studies, while no data from a quantitative study was utilized in reporting results. Moreover, all previous discussions focused on process and no study clearly defined or illustrated corporate capability for personalized medicine development.

In contrast, as reviewed in Chapter 2, there are a number of articles describing the corporate capability of traditional drug development using statistical procedures

(Bierly and Chakrabarti, 1996; Deeds et al., 2000; Graves and Langowits, 1993; Hoang and Rotharmel, 2010)

For example, Deeds et al. (1999) suggested that NPD capability can be measured by a firm's location, scientific capabilities, external contacts, and the functional and educational backgrounds of top managers (Deeds et al., 2000). Additionally, Hoang and Rothaermel (2010) distinguished between external and internal experiences of both exploration and exploitation. Here, it was found that the combination of internal exploration and external exploitation improves R&D outcomes, while the combination of internal exploitation and external exploration reduces R&D project performance (Hoang and Rothaermel, 2010).

However, there is one major difference between development of personalized medicine and traditional drugs. In particular, this is the 'synchronized' co-development of two products. In other words, traditional drug development only requires the development of one product (i.e., a drug), while personalized medicine development requires that development of both a drug and CoDx. Moreover, in order to gain regulatory approval at the same time, it is necessary for the two products to be developed simultaneously, through very close collaboration between pharmaceutical companies and their diagnostic partners. Therefore, it is not appropriate to simply apply the results obtained from previous studies to personalized medicine development.

Congruent with this situation, the first research question raised in this thesis is as follows: *What are the key factors and how do these key factors affect corporate capability of personalized medicine development in pharmaceutical firms?*

As described above, a number of previous studies describe corporate capability of new product development or knowledge management for drug development. However, while some studies describe the CoDx development process (FDA, 2005; Jørgensen, 2012; Metcalfe, 2010; Scherf et al., 2010; Winther and Jørgensen, 2010), no study thus far that describes diagnostic firms' corporate capability of CoDx development. It is obvious that an understanding of diagnostic firms' capability for developing CoDx is essential when considering the corporate capability of personalized medicine development.

Therefore, to clarify this point, the second research question raised is as follows: *What types of knowledge sources exist, and what corporate capability is required for diagnostic firms to manage these sources and interact with their stakeholders for CoDx development?*

2.7. Thesis objectives

With these two research questions in mind, this thesis conducted two studies to further understand corporate capability (i.e., organizational capabilities that enable

firms to effectively deal with organizational problems in a firm-specific way), of personalized medicine development from pharmaceutical and diagnostic firms' points of view, respectively (Figure 14). The outline for the thesis is provided below.

First, in Chapter 3, quantitative analysis was conducted to illustrate the corporate capability of personalized medicine development in the pharmaceutical industry (PMD capability). In this analysis, the first step is to define three factors that illustrate PMD capability. Second, several hypotheses are formulated and observed variables are collected to develop a research model called the PMD capability model. Finally, in order to validate the research model, empirical analysis is conducted using structural equation modeling (SEM).

Next, in Chapter 4, a framework was developed to illustrate diagnostic firms' corporate knowledge sourcing and management capability of CoDx development. First, three key knowledge elements necessary for CoDx development are defined. Second, a unique framework is constructed to detail firms' ability to manage this knowledge. Finally, the proposed framework is applied to several CoDx development cases to test its practical utility.

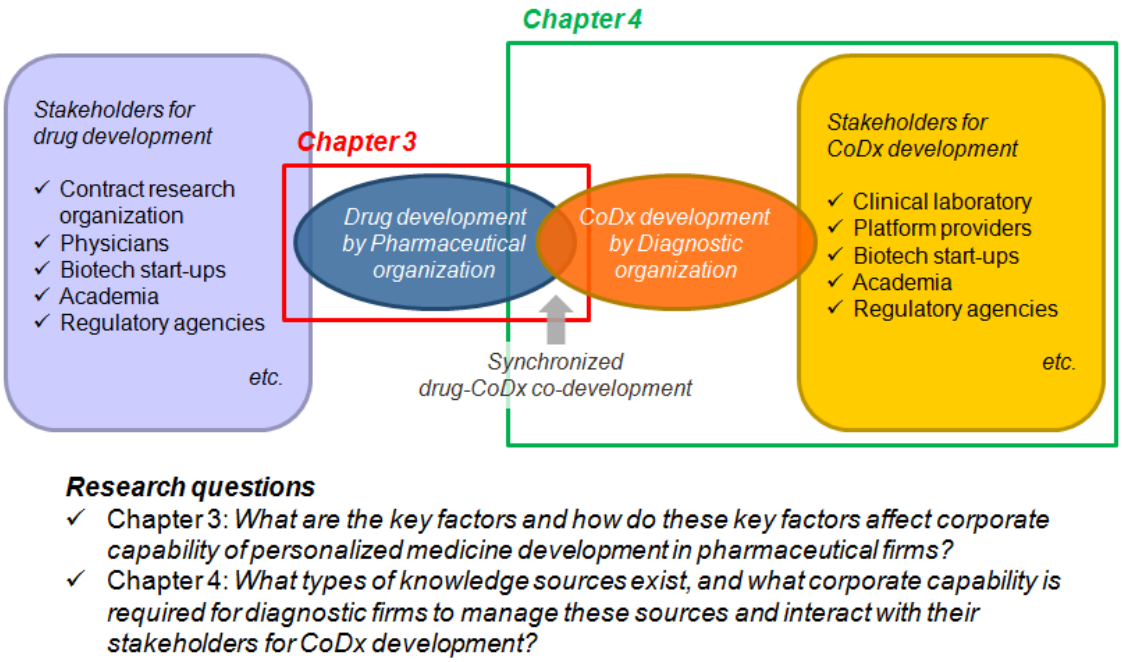


Figure 14. Scope of this thesis (source: Haruya, original)

Chapter 3: Corporate Capability of Personalized Medicine Development in the Pharmaceutical Industry

3.1. Introduction

Despite the recent rise in academic and practitioner interest in personalized medicine development (Amir-Aslani and Mangematin, 2010; Jørgensen, 2011; Tutton, 2012; McClellan et al., 2013), no study has assessed the corporate capability of personalized medicine development in the pharmaceutical industry (PMD capability). Therefore, it is important that increased research efforts be devoted to developing a valid measure to evaluate that capability, which can be considered a useful tool in the pharmaceutical industry.

Based on the previously gap in the literature (see Chapters 1 and 2 for details), a research question was raised: *What are the key factors and how do these key factors affect corporate capability of personalized medicine development in pharmaceutical firms?* In order to address this research question, in this chapter, a study aiming to develop a model illustrating PMD capability using several key influencing factors is conducted (Haruya and Kano, 2015).

The study scheme is organized as shown in Figure 15. First, three factors are defined to illustrate PMD capability. Second, several hypotheses are formulated and observed variables are collected to develop a research model called the PMD capability model. Finally, in order to validate the research model, empirical analysis is conducted using structural equation modeling (SEM).

