PRECISION MEDICINE REIMBURSEMENT POLICY LANDSCAPE

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น.ส.นิสิตา จิรวุฒิกรกุล

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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ที่มา: การแพทย์แม่นยำ (Precision medicine) เป็นการรักษาที่ใช้การตรวจพันธุกรรมเฉพาะบุคคลเพื่อเพิ่มประสิทธิผลในการรักษา ซึ่งการเข้าถึงการแพทย์แม่นยำยังถูกจำกัด จากปัจจัยหลายด้าน อาทิ ความก้าวหน้าด้านเทคโนโลยีของแต่ละประเทศ ความรู้และความเชี่ยวชาญของบุคลากร รวมถึงต้นทุนของเทคโนโลยีที่ใช้นั้นมีราคาแพง จากปัจจัยต่าง ๆ เหล่านี้ ทำให้แต่ละประเทศมีความสามารถในการเข้าถึงการแพทย์แม่นยำได้แตกต่างกัน นอกจากนี้หลักฐานเชิงประจักษ์ที่เกี่ยวข้องกับนโยบายการเบิกค่าใช้จ่ายในการทดสอบสำหรับการแพทย์แม่นยำนั้นมีอยู่อย่างจำกัด วัตถุประสงค์: เพื่อค้นคว้าและรวบรวม ข้อมูลนโยบายการเบิกค่าใช้จ่ายในการทดสอบสำหรับการแพทย์แม่นยำของแต่ละประเทศ รวมถึงปัจจัยที่อาจส่งผลต่อการตัดสินใจของผู้กำหนดนโยบาย และนำข้อมูลเปรียบเทียบระหว่างกลุ่มประเทศรายได้สูง และกลุ่มประเทศรายได้ปานกลางระดับสูง วิธีวิจัย: การศึกษานี้เป็นการทบทวนวรรณกรรมแบบเจาะจง (Targeted review) โดยรวบรวมข้อมูลจากฐานข้อมูล PubMed MEDLINE Embase และ Cochrane Library และการสืบค้นสารสนเทศด้วยระบบมือ เพื่อหาหลักฐานที่เกี่ยวข้องกับการแพทย์แม่นยำที่ถูกเลือก 13 ชนิด ใน 8 ประเทศ ข้อมูลที่ถูกรวบรวมมาถูกวิเคราะห์โดยวิธีวิเคราะห์เนื้อหา (Content Analysis) ผลการศึกษา: ค่าใช้จ่ายในการทดสอบตัวบ่งชี้ *HER2/neu* และ*BCR-ABL* สามารถเบิกได้ในทุกประเทศที่ทำการศึกษา ขณะที่การทดสอบการกลายพันธุ์ของ *EGFR* ในมะเร็งปอด (*EGFR* mutation) เบิกได้เฉพาะกลุ่มประเทศรายได้สูง การทดสอบตัวบ่งชี้ทางเภสัชพันธุศาสตร์สำหรับการคัดกรองการเกิดอาการไม่พึงประสงค์ที่รุนแรงจากยาพบว่า การทดสอบความผิดปกติของยีน *HLA-B*15:02* และ *HLA-B*57:01* สามารถเบิกค่าใช้จ่ายได้ในกลุ่มประเทศรายได้สูงมากกว่าในกลุ่มประเทศรายได้ปานกลางระดับสูง การทดสอบตัวบ่งชี้เภสัชพันธุศาสตร์เพื่อใช้ในการปรับขนาดยาส่วนใหญ่ไม่สามารถเบิกค่าทดสอบได้ ยกเว้นการทดสอบตัวบ่งชี้ทางเภสัชพันธุศาสตร์ *TPMT* สามารถเบิกได้เป็นส่วนใหญ่ในกลุ่มประเทศรายได้สูง การทดสอบยีนเพื่อทำนายความเสี่ยงในการเกิดโรคมะเร็งนั้นพบว่า กลุ่มประเทศรายได้สูงส่วนใหญ่ครอบคลุมค่าใช้จ่ายในการทดสอบยีน *BRCA1* และ *BRCA2* โดยปัจจัยที่ส่งผลในเชิงบวกต่อการตัดสินใจการเบิกจ่าย ได้แก่ วัตถุประสงค์ในการทดสอบการแพทย์แม่นยำ งบประมาณในการดูแลสุขภาพ ข้อเสนอแนะของหน่วยงานกำกับดูแล ความถี่ของยีนที่พบในกลุ่มเชื้อชาติ และการประเมินความคุ้มค่าทางเศรษฐศาสตร์ ข้อสรุป: การเข้าถึงการแพทย์แม่นยำยังคงมีข้อจำกัดในกลุ่มประเทศรายได้ปานกลางระดับสูงนั้น และควรมีการกำหนดเกณฑ์สำหรับการกำหนดนโยบายในการตัดสินใจเบิกค่าใช้จ่ายในการทดสอบสำหรับการแพทย์แม่นยำ

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
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KEYWORD: precision medicine, reimbursement policy, pharmacogenetic testing, precision medicine test

Nisita Jirawutkornkul : PRECISION MEDICINE REIMBURSEMENT POLICY LANDSCAPE. Advisor: Assoc. Prof. Pol.Lt. PUREE ANANTACHOTI, Ph.D.

Background: Access to precision medicine is limited due to many factors such as precision medicine technology of each country, high-cost technology that requires high finance, limitations on knowledge and competency of personnel and access to precision medicine. Each country manages access to precision medicine differently. The existing evidences of precision medicine reimbursement policy were limited. Objective: To explore reimbursement decision of precision medicine focusing on diagnostic tests and factors associated with reimbursement decision among high-income and upper-middle-income countries. Methods: A targeted review of literatures was conducted through PubMed, MEDLINE, Embase, Cochrane Library, and hand-searching. The study included 13 selected precision medicine and eight selected countries. Content analysis was used. Results: Two precision medicine tests; *HER2/neu* and *BCR-ABL* gene, were reimbursed in all countries, while *EGFR* mutation test was reimbursed in all high-income countries. Among pharmacogenetic tests for severe ADR screening, only *HLA-B*15:02 and HLA-B*57:01* were more likely to reimburse in high-income countries than upper-middle-income countries. Most of pharmacogenetic tests for dose adjustment were not reimbursable, except for *TPMT* gene test which was more likely to get reimbursed among high-income countries. Genetic risk predictors for cancer development, *BRCA1* and *BRCA2* gene test was covered by most high-income countries. Factors positively affected reimbursement decision were purpose of precision medicine test, health care budget, regulatory agency's recommendation, carrier gene frequency in ethnic groups, and economic evaluation. Conclusion: Access to precision medicine is still limited in upper-middle-income countries. Criteria for precision medicine reimbursement decision should be established.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
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Nisita Jirawutkornkul

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CHAPTER I INTRODUCTION

1. BACKGROUND AND RETIONALE

Genetic science has been explored since 1865. The knowledge of human genomics provides basic understanding of the disease prognosis and treatment at the molecular level, especially for genetic disorders (38). A thorough understanding of human genomics is used in the development of medicines to treat diseases as well as development of diagnostic tests that accurately predict diseases (40). Human genomic knowledge is used to tailor treatment choice for individual patients (41-43).