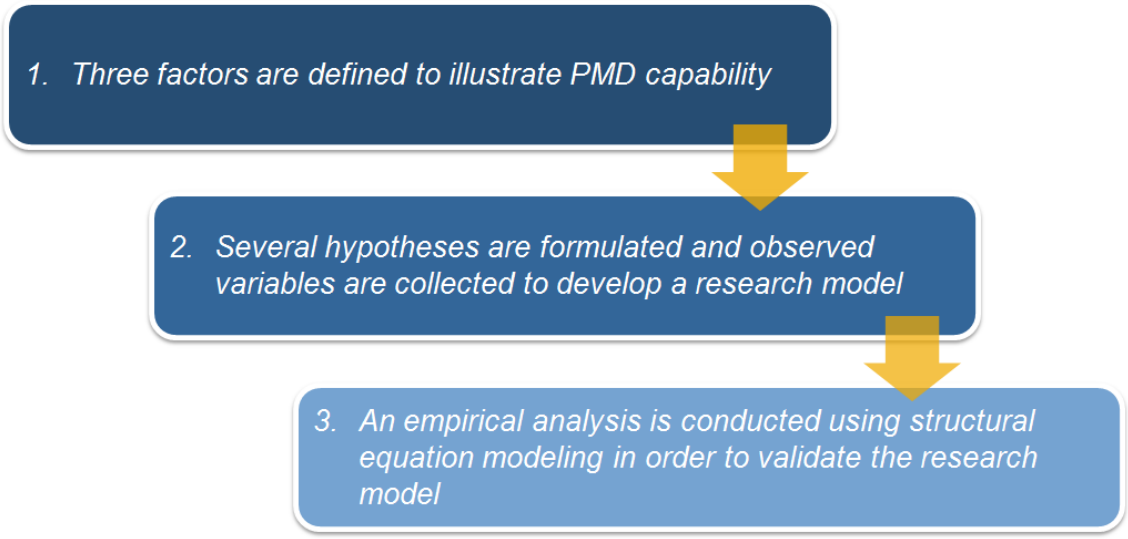


Figure 15. Chapter 3 scheme (source: Haruya, original)

3.2. Methodology

3.2.1. Definition of PMD capability

Here, the first question to solve is how to define PMD capability. In previous studies, the clearest definition is to recognize development capability as the number of products that have reached the market (Hoang and Rothaermel, 2010; Graves and Langowits, 1993; Deeds and Hill, 1996; Bierly and Chakrabarti, 1996). When discussing the capability for developing general products, this definition seems reasonable. However, it is difficult to follow the same method for drugs categorized as personalized medicine because there are insufficient cases of successful launches of

these kinds of products. Therefore, it is assumed using the number of launched products as the dependent variable when discussing PMD capability is inappropriate.

Moreover, when discussing corporate capability of product development, the number of patents is sometimes utilized as a measure (Bierly and Chakrabarti, 1996; Rothaermel and Deeds, 2004). Thus, the number of patents related to biomarker knowledge could act as another definition of PMD capability. However, the number of patents was not used in this study since it was difficult to identify what patent belonged to a particular pharmaceutical company or product using public databases (Millonig, 2015).

In contrast, with the recent growth in technologies such as proteomics, metabolomic analysis, genetic testing, and molecular medicine, there has been a rapid rise in the number of personalized medicine products under development in the pharmaceutical industry (Love et al., 2012; PricewaterhouseCoopers 2009, 2011). Thus, the decision was made to focus on activities in the clinical development stage. Consequently, in this study, PMD capability is defined as the number of pipelines for drugs seeking a drug–CoDx combination.

3.2.2. Definition of PMD capability key factors

As described earlier, new product development is a key strategic activity in many firms because new products significantly contribute to sales. Some published articles have described measures for the corporate capability of NPD (NPD capability) in the

pharmaceutical industry. For example, Deeds et al. (1999) suggested that NPD capability could be measured by a firm's location, scientific capabilities, external contacts, and the functional and educational backgrounds of top managers (Deeds et al., 2000). Additionally, Bierly and Chakrabarti (1996) described NPD capability by focusing on two fundamental constructs: technological learning (e.g., internal and external learning) and strategic flexibility (e.g., breadth of the knowledge base and financial, marketing, and manufacturing flexibility) (Bierly and Chakrabarti, 1996).

It is clear that NPD capability is the first key factors influencing PMD capability. However, previously described NPD models are typically unsuitable to describe PMD capability because drugs and CoDx must be simultaneously developed for personal medicine development. Since there are two options for pharmaceutical companies to co-develop CoDx (i.e., via external partnerships or in-house cooperation), the second and third key influencing factors for PMD capability are defined as corporate capability of CoDx co-development with external parties (External CoDxD capability) and corporate capability of CoDx co-development with an internal organization (Internal CoDxD capability), respectively.

3.2.3. Hypotheses

Based on the definitions of the three key influencing factors illustrating PMD capability (i.e., NPD capability, External CoDxD capability, and Internal CoDxD

capability), six hypotheses and a research model (the PMD capability model) (Figure 16), were developed as follows:

- *Hypothesis 1: NPD capability has a positive effect on PMD capability*
- *Hypothesis 2: NPD capability has a positive effect on External CoDxD capability*
- *Hypothesis 3: External CoDxD capability has a positive effect on PMD capability*
- *Hypothesis 4: NPD capability has a positive effect on Internal CoDxD capability*
- *Hypothesis 5: Internal CoDxD capability has a positive effect on PMD capability*
- *Hypothesis 6: Internal CoDxD capability has a positive effect on External CoDxD capability*

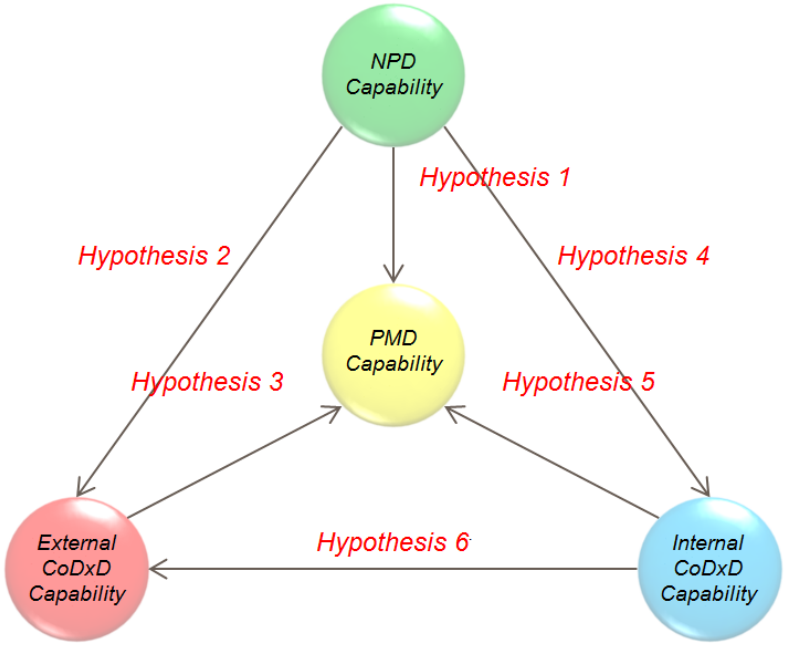


Figure 16. The PMD capability model (source: Haruya and Kano, 2015)

Firstly, it was hypothesized that there are two ways to show the effect from NPD capability to PMD capability: direct and indirect effects. The direct effect was described as the path from NPD capability to PMD capability. Thus, *Hypothesis 1* was formulated to test whether or not it is appropriate to measure PMD capability using only NPD capability.

In contrast, the indirect effects related to CoDx co-development capability can be measured by both external partnerships and in-house cooperation. Consequently, the former was described as the path from NPD capability to PMD capability via External CoDxD capability, while the latter was described as the path via Internal CoDxD

capability. Therefore, *Hypotheses 2–5* were formulated to test the validity of these effects.

As previously discussed, one of the most important actions for successful CoDx co-development is initiating pharmaceutical and diagnostic organization collaboration in an early stage of drug development (Jørgensen, 2012; Moore et al., 2012). In addition, trust, harmonized goals, and clear communication at all levels is crucial to collaboration success for both external and internal business partnerships. As such, the advantage of in-house cooperation might be that it can overcome issues with regard to the overall value of the CoDx co-development process compared with external partnerships. Therefore, Internal CoDxD capability can be thought to have a stronger effect on PMD capability than External CoDxD capability.

Finally, it was hypothesized that a pharmaceutical company with Internal CoDxD capability should have in-depth knowledge regarding successful CoDx co-development collaboration, which is important for partnerships with diagnostics companies. Hence, *Hypothesis 6* was formulated to test if there is a positive effect from Internal CoDxD capability to External CoDxD capability.