The right drug for the right person'- is the core concept of precision medicine. Precision medicine is sometimes called personalized medicine, individualized medicine, stratified medicine, or P4 medicine. All these terms have similar concept and can be used interchangeably, but each of them has slightly different explanation (45).

Precision medicine focuses not only on the medicine itself, but also on the matched diagnostic test which is equally important. Because the drug or treatment is specific to one particular gene, prescribing decision relies heavily on the screening test results. Research and development of diagnostic tests is frequently conducted in pre-clinical phase with novel drugs (46). All drugs and their matched diagnostic tests are required to be approved by the regulatory agency in respect of safety and efficaciousness (48, 49).

As of December 2017, it was reported that the total numbers of FDA-approved drugs and their biomarkers were 207 and 336 respectively (10). Haematology/oncology was a dominant therapeutic area which accounted for 38% of precision medicine, followed by psychiatry (12%), viral infection (11%), neurological disorder (7%), and cardiovascular disease (6%) consecutively (51). Precision medicine had grown 25% from 2005 to 2016 and continue to grow onward (54, 55).

In this study, the benefits of precision medicine can be classified into three areas. First, precision medicine was used to support decisions to prescribe drug candidates e.g. trastuzumab (Herceptin®) would be prescribed only to patients who

had *HER2/neu* oncogene overexpression (56-59). Second, precision medicine was used to prevent adverse drug reaction and to guide the physicians to select appropriated dose of medicine among patients who had specific gene e.g. prevention of Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) caused by allopurinol (60, 61) and carbamazepine (62-66) in patients with *HLA-B*58:01*, *HLA-B*15:02*, and *HLA-A*31:01* gene expression, and genetic polymorphism in drug metabolism like *TPMT* genetic testing for azathioprine dose adjustment to reduce the risk of bone marrow suppression (68), *UGT1A1* genetic testing in colorectal cancer patient who treated with irinotecan (26, 27), or several cytochrome (CPY) P450 enzymes which related to the drug metabolized including *CPY2C19* and clopidogrel (3, 69), *CYPC29/VKORC1* and warfarin (8, 9), and *CPY2D6* and tamoxifen (11, 71). Third, precision medicine was used to raise awareness among patients who were more prone to develop some diseases e.g. those with *BRCA*1/2 genes mutation are more likely to develop breast cancer or ovarian cancer (72, 73).

Benefits of precision medicine are promising. Many healthcare professionals expect that precision medicine should help reducing healthcare expenditure. However, it was however found that many precision medicines were not covered by many health insurance plans. Many factors were associated to limited health insurance coverage which ranged from inadequate numbers and quality of laboratories, lack of clinical guidelines, proof of cost effectiveness, and budget impact information (74-78).

At present, health insurance systems across countries have well-defined criteria on drug reimbursement and coverage decision. However, most biomarker tests' or diagnostic tests' reimbursement policy was not clearly established. Variations in diagnostic test coverage policy were noted. In the USA, most diagnostic tests were reimbursed if they were part of a medical treatment process. However, some screening tests can be reimbursed only if patients are at risk and met certain criteria (81). In China, diagnostic test utilized under a medical procedure can be reimbursed. Reimbursement rate is regulated at the local level, and thus varies province by province. Mostly, patients had to share cost (83). In Thailand, diagnostic tests which are important parts of

precision medicine are classified as medical devices. Coverage policy of diagnostic tests varies across three public health insurance schemes; Civil Service Medical Benefits Scheme (CSMBS), Social Security Insurance Scheme (SSS) and Universal Coverage Scheme (UC). There were only two previous studies that mentioned about the reimbursement of precision medicine, although these studies were limited in terms of the tests and countries (86, 87).

This study aimed to review health insurance coverage policy regarding precision medicine emphasizing diagnostic tests. Comparative reimbursement decisions of selected precision medicines across some upper-middle-income and high-income countries were also evaluated. The results from this study can provide a comprehensive and extensive review of how different precision medicines were managed under various national health insurance programs across countries. The disclosed current precision medicine reimbursement status would urge the health insurers and healthcare providers to think about adoption of precision medicine holistically.

2. RESEARCH QUESTIONS

1) What was a reimbursement status for each selected precision medicine focusing on the diagnostic tests/biomarkers?
2) What were factors possibly related to reimbursement decisions of precision medicine focusing on the diagnostic tests/biomarkers?

3. OBJECTIVE OF THE STUDY

1) To assess health insurance coverage of precision medicines focusing on the diagnostic tests/biomarkers.
2) To access factors possibly related to precision medicine reimbursement decision.

4. CONCEPTUAL FRAMWORK

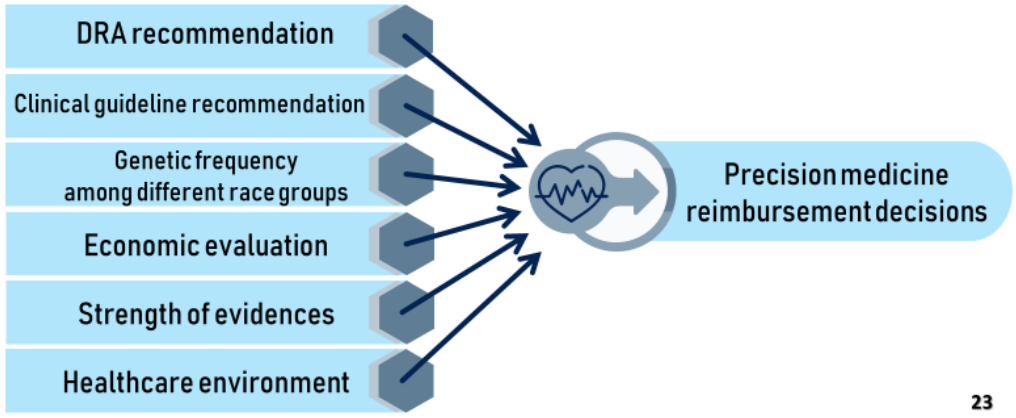


Figure 1 Conceptual framework

5. EXPECTED BENEFITS

The study will provide the factors affecting reimbursement decisions of precision medicines including diagnostic tests/biomarker tests, when manage under various national health insurance systems across countries.

Gap identified will urge the health insurers and healthcare provider to think about how to set up a benefits package for precision medicines which include not only the pharmaceutical products, but the diagnostic test as well.