3.2.4. Observed variables

PMD capability, NPD capability, External CoDxD capability, and Internal CoDxD capability can be considered as latent variables, and observed variables need to be linked each latent variable in order to validate the developed research model using a

statistical procedure. Figure 17 presents the PMD capability model that includes observed variables.

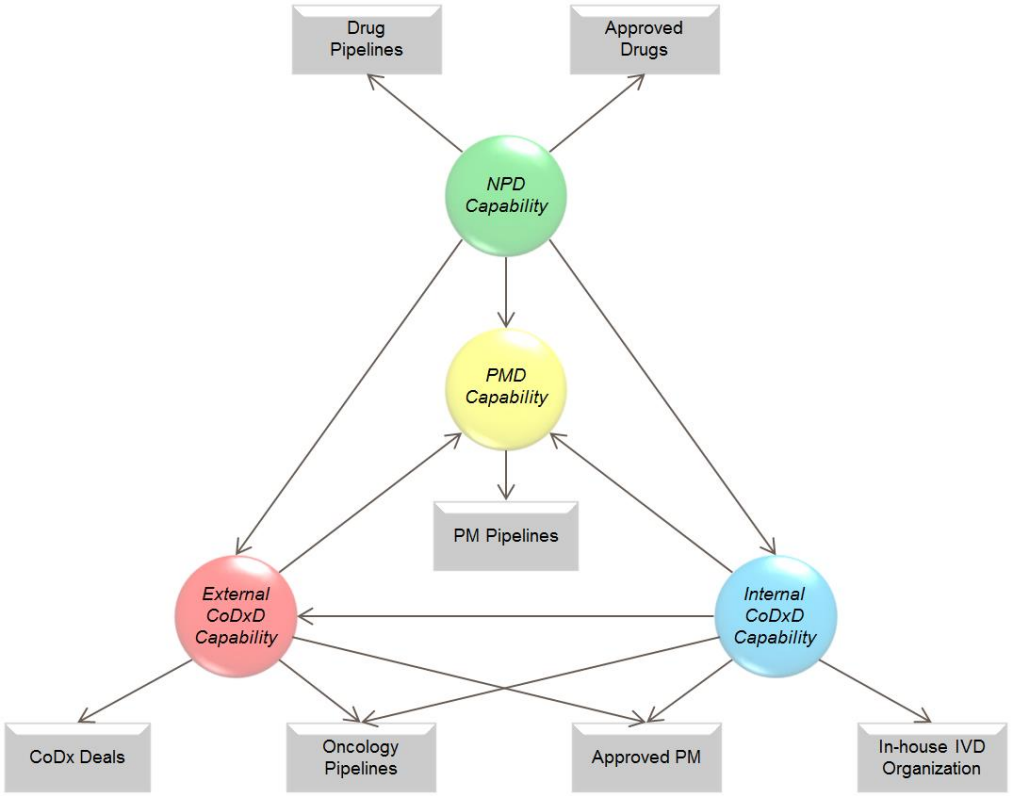


Figure 17. The PMD capability model with observed variables (source: Haruya and Kano, 2015)

PM pipelines

As described earlier, PMD capability is defined as the number of pipelines for drugs that seek a drug–CoDx combination. In this study, it was termed as *PM pipelines*, which is defined as an observed variable for PMD capability. Although a number of drugs have recently been co-developing with CoDx in the preclinical development stage or phase I, the pipelines used for investigations in this study were limited to those in phases II and III in order to exclude products under exploratory development.

Drug pipelines

In the pharmaceutical industry, the number of drugs under development is a common indicator of technological competence or expertise (Deeds et al., 1997). The amount and types of new drugs in a company's drug pipeline reveal the firm's current NPD capabilities to the market. Thus, the variable *Drug pipelines* was defined as the first observed variable that could be affected by NPD capability. Data for this variable were established as the number of drugs under development during phases I–III as of December 2012.

Approved drugs

Similar to the number of drugs under development, the number of drugs that have reached the market is also frequently used as an indicator of NPD capability (Graves

and Langowits, 1993; Deeds and Hill, 1996; Bierly and Chakrabarti, 1996). Hence, the variable *Approved drugs* was defined as the second observed variable that could be affected by NPD capability. Given the number of mergers and acquisitions in the pharmaceutical industry in the first decade of 2000 (e.g., Glaxo Wellcome and SmithKline Beecham in 2000, Aventis and Sanofi-Synthélabo in 2004, and Pfizer and Wyeth in 2009), to represent this variable, data about the capabilities of existing companies included the number of U.S. FDA-approved drugs from January 2010 to December 2012.

CoDx deals

Recently, the rising number of CoDx partnerships between pharmaceutical and diagnostics companies has highlighted the increasing number of pharmaceutical firms that are seriously considering the need for biomarker and diagnostic programs to accompany their drug development efforts (PricewaterhouseCoopers, 2009, 2011). Therefore, the variable *CoDx deals* was used to describe the number of CoDx partnerships and was defined as potentially being affected by External CoDxD capability. For the same reason as *Approved drugs*, these data were gathered from January 2010 to December 2012.

In-house IVD organization

In this regard, whether or not a firm has an in-house IVD organization can be another important observed variable. Although there are differences in the relative capabilities of in-house organizations (PricewaterhouseCoopers, 2011), this study focused on whether or not the investigated pharmaceutical company has its own in-house IVD organization. For this, the dummy variable *In-house IVD organization* was adopted, and was assigned a value of 1 for the presence of an in-house IVD organization and 0 for an absence. In-house IVD organization was defined as an observed variable of Internal CoDxD capability.

Oncology pipelines

Especially in oncology, CoDx developments are considered crucial for the corresponding drugs compared with other major therapeutic diseases in terms of scientific potential and economic attractiveness (Davis et al., 2009; Winther and Jørgensen, 2010; Papadopoulos et al., 2006; Ong et al., 2012). Indeed, most approved drugs that require performing CoDx assays can be categorized as oncology-related (Cheng et al., 2012; Fridlyand et al., 2013; PricewaterhouseCoopers, 2009, 2011; Simon, 2013; Winther and Jørgensen, 2010). Therefore, the number of oncology drugs under development can be considered disease-specific knowledge for personalized medicine, which can be influenced by CoDx co-development capability. In this regard, *Oncology pipelines* was defined as an observed variable of both External and Internal

CoDxD capability, enabling SEM analysis to include an element of exploratory factor analysis. The data for this variable were gathered as the number of drugs in phases I–III as of December 2012.

Approved PM

To date, several drugs that require performing CoDx assays before administration have been approved by the U.S. FDA (FDA, 2013). Although drugs categorized as personalized medicine are now attracting increased attention from various research fields, this is still a new trend in drug development, and there are a limited number of cases of successful launches (FDA, 2013). As such, these achievements can be considered precious experience in personalized medicine development, which may be influenced by CoDx co-development capability. With this in mind, *Approved PM* was also defined as an observed variable of both External and Internal CoDxD capability to allow for the incorporation of exploratory factor analysis within SEM analysis. The data for this variable were gathered as the total number of U.S. FDA-approved drugs that require performing CoDx assays as of December 2012.

3.3. Data and sample

This study's sample focused on pharmaceutical companies which global sales in 2012 were linked in top 20 and considered to have personalized medicine development activities based on the data (i.e., they all had more than one *PM pipeline*, *approved PM*, or *CoDx deal*). As a result, 15 companies (i.e., Abbott Laboratories, Amgen, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck & Co., Novartis, Pfizer, Roche, Sanofi, and Takeda) were selected as the study sample. All data were obtained from published articles or reports, company prospectuses, or the U.S. FDA website. The definitions and values for each observed variable are presented in Table 6 and Table 7, respectively.

Table 6. Definitions of the observed variables (source: Haruya and Kano, 2015)

Variable	Definition
PM pipelines	The number of pipelines in phases II–III for drugs that are co-developing with CoDx as of December 2012
Drug pipelines	The number of pipelines in phases I–III for all drugs as of December 2012
Approved drugs	The number of approved drugs in all countries from January 2010 to December 2012
CoDx deals	The published number of deals between pharmaceutical and diagnostics companies related to CoDx partnerships from January 2010 to December 2012
In-house IVD organization	Presence or absence of an in-house IVD development division or business unit as of December 2012 (1 = presence, 0 = absence)
Oncology pipelines	The number of pipelines in phases I–III for oncology drugs as of December 2012
Approved PM	The number of U.S. FDA-approved drugs that require CoDx assays as of December 2012

Table 7. Values of the observed variables (source: Analyzed based on published articles or reports, company corporate annual reports, or the U.S. FDA website, as of December 2012)

Pharmaceutical companies	PM pipelines	Drug pipelines	Approved drugs	CoDx deals	In-house IVD organization	Oncology pipelines	Approved PM
Abbott Laboratories	1	43	26	0	1	16	0
Amgen	1	47	10	2	0	25	1
Astellas	1	47	31	2	0	15	0
AstraZeneca	3	79	31	3	0	28	0
Bayer	0	46	30	1	1	17	0
Bristol-Myers Squibb	0	66	31	5	0	21	1
Eli Lilly	1	81	18	1	0	37	1
GlaxoSmithKline	6	138	64	3	0	23	2
Johnson & Johnson	1	73	38	0	1	12	0
Merck & Co.	0	91	47	2	0	25	0
Novartis	3	117	66	1	1	36	2
Pfizer	2	90	58	6	0	18	2
Roche	7	103	46	7	1	55	4
Sanofi	1	83	56	2	0	22	1
Takeda	1	53	58	2	0	20	0
Mean ± SD	1.9 ± 2.1	77.1 ± 28.1	40.7 ± 17.2	2.5 ± 2.1	0.3 ± 0.5	24.7 ± 11.0	0.9 ± 1.2

Note: see Appendix 3 for additional information of samples

3.4. Structural equation modeling analysis

3.4.1. Rationale for using structural equation modeling analysis

There are several methods that can be used to estimate relationships among variables (Kleinbaum et al., 2013). When the focus is on the relationship between a dependent variable and one or more independent variables, regression analysis is typically one of the most popular methods. However, regression analysis cannot be used when the goal is to measure relationships among the factors. Moreover, since there is moderate correlation among observed variables in this study (Table 8), as a means of reducing multicollinearity, it is necessary to remove some variables if regression analysis is selected. Therefore, it is considered that regression analysis is not an appropriate method in this study, and it is necessary to find a statistical tool that can estimate causal relationship among factors.

Table 8. Correlation among variables

	PM pipelines	Drug pipelines	Approved drugs	CoDx deals	In-house IVD organization	Oncology pipelines	Approved PM
PM pipelines	1.000						
Drug pipelines	0.707**	1.000					
Approved drugs	0.417	0.680**	1.000				
CoDx deals	0.509	0.337*	0.247	1.000			
In-house IVD organization	0.186	-0.019	0.023	-0.236	1.000		
Oncology pipelines	0.642**	0.489*	0.085	0.448*	0.169	1.000	
Approved PM	0.786**	0.654**	0.376	0.698**	0.168	0.747**	1.000

*: $p < 0.1$, **: $p < 0.01$

Structural equation modeling (SEM) is a statistical technique that can test a conceptual or theoretical model by estimating causal relations among factors (latent variables) using observed variables (Figure 18). SEM analyses include factor analysis, regression/path analysis, and latent growth modeling (Kline, 2010). The term 'structural equation model' most commonly refers to a combination of two elements: a 'measurement model' that defines latent variables using one or more observed variables, and a 'structural regression model' that links latent variables together. In addition, it allows for analysis of complex networks of constructs and indicates how a research model based on strong theoretical knowledge fits the data by estimating overall goodness-of-fit measures (Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005).

Therefore, this method fits the objectives of this study. Consequently, SEM analysis conducted with the AMOS 21 program (IBM) (Arbuckle, 2007) was selected as the analytical method used to demonstrate the validity of the PMD capability model.

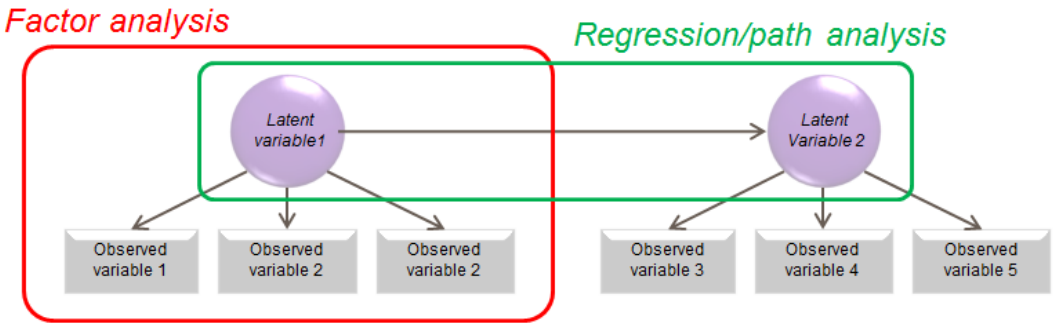


Figure 18. Concept of structural equation modeling (SEM) analysis (source: Haruya, original)

3.4.2. Estimation method and goodness-of-fit chose for structural equation modeling analysis

In this study, maximum likelihood estimation was employed to test the goodness-of-fit of the model using SEM analysis. In addition, because there is no single universally accepted criterion to judge model fit (Heubeck and Neill, 2000), several widely accepted goodness-of-fit indexes were used (Table 9): comparative fit index (CFI), goodness-of-fit index (GFI), root mean square residual (RMR), and root mean square error of approximation (RMSEA).

CFI implies an improvement in the target model's fit compared with the baseline model, with recommended values of greater than 0.97 (Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005). GFI implies testing how much better the model fits compared with 'no model at all.' Typically, values greater than 0.90 indicate an acceptable fit for this index (Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005). RMR is an overall badness-of-fit measure that assesses the average differences between the values predicted by a model and the values actually observed in the sample. Here, values lower than 0.05 indicate a good model fit (Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005). Finally, RMSEA indicates the lack of fit in a model compared with a perfect model. Therefore, for a close fit, the value needs to be small (i.e., up to 0.05) to represent a close fit (Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005).

Table 9. Selected indexes to estimate goodness-of-fit of the model (source: Schermelleh-Engel et al., 2003; Bol et al., 2010; Tomarken and Waller, 2005)

Goodness-of-fit indexes	Value indicated good fit of the model
Comparative fit index (CFI)	> 0.97
Goodness-of-fit index (GFI)	> 0.90
Root mean square residual (RMR)	< 0.05
Root mean square error of approximation (RMSEA)	< 0.05

3.5. Results

Firstly, Table 10 presents the values of each index from the SEM analysis in this study. It is clear that all indexes showed a value greater than the described thresholds, implying that the hypothesized research model exhibited a good overall fit.

Table 10. Results of goodness-of-fit (source: Haruya and Kano, 2015)

Goodness-of-fit indexes	Results	Value indicated as good fit of the model
Comparative fit index (CFI)	1.00	> 0.97
Goodness-of-fit index (GFI)	0.903	> 0.90
Root mean square residual (RMR)	0.050	< 0.05
Root mean square error of approximation (RMSEA)	0.000	< 0.05

Next, the results of all hypothesized paths in the PMD capability model are presented in Figure 19. The paths between the latent and observed variables showed strong effects (path coefficient > 0.5) and were statistically significant ($p < 0.05$). The only exceptions were the non-significant path from Internal CoDxD capability to *Oncology pipelines*, while the path from Internal CoDxD capability to *Approved PM* showed weak effects (path coefficient = 0.49).

In terms of the paths from NPD capability to External CoDxD capability (*Hypothesis 2*) and from External CoDxD capability to PMD capability (*Hypothesis 3*), the results were statistically significant ($p < 0.05$), with path coefficients of 0.58 and 0.57, respectively. This implied a strong positive influence from NPD capability to External CoDxD capability and from External CoDxD capability to PMD capability, supporting *Hypotheses 2* and *3*.