CHAPTER II LITERATURE REVIEW

This chapter provides a background of precision medicine and an overview of the health insurance coverage policies to review and fully understand the scope and concept of precision medicine.

1. PRECISION MEDICINES

1.1 What is precision medicine?

Although 'one-size-fits-all approach' has long been accepted in the past, Hippocrates also had a distinctive view as he mentioned *"Give different drugs to different patients, for the sweet ones do not benefit everyone, nor do the astringent ones, nor are all the patients able to drink the same things"* (89)

The 'one-size-fits-all approach' has been proved inaccurate in the past few decades (91, 92). The term 'precision medicine' was firstly introduced by Arnold (1990) who described a patient-centred care concept (93). In 2001, precision medicine became more concrete as it helped in diagnosing and prescribing targeted therapy by looking at an individual's patient molecular profile (95). Since then, it has been affecting drug discovery and development process until today. The milestones in precision medicine presented in Figure 2.

Precision medicine was broadly defined by the National Cancer Institute (96) as "A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease." However, there were many different terms used interchangeably to describe this concept *(45, 97)*. Table 1 showed some of the definitions of precision medicine.

Terms	Definition
Personalized medicine (PMC)	“The tailoring of medical treatment to the individual characteristics of each patient.” (99)
Precision medicine (Jameson, J.L., 2015)	“Treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations.” (97)
Individualized medicine (Topol, E.J., 2014)	“Individualized medicine relates not only to medicine that is particularized to a human being but also the future impact of digital technology on individuals driving their health care.” (102)
Stratified medicine (Trusheim et al, 2007)	“Using clinical biomarker and include any diagnostic test to match a preferred treatment with a specific patient.” (103)
P4 medicine (Hood, L., 2008)	“Clinical application of the tools and strategies of systems biology and medicine to quantify wellness and demystify disease for the wellbeing of an individual.” (104)

Table 1 Definition of precision medicine

A systematic literature review in 2013, had included terms such as “individualized medicine” and “personalized medicine” and “precision medicine” as precision medicine. They concluded that 1,025 definitions shared common explanation and meanings (105). The term ‘precision medicine’ largely intercepted with other terms e.g. ‘individualized medicine’, ‘personalized medicine’ and ‘stratified medicine’. Essentially, ‘P4 medicine’ that consists of four words which were predictive, preventive, personalized (or precision) and participatory, and these described the development of systematic medicine to make the whole concept complete and perfect. Although other terms were described as a broad concept, P4 medicine was often referred to as a tool, system, and method of treatment. It could be concluded that precision medicine started with a genetic test. The knowledge about individual’s genetic result would help the doctor to appropriately select drug candidate, follow up patients who may be at risk of adverse drug reaction, or identify higher-risk patients who could develop some diseases.

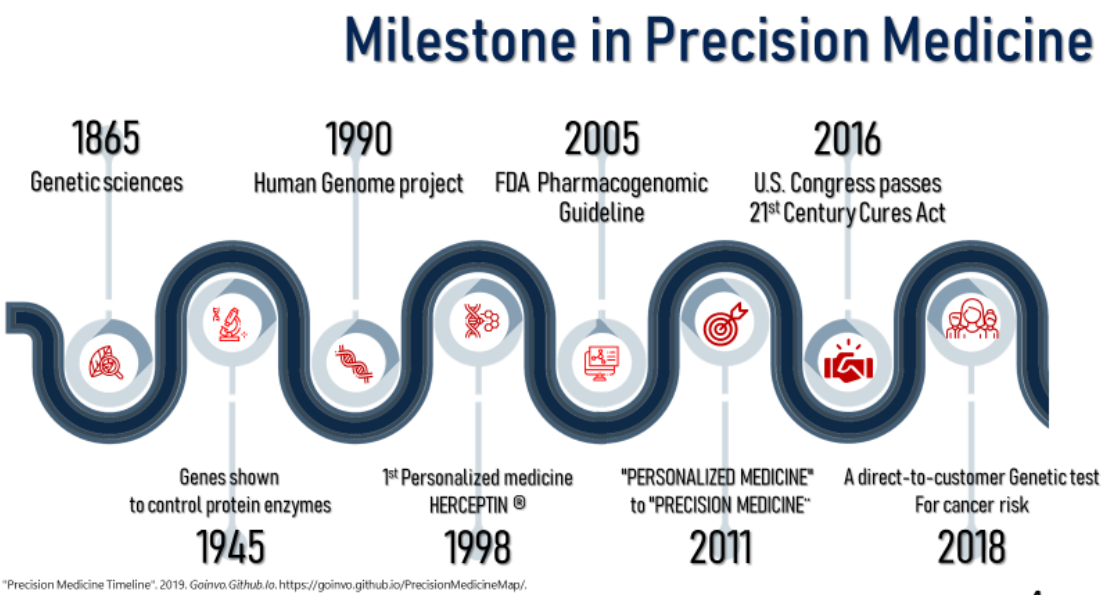


Figure 2 Milestone in precision medicine

1.2 How does the precision medicine work?

Precision medicine shifted '*one-size-fits-all approach*' and '*trial-and-error approach*' to a new paradigm in treatment through the patient's unique genetic profile (106, 107). In brief, *'Improving the optimal treatment and preventing prognosis of the disease by using individual genetic information for each patient'* ultimately described the concept of precision medicine. Genetic testing is an important treatment tool that helps in guiding how physicians manage their patient's treatment plan.

Until 2016, the numbers of matched-precision medicines and genetic testing approved by U.S. FDA accounted for more than 27%. In 2007, the U.S. FDA approved 207 precision medicines matched with 336 biomarkers (Figure 3). These numbers accounted for 42% of the total number of approved drugs and 73% of the total number of all approved cancer drugs. Genetic testing became an important component of precision therapy (109).

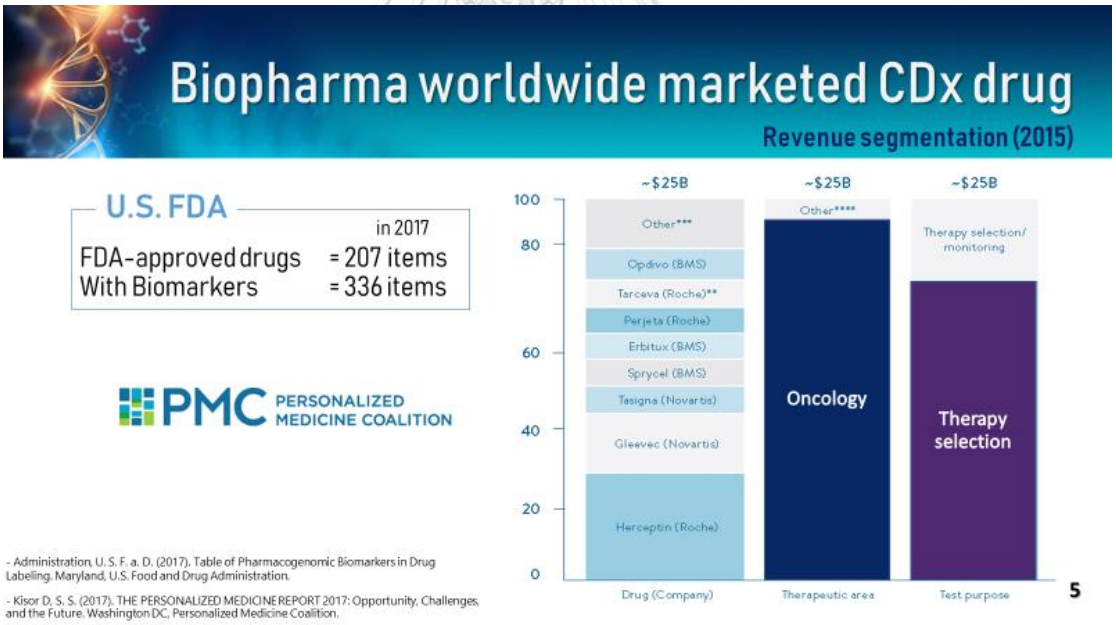


Figure 3 Biopharma worldwide marketed companion diagnostic drugs

Genetic testing method was categorized into three major types. The classification of genetic testing is related to genetic abnormality which is shown below (110, 111).

- *Cytogenetic testing* – This type of testing is used for measuring the whole chromosomes or long length DNA to identify structural chromosome abnormalities. Specimens such as blood, bone marrow, tumor tissue, or many other types of body fluids or tissues are collected. A fluorescent in situ hybridization (FISH) is a common cytogenic technique, which uses a small probe which paints colors of fluorescent dye on a part of a chromosome for localization of a specific DNA sequence abnormality (110).
- *Biochemical testing* – Biochemical testing is a study at the level of proteins, such as regulatory proteins, hormones, enzymes, receptors and transporters etcetera. The gene mutation can result in failure of protein function or genetic disorder. The testing techniques can be done directly in several ways. For example, using a spectrophotometric method for measuring the activity of serum Alkaline Phosphatases, using ELISA for measuring monitor *MAP* kinase activity, and high-performance liquid chromatography (HPLC) for scanning genes for variants, including *BRCA1/2*, alpha-thalassemia (*HBA1/2*), Duchenne–Becker muscular dystrophy (*DMD*), and all coding exons of *TSC1* and *TSC2*.
- *Molecular testing* – Molecular testing measures small DNA mutations or short lengths of DNA to identify gene mutation. The examples of molecular techniques are as follows; polymerase chain reaction-based assays (PCR), hybridization, comparative genomic hybridization (CGH), chromosomal microarray analysis (CMA), and DNA microarray analysis etcetera. A diagnostic test for Alzheimer's disease was also uses the molecular testing with reverse transcriptase-polymerase chain reaction (RT-PCR) for Prostate-specific antigen (PSA) detection (113).

Besides these three types of genetic tests, there were more testing technique classified such as (110).

- *New-born Screening* – In the United States, a blood sample is collected within 48 hours from new-born babies after their birth. The purpose is for preliminary screening of any medical conditions, or to prevent and treat the disease promptly. The examples of diseases or conditions that can detected from new-born screening were:
    - Congenital adrenal hyperplasia (CAH)
    - Congenital hypothyroidism
    - Cystic fibrosis (CF)
    - Galactosemia
    - Maple syrup urine disease (MSUD)
    - Phenylketonuria (PKU)
    - Sickle cell disease
- *Carrier Testing* – This testing normally targets couples who plan to have a baby, especially for a person with recessive genetic disorder. Examples of diseases include the sickle cell anaemia, thalassemia, cystic fibrosis, and Tay-Sachs gene (110).
- *Prenatal Diagnosis Testing* – This testing usually is offered to pregnant women with high risk of birth defects in order to determine the best choice for special management of pregnancy or delivery of the baby (110).
- *Diagnostic/Prognostic Testing* – Genetic testing can be used to diagnose and confirm a disease or rule out a specific genetic condition. Furthermore, the genetic testing is used to monitor the prognosis of the disease including treatment response. The results can be used to select the suitable treatment for an individual (110).
- *Predictive/Predisposition Testing* – The advantage of this test is the detection of gene mutation in a person who has higher risk with family

history of genetic diseases. These tests are useful for early prevention or controlling other factors which may cause the disease development (110).

1.3 Clinical applications of precision medicine

In 2013, Statista, an online statistics portal, reported that precision medicine was frequently found among the following diseases or symptoms; haematology/oncology (38%), psychiatry (17%), infectious disease associated with virus (10%), cardiovascular disease (7%), and others (28%) (116). Furthermore, the Center for Devices and Radiological Health under U.S. FDA presented the list of medical devices which play a role as precision medicine in 2017 (117) and found that precision medicine played a critical role in many therapeutic areas. Thus, this part will demonstrate some interesting therapeutic areas of precision medicine.

1.3.1 Oncology

Cancer is a group of diseases which are associated with an uncontrolled growth of abnormal cells and can spread into any part of body (118). It is recognized as a genetic disease that is caused from gene mutations which are inherited from ancestors (119).

According to the GLOBOCAN 2012 worldwide statistic, approximately 14.1 million people were diagnosed as cancer incidence cases. More than 32 million people live with cancer, and more than 8 million people pass away because of cancers. Over 70% of cancer incidence cases come from low and middle-income countries (118, 120). Three main strategies are recommended to reduce cancer risk. Firstly, health behaviour modification is recommended e.g. smoking cessation, reduction of alcohol consumption and weight management (121). Secondly, cancer screening is recommended in the hope that early detection would lead to curable or progress free survival outcome (122). Finally, timely access to treatments e.g. radiotherapy, surgery, chemotherapy, targeted therapy, and palliative care etcetera, were recommended (109).

Presently, the trends of drug research and development have been shifting to targeted therapy as there are differences between normal cells and cancer cells. These biomarkers are used for diagnosis, prognosis, and epidemiology of cancer. Examples of biomarkers which have been used in cancer management are presented in the Table 2.