Although the path from Internal CoDxD capability to PMD capability (*Hypothesis 5*) was statistically significant ($p < 0.1$), its path coefficient was 0.37. Thus, the path was supported, but there was only a weak influence of Internal CoDxD capability and PMD capability.

In contrast, neither statistically significant nor strong influences could be confirmed for *Hypotheses 1*, *4*, and *6*. Specifically, the path from NPD capability to PMD capability revealed a path coefficient of 0.33 ($p = 0.20$), while that from NPD capability to Internal CoDxD capability was -0.02 ($p = 0.92$). Additionally, the path

from Internal CoDxD capability to External CoDxD capability was -0.29 (p = 0.32). Therefore, SEM analysis did not support these paths.

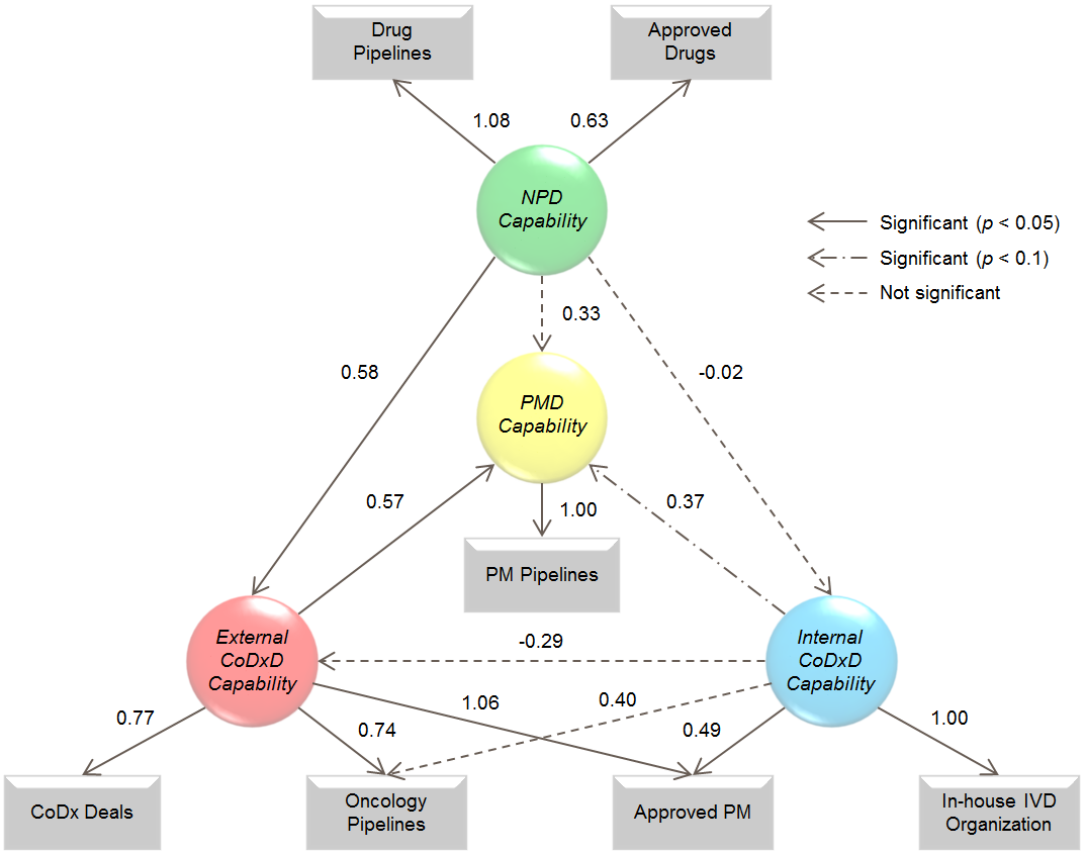


Figure 19. Results of SEM analysis (source: Haruya and Kano, 2015. See Appendix 4, Appendix 5, Appendix 6, and Appendix 7 for details)

3.6. Discussion

In this study, a model was developed to illustrate PMD capability using three key influencing factors: NPD capability, External CoDxD capability, and Internal CoDxD capability. Then, six hypotheses were developed and the causal relationships between the factors and PMD capability as well as among the factors were analyzed using SEM analysis. Overall, SEM analysis indicated a good fit for the model, and three noteworthy findings were obtained.

3.6.1. Relationship between PMD capability and NPD capability

The first finding pertains to the relationship between PMD capability and NPD capability. Although two types of effects on PMD capability from NPD capability were hypothesized, analysis revealed only an indirect effect. In particular, this effect occurred via External CoDxD capability, as confirmed in the results of the hypothesis tests (Figure 20).

This finding implied that robust NPD capability is a necessary but not sufficient condition for PMD capability. One possible reason for this result could be the pharmaceutical firms' diverse business strategies. That means that it is clear that companies with a robust NPD capability have an advantage when developing personalized medicine. However, since there remain many challenges in this field (Ferrara, 2007; Moore et al., 2012; Jørgensen, 2011; Schmidt, 2012; Lehrach, 2012),

not all such companies can or want to invest resources into personalized medicine development. Consequently, it was indicated that key factors for personalized medicine development differ from those for traditional drug development.

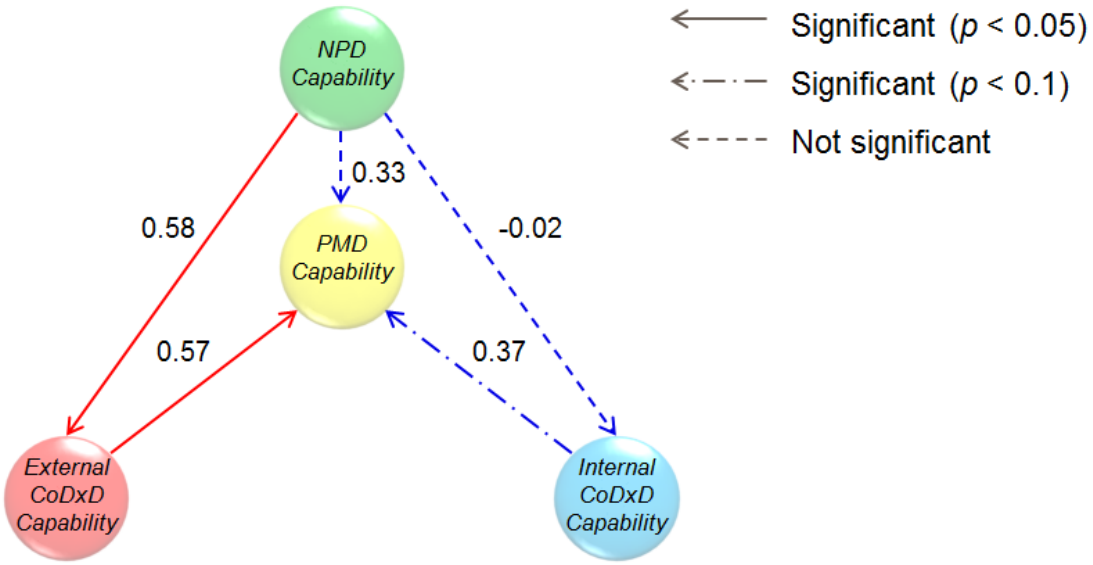


Figure 20. Relationship between PMD capability and NPD capability (source: Haruya and Kano, 2015)

3.6.2. Effect from external/internal CoDxD capability to Oncology pipelines and Approved PM

The second finding is that *Oncology pipelines* and *Approved PM* were loaded much stronger by External CoDxD capability than by Internal CoDxD capability (i.e., the path from Internal CoDxD capability to *Oncology pipelines* was not statistically significant, while that to *Approved PM* showed a weak coefficient) (Figure 21).