Biomarkers/Gene	Disease	Benefits
AFP (alpha-1-fetoprotein)	Liver cancer	Rising AFP levels are associated with liver cancer.
BCR-ABL	Chronic Myeloid Leukemia	Drug candidate for tyrosine kinase inhibitor with BCR-ABL positive (imatinib, nilotinib and dasatinib)
BRCA1 / BRCA2	Breast/Ovarian Cancer	Predict the chance of developing breast/ovarian cancers
BRAF V600E	Melanoma/Colorectal Cancer	Drug candidate for MEK inhibitor (dabrafenib and trametinib)
CA-125	Ovarian Cancer	Predict the chance of developing ovarian cancers
CA19.9	Pancreatic Cancer	A screening test for cancer
CEA	Colorectal Cancer	A screening test for early detection of cancer
EGFR	Non-small-cell lung carcinoma	Drug candidate for EGFR inhibitors (gefitinib, erlotinib, afatinib)
PSA	Prostate Cancer	A screening test for prostate cancer
S100	Melanoma	This is the marker for tumors

		and epidermal differentiation which is used for melanoma screening.
Oncogene GOLPH3	Lung/Ovarian/Breast/Prostate cancer and melanoma	Drug candidate for rapamycin

Adapted from: K. K. Jain (2016) (125)

Table 2 The examples of biomarkers for cancer management.

Between 2000 and 2010, oncology remained an attractive area for the drug discovery and development among pharmaceutical industries, with the number of pharmaceutical products in clinical development more than doubled and expected to increase over 33% in the next five years (127). From 2014 – 2016, U.S.FDA had approved anti-cancer drugs which accounted for 27% of new drugs in that period (109). According to the existing evidences, it could be inferred that cancer treatment pathway will turn into the precision medicine approach.

1.3.2 Infectious disease

Infectious disease could be caused by viruses, bacteria, parasites, or fungi. Worldwide statistics showed that three leading cause of death in 2016 came from lower respiratory infections, diarrheal diseases, and tuberculosis. It was also reported that HIV/AIDS and malaria were other leading causes of death in low-income countries (129). Infection therapy involves individualized therapy based on the genetic difference of the infected agents. The examples of precision medicine which apply in infectious area are provided below.

- For sepsis

The early detection and early proper antibiotics administration are very important for severe sepsis. The molecular diagnostic technique was faster than conventional biomarkers to assess the host's immune status. SeptiFast (Roche Diagnostics) can detect the DNA of 25 different bacterial and fungal species in a few hours.

- HIV causes the disruption of the immune system.

All HIV-infected patients could live longer if they were treated with antiviral therapy. After HIV infection, viruses rapidly increase while the immune system suppresses the viral load. This provided the reason why some patients could control HIV with the first regimen. The element of endogenous retroviral was associated with *HLA-B*57:01* and nearby located *HLA-C* gene. This finding highlighted the importance of genetic variation in humans as the way to combat infectious agents. Furthermore, the pharmacogenomics was used to examine the variation of drug response such as genetic variation in *CYP450* and transport genes or mitochondrial genes and lipid metabolism, e.g. physicians use SensiTrop® test as a HIV Co-receptor tropism which is used to identify patients who will benefit from Selzentry® (Maraviroc). Moreover, the pharmacogenomics screening for *HLA-B*57:01* could be used to predict the hypersensitivity reaction to abacavir, before starting medication.

- For hepatitis C infectious

Treatment regimen of hepatitis C varies according to genotype. Thus, this requires screening to identify the genotype of the hepatitis C strain, so a physician can select the appropriate Direct-acting Antiviral Agents (DAAs) or the older therapies like PegIFN-α combined with ribavirin (RBV) of which the duration of treatment varies by the genotype of the hepatitis C strain.

In addition to the examples mentioned above, precision medicine is also applied to treat tuberculosis, malaria, fungi infection, or vaccine development (125).

1.3.3 Cardiovascular disease

Cardiovascular diseases (CVDs) are among the leading causes of death. More than 17.7 million people died from CVDs in 2015, which accounted for 31% of deaths worldwide (130). Two main risk factors; non-modifiable and modifiable risks, increased chances of developing CVDs. Many modifiable risks such as high level of blood cholesterol and triglycerides, high blood pressure, diabetes, cigarette smoking, excessive alcohol consumption, obesity, and stress, were dependent on patients'

behavior. However, age, gender, and genetic factors were non-modifiable risk factors (131). In 1990, the National Institute of Health (NIH) started a project called the Human Genome Project (HGP). Since then, trends of CVDs drug research and development has been shifted to pharmacogenetics, and genomic predisposition markers. Although, only 7% of cardiologists were taking precision medicines into their clinical treatment in United States, but M.S. Lee and colleagues in their study (2012) believed that precision medicine will certainly have increasing role in treating cardiovascular disease in the future (132).

There were many studies related to the heritable factors. A good example of pharmacogenetics testing, which represents variability of drug efficacy and safety was warfarin and clopidogrel. The *CYP2C9* enzymes metabolize S-warfarin, while the inhibition of vitamin K epoxide reductase complex 1 (*VKORC1*) reduced activation of vitamin K forms. This mechanism caused an anticoagulation effect of warfarin. Thus, the patients who carry either the *CYP2C9*2* or *CYP2C9*3* alleles and *VKORC1*, had higher risk of bleeding compared to those without the specific genes (133). Clopidogrel is metabolized by *CYP2C19* enzymes. Patients who carried one or two reduced-functions of *CYP2C19* alleles had higher risk of ischemic stroke or myocardial infraction (134). Moreover, diagnostic test is used to monitor the rejection of cardiac transplantation (AlloMap®) or to predict the risk of an irregular heartbeat in patients with mutations in three major *LQTS*- susceptibility genes (*KCNQ1, KCNH2,* and *SCN5A*) (135).

There are many examples about using genetic information to support clinical decision-making (132). Table 3 illustrated the example of biomarker or diagnostic tests in CVDs field.

Biomarkers testing	The benefits of PMs	Indications
CYP2C9	Dose adjustment ADR prevention	- Affects the metabolism of warfarin in the liver. - Increases bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles.
VKORC1	Dose adjustment ADR prevention	- Associated with lower dose requirements for warfarin through leading to differential rates of vitamin K recycling
CYP2C19	Drug candidate	- Loss-of-function alleles result in diminished conversion of clopidogrel to its active metabolite. - Increase the risk for major CV events and coronary stent thrombosis.
Familion® 5-gene profile	Drug candidate Genetic predisposition	- Guides prevention and drug selection for patients with inherited cardiac channelopathies such as Long QT Syndrome (LQTS), which can lead to cardiac rhythm abnormalities.
Potassium channel *KCNQ1* and *KCNH2* genes	Genetic predisposition	- Cause long QT1 syndrome and long QT2 syndrome, respectively, with different eliciting factors and treatment recommendations.
Sodium channel *SGN5A* gene	Genetic predisposition	- Lead to long QT3 syndrome, Brugada syndrome, or both through defects in cardiac sodium ion channels.
Protein C or cofactor, protein S deficiencies	Monitor side effect	- Associated with tissue necrosis following warfarin administration.