Consequently, this result may imply that *Oncology pipelines* represent disease-specific knowledge for personalized medicine, while *Approved PM* may represent experience with personalized medicine development. Although such knowledge and experience are important when internally co-developing CoDx, it is reasonable to suppose that external partners place more importance on these observed variables.

Based on the results presented herein, we can conclude that disease knowledge, experience with personalized medicine development, and collaboration on CoDx co-development are key components for External CoDxD capability. However, the only key component for Internal CoDxD capability is the presence of an in-house IVD organization.

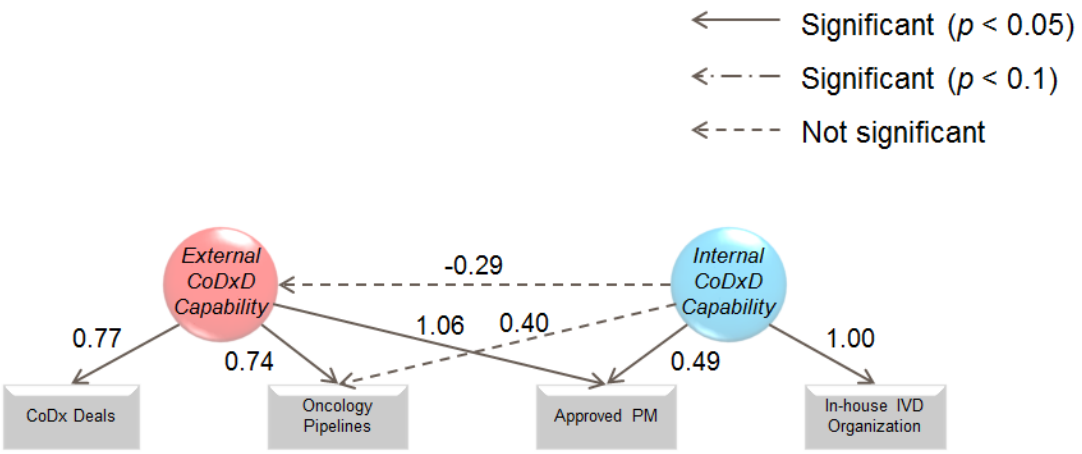


Figure 21. Effect from External CoDxD capability and Internal CoDxD capability to the observed variables (source: Haruya and Kano, 2015)

3.6.3. *Effect of External CoDxD capability and Internal CoDxD Capability to PMD Capability*

The last finding is that the effect of External CoDxD capability is stronger than Internal CoDxD capability, although it was confirmed that both External CoDxD capability and Internal CoDxD capability contribute to PMD capability (Figure 22). Based on previous studies (Cheng et al., 2012; Moore et al., 2012; Roche, 2011), it can be assumed that Internal CoDxD capability will have a stronger influence on PMD capability compared with External CoDxD capability since companies with an in-house IVD organization should more easily contribute to PMD capability than those that do not. Surprisingly, the results of hypothesis testing differed. Specifically, the result showed a path coefficient of 0.37 from Internal CoDxD capability to PMD capability, which implied that Internal CoDxD capability has a limited influence on PMD capability. In other words, the key factor to promoting CoDx co-development seems to be external partnerships rather than in-house cooperation.

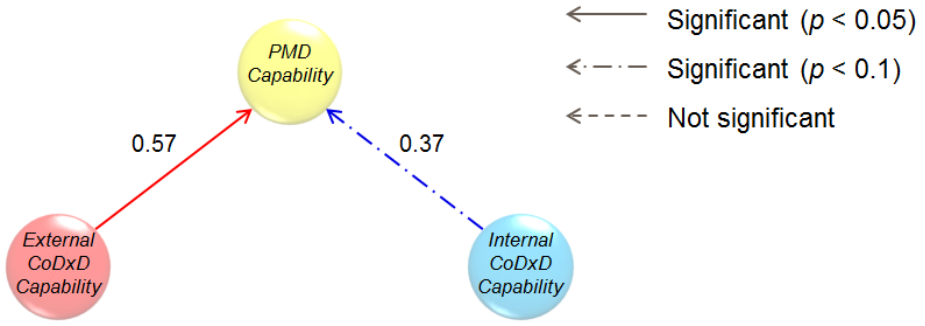


Figure 22. Effect of External CoDxD capability and Internal CoDxD Capability to PMD Capability (source: Haruya and Kano, 2015)

One of the reasons for this result might be difficulty achieving successful CoDx co-development through simple reliance on one internal IVD organization. In CoDx development, various first-line technologies as well as flexible and cost-efficient platforms are necessary in order to meet the wide variety of drug development needs (Love et al., 2012; Moore et al., 2012). As a result, this makes it difficult for pharmaceutical companies that have in-house IVD development capability to cover all necessary resources for CoDx development. Consequently, Internal CoDxD capability does not significantly influence PMD capability. The same logic might explain why the path between Internal CoDxD capability and External CoDxD capability has neither a statistically significant nor a strong effect.

3.6.4. Managerial implications

Based on the results of SEM analysis, it was indicated that the critical path contributing to PMD capability is from NPD capability via External CoDxD capability (Figure 23). This implies that, regardless of whether or not pharmaceutical companies have an in-house IVD organization, increasing corporate capability in co-developing CoDx with external diagnostic firms is essential for personalized medicine development in the pharmaceutical industry.

However, this does not mean that having strong corporate capability in in-house cooperation for CoDx co-development is negligible. That is, study results also showed that the path from Internal CoDxD capability to PMD capability was statistically

significant ($p < 0.1$), although its coefficient was small (0.37). Thus, the managerial implication of this finding is that having corporate capability in in-house cooperation is not sufficient for personalized medicine development. In other words, it appears that having an in-house IVD organization is not critical for the development of personalized medicine by pharmaceutical firms. Moreover, even for those firms that have an in-house IVD organization, it would be important for managements to continue to increase corporate capability in co-developing CoDx with external diagnostic firms for personalized medicine development in the pharmaceutical industry.

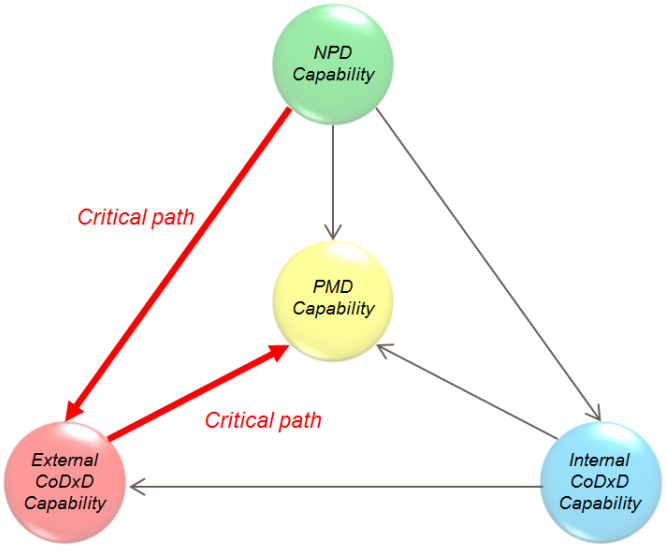


Figure 23. Critical paths in the PMD capability model (source: Haruya and Kano, 2015)

Roche provides a good example when demonstrating this implication. Roche is a pharmaceutical company with an internal IVD organization (i.e., Roche Diagnostics), and is viewed as one of leading companies in the personalized medicine era (PricewaterhouseCoopers, 2009; 2011).

Over the past decade, Roche has launched more than four new drugs that require CoDx testing before therapeutic treatment (Table 11). When the partners for CoDx co-development (i.e., CoDx manufacturers) are examined, it is evident that two of four cases were not corroborated with Roche Diagnostics. Thus, this provides clear evidence that even those pharmaceutical companies with internal IVD organization are collaborating with external diagnostic companies for CoDx development.