PhyzioType SINM	ADR prevention Genetic predisposition	- Predicts risk of statin-induced neuromyopathy, based on a patient's combinatorial genotype for 50 genes.
LDLR	Genetic predisposition	- Doses should be individualized according to the recommended goal of therapy, Homozygous Familial hypercholestremia (10-80 mg/day) and Heterozygous (10-20 mg/day).
Factor V Leiden (F5) and prothrombin (F2) genes	Genetic predisposition	- Polymorphisms R506Q and 20210G>A, respectively, in these coagulation factors result in an inherited hypercoagulable state. - Test for factor V Leiden is indicated for venous thrombosis in any individual younger than 50 years or in unusual sites.
9p21 region	Genetic predisposition	- Associate with CAD and MI as well as intracranial and aortic aneurysms.
4q25 region	Genetic predisposition	- Associate with atrial fibrillation.
Corus™ CAD	Diagnosis	- Use it for screening and diagnosing CAD.
TnI, BNP, CRP	Diagnosis Genetic predisposition	- Use it for prognosing ACS.
SLCO 1B1	Genetic predisposition	- Use it for pharmacogenomics clinical decision on statins drug or dose.
Platelet aggregation assay, Paraoxonase I (*PONI*) genotype	Dose adjustment Drug candidate	- Use it for aspirin dose, clopidogrel dose, or need for combination antiplatelet therapy.

Bradykinin type I (*BKI*) receptor Haplotype, Angiotensin II type I receptor haplotype	Genetic predisposition	- Use it for treatment benefit of angiotensin converting enzyme (ACE) inhibitor.
Apolipoprotein A5 (*ApoA5*) genotype	Genetic predisposition	- Use if for benefit of fenofibrate.
Niemann-Pick Cl Like I (*NPCILI*) haplotype	Genetic predisposition	- Use it for benefit of ezetimibe.
KIF6 Gene	Genetic predisposition	- Use it for greater benefit from Statins.
AlloMap® gene profile	Monitor graft reject	- Use it for monitoring transplant rejection.

Adapted from: Lee, M.-S., et al. (2012) (132)

Table 3 The example of biomarker or diagnostic tests in CVDs

1.3.4 Pharmacogenomics and adverse drug reaction (ADR)

Adverse drug reaction (ADR) is the undesirable symptom which occurs from medicines and is a common cause of illness and death. Approximately 17 % of all patients who took medication have ADRs, and 3.5% of hospitalizations were caused by ADRs. (136) ADRs were divided into two types which were;

Type A reactions - are the dose-dependent from the pharmacology of the medicine which is predictable ADR. Severity of symptoms depend on an individual, so that a patient with ADR type A has high morbidity but low mortality. The cytochrome P450 enzymes play an important role in molecular mechanisms of drug metabolism. For example, the genetic variation influences the ability of drugs degradation. The levels of

CPY450 enzymes will directly affect the level of drugs metabolites and clinical response. The variation of *CYP2C9* polymorphism has an effect on the degradation of the warfarin. Furthermore, clopidogrel is converted to the active metabolite by *CYP2C19*, the genetic variation of *CYP2C19* affect the level of active metabolite.

Type B reactions - are unpredictable and idiosyncratic reactions which rarely occur during the clinical trial. Therefore, the prevalence of type B reactions were low morbidity and high mortality. The genetic variation may have an effect on type B reaction (137). A previous study showed that human leukocyte antigens' (*HLA*) alleles genetic associations with medication. The example of *HLA* alleles, which are associated with drug induced hypersensitivity reactions, are *HLA-B*15:02* associated with carbamazepine induced SJS/TEN(138-141), *HLA-B*58:01* associated with allopurinol induced SJS/TEN (19, 60, 61, 142), *HLA-A*31:01* with carbamazepine induced SJS/TEN/DRESS (143, 144), and *HLA-B*57:01* associated with abacavir induced hypersensitivity reaction (18, 145-148).

1.4 Benefits of precision medicine

According to type of testing, genetic testing is a part of precision medicine, that is leading to the tailoring of medical treatment for each patient. Moreover, the potential benefits of precision medicine are evident from recent researches and clinical practices. They can be summarized as follows:

- *From reaction to prevention on therapeutics trends.*

From many past pieces of research, they found that women who have *BRCA1* and *BRCA2* gene mutations, have increased risk of breast and ovarian cancer. Therefore, the National Cancer Institute for women who are at risk, offers *BRCA* gene testing. For example, women who have ancestors with breast or ovarian cancer may be at risk. If the test result is positive, it does not mean that they will be cancer in the future, but they have inherited a harmful *BRCA1* or *BRCA2* gene mutation and have a chance to pass this gene mutation to their children. Women with a harmful *BRCA1* or *BRCA2* gene mutation should consult a doctor to monitor and manage cancer risk such as they

should have a mammogram every year instead of every 2 years or get a clinical breast examination to detect an early stage of breast cancer. (17, 126, 149)

- *Treatment guidelines change from 'trial-and-error' to 'targeted therapy'.*

The mechanism of targeted therapy is involved with drugs or biological substances which bind to specific molecules that can block the growth and spread pathway of cancer. These molecular targets and proteins are found in cancer cells or in cells related to cancer growth, like blood vessel cells. The well-known example is trastuzumab which binds to the segment of human epidermal growth factor receptor 2 protein (*HER2*) which is overexpressed in breast cancer cells to inhibit cancer cell proliferation. Therefore, the result of *HER2* gene have to report as positive, before prescribing trastuzumab as monotherapy or combined with the other drugs (56, 57, 150).

- *Adverse drug events are prevented by genetic screening.*

A result of previous systematic review shown that 5.3% of hospital admissions were related with adverse drug reactions (ADRs), and some ADRs are caused by genetic variations, so for example screening patients at risk of drug-induced SCARs such as *HLA-B*15:02* which is a screening marker for carbamazepine-induced SJS/TEN in Han Chinese. For example, a patient carrying *CYP2C9*2/*3* gene and *VKORC1* allele, which affect the anticoagulant efficacy of warfarin, might experience serious side effects bleeding complication. Therefore, the result of genetic testing can be used to adjust the dose of warfarin (8, 151). There have been many studies involving the *TPMT* gene testing before starting azathioprine, and the result indicated that type of *TPMT* gene can lead to select the right dose of azathioprine to reduce the risk of myelosuppression (24, 25, 68, 152).

- *Specification on individual drug candidate*

For cancer, the previous studies identified that patients who have been diagnosed with non-small cell lung cancer (NSCLC) should receive the epidermal growth factor receptor (*EGFR*) mutation test because *EGFR* is a tyrosine kinase receptor, which highly expresses in carcinoma cell. This result will be used to select the

appropriate therapy with tyrosine kinase inhibitors (TKIs) such as gefitinib or erlotinib (6, 153). Furthermore, patients who were diagnosed with breast cancer, also received the human epidermal growth factor receptor 2 (*HER2*) testing to determine their *HER2* status then Trastuzumab can be used in *HER2*-positive patients (31). This study recruited another type of cancer which is chronic myeloid leukaemia (CML) to represent hematologic cancer. Types of targeted therapy for CML is TKI which will block the kinase protein inside leukemia cells such as imatinib nilotinib or dasatinib. In CML patients have expression of the abnormality of *BCR-ABL* gene, so the *BCR-ABL* gene must be screened prior the TKIs initiation (4, 5). Many studies and guideline recommendations state that targeted cancer therapy has improved disease free survival and overall survival in cancer patients (4, 5, 154, 155).

- *Increase Patient Adherence*

Some biomarkers can be used to predict risk of disease which can be developed in the future. The results of a genetic predisposition testing may increase patient awareness to make lifestyle changes such as *KIF6* genotyping testing, This biomarker has been reported to be a potential risk factor for coronary artery disease and also used to predict responsiveness of statins therapy, which may improve a patient's medication adherence (132, 156).

- *Decrease or avoid high-risk invasive testing procedures*

Recent studies suggested molecular testing which a non-invasive blood test. It can be used to detect disease complications such as endomyocardial biopsy is a medical procedure that is used for detecting graft rejection in heart transplant patients. However, the physicians can use Heartsbreath test, which is a non-invasive blood test, instead to identify the risk of acute cellular rejection in patients who have had a heart transplant within the last year and an endomyocardial biopsy within the prior month. This genetic test can reduce the patients' anxiety and pain (157).

1.5 The purpose of precision medicine testing

The findings of this literature could indicate the purpose of genetic testing in precision medicine in three categories in which this study was interested, which were

1.5.1 Targeted cancer therapies

Targeted cancer therapy was called "molecularly targeted drugs" which block of specific molecules or biomarkers that are involved in growth and spread of cancer cells. The patient had to get genetic testing, and the result would guide the treatment.

1.5.2 Pharmacogenetics testing

Pharmacogenetics testing can be dived into two groups which are 1) the prevention of adverse drug reaction (this test was screening the *HLA* alleles for screening chance of severe cutaneous adverse drug reaction; SCARs) and 2) dose adjustment and monitor side effects (which is performed in drug metabolized enzymes to monitor and adjust the dose of the drug).

1.5.3 Genetic risk predictors for determining the development of disease

BRCA1 and *BRCA2* genes have very strong relationship with chance of breast and ovarian cancer development. The women who had high risk of *BRCA1* and *BRAC2* mutation are those aged 50 years and diagnosed with breast cancer, and those who have family history of diagnosis with cancer. The result of *BRCA* gene mutation test gave various results, for example, positive result which indicated that people had higher risk of developing cancer, negative result which was difficult to interpret because the result might depend on the family history and *BRCA1* and *BRCA2* mutation related with their blood or not, or uncertain result, in which it was not known if the genetic change was harmful.

1.6 The history, current status, and future trends of precision medicine

Precision medicine has become the new option for medical treatment. In drug discovery phase, researchers will design a product to stop or turn the progress of disease back. Many researchers potentially develop a medicine, even target medical products which are specific to the genetics. Then in the development phase, researchers conduct the experiments to gather the basic information such as medical

pharmacokinetics and pharmacodynamics, mechanism of action, unintended effect or side effect, drug interaction, and efficacy compared to the other drugs etcetera. After in vitro, the experiments will move to in vivo experiments which are conducted for the effect occurring on the organism, in both animals and humans (158). The discovery and development of the drug starts from the compound which is developed into a pharmaceutical product. In the last decade, the usage of precision medicine has been increasing, and the way of drug research and development has changed to a basic understanding of pathology at the molecular level.

Since early 1960s, the core concept of precision medicine has been mentioned. Then the term 'precision medicine' was used for the first time in a publication in 1999 (159).

In 1995, DNA microarrays, called biochips, were developed for measuring the level of gene expression by hybrid two strands of DNA then labelling with fluorescent probe at specific target sequences and measuring the intensity of fluorescence signal. DNA microarrays allow the researchers to conduct SNP genotyping efficiently for the development of protein-based diagnostics (160).

In 1998, Dr. Axel Ulirich and Dr. Dennis Slamon discovered and developed the first companion diagnostic test. Herceptin® (trastuzumab) was approved by the U.S.FDA and launched into the market. It a monoclonal antibody which is used for treatment of breast cancer which is *HER2/neu* receptor positive (56, 161). This was the beginning of new paradigm treatment which demonstrated an adoption of pharmacogenomic intervention rapidly and successfully.

Examples of application of precision medicine in clinical practice

These examples present the precision medicine which potentially influences the real-world practice.

- **Abacavir** (ABC) is a nucleoside analogue which is used to prevent and treat patients with HIV/AIDS by inhibiting reverse transcriptase that terminates the DNA polymerization process. In 2002, the study of S. Mallal (146) and S. Hetherington (162) found that patients carrying *HLA-B*57:01* gene have

higher chance of a development of hypersensitivity reaction to abacavir. All patients who carry this gene must discontinue ABC immediately. Later, U.S. FDA approved drug label which recommended screening *HLA-B*57:01* allele before starting abacavir in July 2008 (163).

- **Warfarin** is an oral anticoagulant, used to treat many diseases related to blood clot such as atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism, and prevent stroke in patients with some conditions. The common ADR is bleeding. Efficacy of warfarin can be measured by monitoring INR. According to the study of G.P. Aithal, the result presented that those who carry *CYP2C9*2* and *CYP2C9*3* potentially have more chance of bleeding complications (133, 151). This study illustrated that patient's genetic profile can protect the ADR.
- In addition to preventing potential ADR, the genetic profile may also help in predicting the development of disease. For example, the genetic inheritance such as women with *BRCA1* and *BRCA2* mutation have higher risk of ovarian and breast cancer development. The recent studies also showed that older women are at higher risk than younger (72, 73, 164). Although, the result of *BRCA* mutation test is negative, it does not mean that the patient has no chance of breast cancer or ovarian cancer. This result just lets the patient know that risk of cancer cannot be detected by this test (149).

In 2014, 42% of total number of U.S. FDA-approved medicines and 73% of medicines in oncology are precision medicines. Moreover, the proportion of precision medicine which has been approved by U.S.FDA, has increased up to 25% since 2005-2016 (165). This statistic is compiled annually by an independent organization called the Precision Medicine Coalition (PMC). The PMC is the combination of public and private sectors of the United States.

The promising areas of precision medicine with six major benefits include screening, diagnosis, monitoring, prognosis, predisposition, and pharmacogenomics, in order to increase efficacy of treatment and reduce the number of failed treatments (95).

After this, the precision medicine and pharmacogenomics testing techniques will be researched and developed substantially with an increasing rate in the future.