Table 11. Selected drugs launched by Roche (source: Roche corporate annual reports)

Drugs	CoDx	CoDx Manufacturers
Zelboraf	Cobas 4800 BRAF V600 Mutation Test	Roche Diagnostics
Tarceba	Cobas EGFR Mutation Test	Roche Diagnostics
Perjeta	HER2 IQFISH PharmDx, HercepTest	Dako
Kadcyla	HER2 IQFISH PharmDx, HercepTest	Dako

EGFR: Epidermal growth factor receptor; FISH: Fluorescence in situ hybridization; HER2: Human epidermal growth factor receptor 2

This trend is also exciting during the development stages. According to the 2009 and 2011 PricewaterhouseCoopers reports, Roche created 10 and 4 external CoDx

partnerships during 2004-2008 and 2009-2010, respectively (PricewaterhouseCoopers, 2009; 2011). This implies that substantial personalized medicine development is currently occurring at Roche in collaboration with external diagnostic partners in addition to in-house cooperation of drug-CoDx development.

3.7. Chapter 3 conclusion and next steps in Chapter 4

In Chapter 3, PMD capability was defined as the number of pipelines for drugs seeking the drug–CoDx combination. Accordingly, three latent variables (i.e., NPD capability, External CoDxD capability, and Internal CoDxD capability) were defined as key influencing factors and a model was developed to illustrate PMD capability using six observed variables: *Drug pipelines*, *Approved drugs*, *CoDx deals*, *In-house IVD organization*, *Oncology pipelines*, and *Approved PM*. The proposed research model was then validated using SEM analysis, and the results indicated a good fit of the model and showed that the critical path toward PMD capability is from NPD capability via External CoDxD capability.

In this chapter, a major contribution was made to understanding corporate capability of personalized medicine development from the perspective of pharmaceutical firms. Particularly, the study provided a clear answer to arguments regarding the options to access CoDx co-development (i.e., corporate capability of

CoDx co-development with external parties would be essential for personalized medicine development in the current pharmaceutical industry) through quantitative analysis. Therefore, from a scientific and business strategy perspective, it can be suggested that the management of all pharmaceutical companies continue to seek opportunities for crucial external partnerships, regardless of whether or not the company has an in-house IVD organization.

In contrast, in order to further clarify capability in synchronized co-development, it is also important to establish greater understanding from the perspective of diagnostic firms. Therefore, Chapter 4 will focus on illustrating corporate capability of personalized medicine development based on diagnostic firm capability.

3.8. Limitations

In previous studies, one of the clearest definitions for development capability was the number of products that have reached the market (Hoang and Rothaermel, 2010; Graves and Langowits, 1993; Deeds and Hill, 1996; Bierly and Chakrabarti, 1996). However, in this study, instead of utilizing this existing definition, *PM pipelines* (i.e., the number of drugs under clinical development seeking a drug–CoDx combination) was selected as the observed variable for PMD capability. The reason the number of personalized medicines that have reached the market was not used as the definition of PMD capability is because there are insufficient cases of successful launches of these

products. Therefore, it is assumed that the use of this number is inappropriate. Consequently, the focus of this study was on activities in the clinical development stage and the observed variable for PMD capability was defined the number of pipelines for drugs that seek a drug–CoDx combination.

I believe that this is currently the most reasonable way to illustrate PMD capability because personalized medicine development is still a new trend. However, when the market matures and more samples are available, the definition of observed variable for PMD capability could be reverted to launched personalized medicine, as defined in previous works. Therefore, *PM pipelines* should be used as definition of PMD capability only at this point in time.

Similarly, the total number of *PM pipelines* in each company is currently limited, and personalized medicine development trends could dramatically change over time. Therefore, the results obtained from this study should be limited to trend analysis in the early 2010s. As a result, future research could reassess these trends following the maturation of personalized medicine in the pharmaceutical industry.

At that time, it may be possible to divide *PM pipelines* into discovery, phase I, II, and III stages. This would facilitate a deeper understanding of the actual condition of personalized development in the pharmaceutical industry.

Chapter 4: Corporate Capability of Personalized Medicine Development in the Diagnostic Industry

Chapter 5: Integrated Conclusion

Appendixes

Appendix 1. Data of Figure 2

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
The number of studies including biomarker assessments	85	148	180	287	328	392	481	487	567	627	539	554	441
The number of all of studies	1572	2191	2824	3758	4377	5055	5344	5843	6082	6105	6305	6007	4802
Rate of studies including biomarker assessments	5	7	6	8	7	8	9	8	9	10	9	9	9

Note: reduction of the number of studies including biomarker assessments during last few years could be because the delay of publication of study information into ClinicalTrials.gov.

Appendix 2. The pros and cons of chief technologies commonly adopted for CoDx (source: Rajan et al., 2011)

CoDx Technologies	Definition	Pros	Cons
Immunohistochemistry (IHC)	Method of determining if specific antigen is present in tissues by staining antibodies with markers such as fluorescent dyes or enzymes.	Well established, routinely used technology; relatively inexpensive; relatively rapid turnaround time with availability of automated systems; shows exact location of protein within tissue; largely used on fixed tissues, cell morphology preserved and antibodies not displaced.	Not quantitative: no direct correlation between staining and amount of protein; false positive possibility when fluorescence is not limited to a specific cell type; low reproducibility; cannot distinguish between expression due to gene amplification versus other, non-genetic causes; accuracy depends on antibody employed (monoclonal vs. polyclonal)
Fluorescence in situ hybridisation (FISH)	Cytogenetic technology that uses fluorescent or colorimetric probes to detect and localize the presence or absence of specific DNA sequence alterations such as translocations and amplifications on chromosomes.	Independent of antibody, provides unambiguous evidence of genetic alterations, highly sensitive and specific to target sequence; quantitative; direct detection, thereby faster; easily detected with many color systems; relatively large number of cells can be analyzed.	Requires expensive, specialized equipment; relatively time consuming and expensive as results tend to be recorded with camera; fluorescent signals likely to fade; requires significant experience to interpret data.

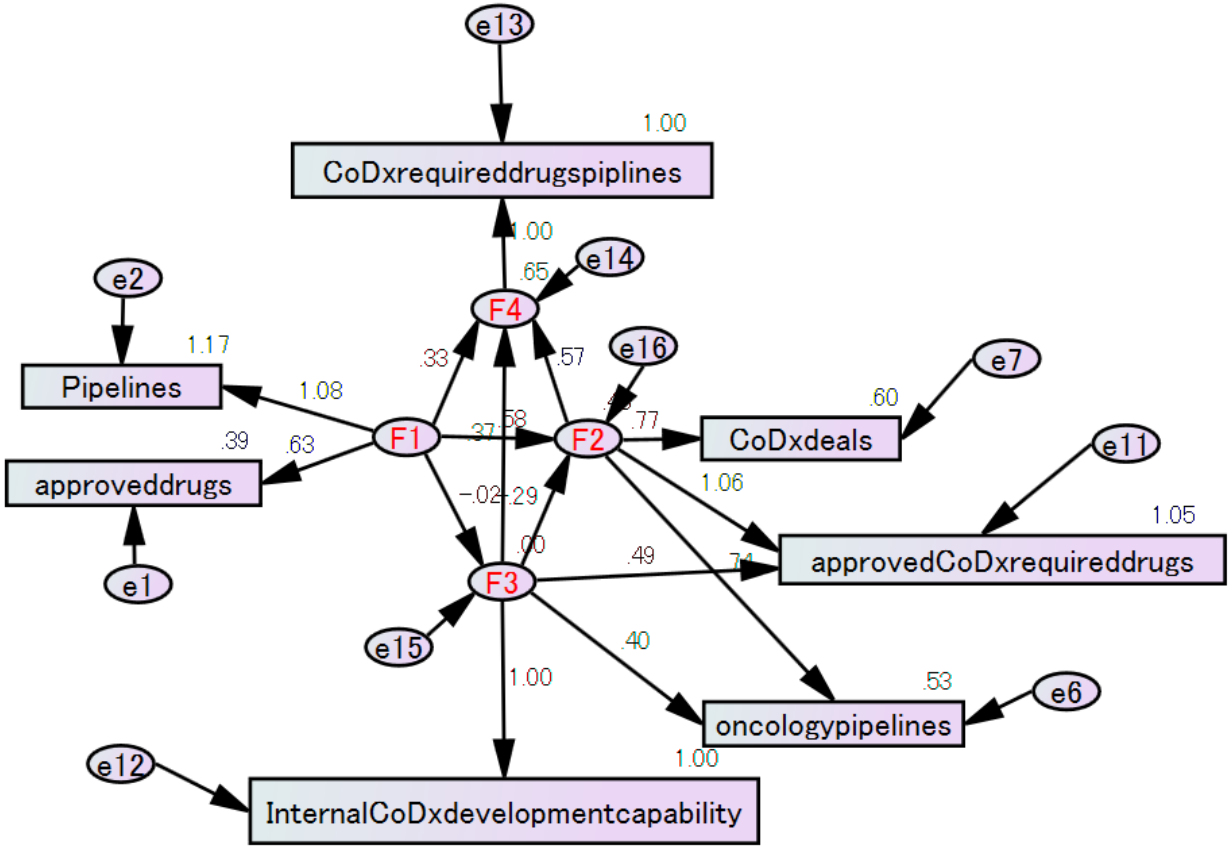
CoDx Technologies	Definition	Pros	Cons
qPCR	Technique based on PCR that detects/amplifies a specific gene or transcript and quantifies the amplified molecules as they accumulate in real-time during the PCR amplification process.	Starting to become well established, standardized technology; very sensitive; quantitative (fluorescent signal is directly proportional to the number of amplicons generated); large dynamic range; detection platforms have quick turnaround time; automated and high throughput; closed reaction: no post-PCR processing with minimum cross contamination.	Expensive; careful controls necessary to interpret data and avoid contamination; primer sets must be designed and validated stringently to ensure accuracy of results; results highly dependent on sample quality; cannot distinguish between a lot of cells with a little transcript or a few cells with a lot of transcript; can only provide information about the genes to which primer sets have been designed.

CoDx Technologies	Definition	Pros	Cons
Arrays	Arrays are a multiplex lab-on-a-chip that consists of biological material hybridized to a solid surface or a bead bound probe in aqueous suspension. They are used for applications such as profiling gene expression, comparing genomic hybridization and detecting single nucleotide polymorphisms.	Massive, parallel, high-throughput interrogation of many genes; miniaturisation; cost effective; patterns of gene expression can be useful for prognostication.	CoDx tests generally need to interrogate only one or a few genes per sample and arrays may be excessive for this purpose; requires careful controls to ensure reproducibility; semi quantitative; not as sensitive as qPCR; labor intensive, requiring distinct sample preparation and amplification steps; only detects unbalanced rearrangements and not balanced translocations or inversions; can only provide information about the genes that are included on the array.
Traditional DNA sequencing	Technology used to determine the primary structure (i.e., sequence of nucleotides) of DNA. Genes amplified by PCR, chain termination methods are used to determine the sequence of the entire DNA.	Extensive detection of somatic mutations; key if target gene can be mutated in multiple different ways; no a priori knowledge of mutation or of gene of interest required.	Expensive; time consuming and labor intensive; not as sensitive as qPCR (requires the mutation to be present in at least 20% of the sample); does not detect certain mutations such as deletions.

Appendix 3. Additional information of sample (source: Cegedim Strategic Data, 2011; 2012; corporate websites, 2011; 2012)

Pharmaceutical companies	Nation	No. of employees	Sales in 2011 (million USD)	R&D expenses in 2011 (million USD)	Sales in 2010 (million USD)	R&D expenses in 2010 (million USD)
Abbott Laboratories	USA	91,000	22,435	4,129	19,894	3,725
Amgen	USA	17,800	15,582	3,116	15,053	2,894
Astellas	Japan	17,085	12,523	2,452	11,697	2,665
AstraZeneca	UK	57,200	32,981	5,523	32,515	5,318
Bayer	Germany	111,800	13,774	2,015	14,136	2,717
Bristol-Myers Squibb	USA	27,000	21,244	3,839	19,484	3,566
Eli Lilly	USA	38,442	22,608	5,021	21,685	4,884
GlaxoSmithKline	UK	97,389	34,293	6,045	36,167	6,351
Johnson & Johnson	USA	118,000	24,368	5,138	22,396	4,432
Merck & Co.	USA	86,000	41,289	8,467	39,811	10,991
Novartis	Switzerland	123,686	47,925	9,583	41,994	8,262
Pfizer	USA	57,400	57,747	9,112	58,523	9,413
Roche	Switzerland	80,127	36,439	7,632	39,389	8,673
Sanofi	France	113,719	40,607	6,041	39,515	5,832
Takeda	Japan	30,814	17,556	3,642	15,541	3,542

Appendix 4. Details of SEM analysis result (Output path diagram)



Appendix 5. Details of SEM analysis result (Regression Weights)

			推定値	標準誤差	検定統計量	確率	ラベル
F3	<---	F1	.000	.004	-.096	.924	
F2	<---	F1	.031	.016	1.926	.054	
F2	<---	F3	-.956	.953	-1.003	.316	
F4	<---	F1	.023	.018	1.291	.197	
F4	<---	F2	.743	.342	2.175	.030	
F4	<---	F3	1.576	.914	1.725	.084	
approveddrugs	<---	F1	.356	.162	2.195	.028	
oncologypipelines	<---	F2	5.096	1.725	2.954	.003	
InternalCoDxdevelopmentcapability	<---	F3	1.000				
CoDxrequireddrugspiplines	<---	F4	1.000				
approvedCoDxrequireddrugs	<---	F2	.774	.191	4.044	***	
CoDxdeals	<---	F2	1.000				
approvedCoDxrequireddrugs	<---	F3	1.174	.570	2.061	.039	
oncologypipelines	<---	F3	8.896	5.791	1.536	.124	
Pipelines	<---	F1	1.000				

Appendix 6. Details of SEM analysis result (Standardized Regression Weights)

			推定値
F3	<---	F1	-.023
F2	<---	F1	.582
F2	<---	F3	-.292
F4	<---	F1	.328
F4	<---	F2	.565
F4	<---	F3	.366
approveddrugs	<---	F1	.628
oncologypipelines	<---	F2	.741
InternalCoDxdevelopmentcapability	<---	F3	1.000
CoDxrequireddrugspiplines	<---	F4	1.000
approvedCoDxrequireddrugs	<---	F2	1.062
CoDxdeals	<---	F2	.773
approvedCoDxrequireddrugs	<---	F3	.493
oncologypipelines	<---	F3	.395
Pipelines	<---	F1	1.083

Appendix 7. Details of SEM analysis result (Factor Score Weights – Estimates)

	approvedCoDxrequireddrugs	CoDxrequireddrugspiplines	InternalCoDxdevelopmentcapability	CoDxdeals	oncologypipelines	Pipelines	approveddrugs
F1	-3.864	-3.036	4.723	.203	.031	1.611	-.435
F3	.000	.000	1.000	.000	.000	.000	.000
F2	1.712	-.069	-1.671	-.090	-.014	-.003	.001
F4	.000	1.000	.000	.000	.000	.000	.000

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Biography

Mei Haruya is a postgraduate student who is enrolled the Bio Intellectual Property Course at the Department of Medical Genome Sciences, The University of Tokyo, Japan. He received his Master's degree in Chemistry from The University of Tokyo. His previous works appear in *Organic Letters*, *Bioorganic & Medicinal Chemistry Letters*, and *R&D Management*. He has several years of industrial experience in pharmaceutical companies as a medicinal chemistry researcher, clinical researcher associate, and project manager. He is now an employee of GlaxoSmithKline K.K.

Conflict of Interest

This study was conducted by Mei Haruya, a postgraduate student working at GlaxoSmithKline K.K. The objectives, methodologies, and outcomes of this thesis are independent from those of the company.

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