1.7 Barriers of precision medicine implementation

Over the last several years, it has been recognized that there were a variety of human responses to treatment and all medical treatments are not equally effective as well as beneficial to all patients. How does precision medicine work? – Biomarkers are used to assist diagnosis, while the targeted therapy is derived from the patient's genetic profile. The basic knowledge of disease at the molecular level is transformed to pharmaceutical development (95). It can be seen that the development of tools for genetic testing did not occur along with the development of the drugs. Although the precision medicine must be used with biomarkers by the mechanism of action, it has not been clearly specified through genetic testing method that it should be applied.

Many evidences have revealed that the precision medicine can optimize the treatment to achieve the best results. It also minimizes ADR risks for drugs use or can predict the chances of developing disease in the future. Whereas, how the patients will access to the precision medicine is another story. Not only the financial factor, but also many other factors, whether safety and efficacy information, economic evaluation profiles, the technological capabilities in each country, and the knowledge and understanding of healthcare providers. Those are only part of the problem why accessing to precision medicine is limited.

In consideration of the healthcare services payment system, the reimbursement for medical services is separately considered from pharmaceutical services in many countries. For example, United States Medicare also provides part D for covering prescription drugs (166). China healthcare system has the National Reimbursement Drug List (NRDL) for prescription reimbursement standard (167-169), and Australia, pharmaceutical services are subsidized by Pharmaceutical Benefits Scheme (PBS) (170). The genetic testing, which is used to identify biomarkers, is often included within some part of medical services for reimbursement.

Genetic testing was focused on real clinical practice. Access to genetic testing has difficultly to decide who is willing to pay more to find a genetic profile (171). The genetic testing proposes only a diagnosis but not a treatment. Although, the result of genetic testing is negative, that does not mean that there is no chance of the disease development. In the laboratory there is the possibility that random or systematic errors can occur, even with very few occurrences (172, 173).

For patient perspective, the genetic testing is interesting to predict genetic predisposition for cancer, but there still needs more counselling and information to increase the attitude and motivation (174). The patients are worried about genetic testing coverage from health insurance system (175). Genetic testing for screening, prevention, and counselling services are mostly excluded from health insurance coverage or patients can pay higher premiums for these. However, some genetic testing might affect medical treatment, if a test might not be reimbursed, so the patients may have to pay out-of-pocket for genetic diagnosis. There also needs more evidence to support whether genetic testing is necessary for diagnosis and medical treatment (171).

The number of licensed laboratories maybe the problem for some countries, especially low-income countries. The licensed laboratories must be certified with the standard and quality assurance to ensure that test results are accurate. An incorrect test result will cause the patient to be at risk for not receiving the necessary therapy or facing with life threatening consequences (176).

Nowadays, most genetic testing is proposed by physicians. The patient's understanding and decision-making process are usually based on the knowledge and information provided as a basis. Whereas, direct-to consumer (DTC) genetic testing is less implemented in practice. The issues of ethical and regulatory concerns are raised to discuss (177). The major issues are all about patient's privacy and genetic discrimination. The potential risks include delivering results with insecurity to a physician or providing confusing information that may cause making a wrong decision with medical treatment, maybe get unnecessary medical procedures, and psychological

distress (177, 178). However, it is unclear what are the exact causes of the ethical issues that requires further discussion.

Moreover, healthcare expenditure is one of the major problems globally and there are many recent articles which have discussed how precision medicine may help to control the long-term healthcare expenditure.

2. HEALTH INSURANCE SYSTEMS

This part provides a brief overview of health insurance systems focusing on public sector in eight countries. The World Bank classifies countries into four income groupings by using gross national income (GNI) per capita (in U.S. dollars). These include low-, lower-middle-, upper-middle-, and high-income economies (179). In 2018, the definition of income groupings are as follows:

1) Low-income economies; GNI per capita is $1,025 or less
2) Lower-middle-income economies; GNI per capita between $1,026 and $3,995
3) Upper middle-income economies; GNI per capita between $3,996 and $12,375
4) High-income economies are those with a GNI per capita is $12,376 or more

Five countries which are Australia, Canada, Singapore, United Kingdom, and United States, are defined as high-income economy countries. The upper-middle-income economy countries include China, Malaysia, and Thailand. These are selected to compare in this study.

2.1 High-income country

2.1.1 Australia

Australia is the 6th largest country in the world, located in the geographical region of Oceania. It has GNI per capita (by purchasing power parity; PPP) with a value of $49,980 in 2018 (180). In Australia, each inhabitant of Australia is covered by a universal health insurance. Medicare is funded by federal government. They provide free access to healthcare services for all Australian citizens, and permanent residents including Norfolk Island and New Zealand citizens. Healthcare services are subsidized through the Medicare Benefits Scheme (MBS) while pharmaceutical services are

subsidized by Pharmaceutical Benefits Scheme (PBS). The data from World Health Organization Global Health Expenditure database also showed that the health expenditure per capita in 2016 was 5,002.36 U.S. dollars (181).

The MBS provides primary care, hospital care, and medical services in public hospital and the medication which is approved for cost-effectiveness by the independent Pharmaceutical Benefits Advisory Committee (PBAC) can be subsidized through the PBS with patients taking responsibility for some co-payment before safety net.

Since January 1, 2019, general patients have paid approximately 40.30 U.S. dollars and 6.5 U.S. dollars for concessional patients for PBS prescriptions while the Safety Net thresholds is 1,550.70 U.S. dollars (for general patients) and 390.00 U.S. dollars (for concessional patients). Any additional medication expenditures after the Safety Net thresholds shall become the responsibility of the government (182).

2.1.2 Canada

Canada is the second largest country by total area in the world after Russia, which covers an area of 9.98 million square kilometres. Canada has a capital named Ottawa and is a federal state composed of thirteen provinces and three territories. The health care system in Canada is publicly funded by federal, provincial and territorial tax revenue. Canadian people know their healthcare system under the name Medicare(183). Referring to the 2016 Health Expenditure database of WHO, Canada's health expenditure was 4,458.21 U.S. dollars per capita, which is ranked 13th in the world (181). Most healthcare services are covered including all necessary basic care such as basic medications, maternity, basic emergency services, mental health care, palliative care and end-of-life care and rehabilitation (184). Each province is covered by different health insurance programs. For example, Alberta has The Alberta Adult Health Benefit program which covers pregnancy with low income, those who have high ongoing prescription drug needs and teenagers aged 18-19 years old. However, Albertans who already have the other government health programs, will not be able to

participate in this program. Ontario has the Ontario's health care plan (OHIP) which pays for basic healthcare needs like full coverage for doctors services, hospital visits and dental surgery stays in hospital setting, eye-health services (covers eye examination once a year for children and elderly), foot-health-services and ambulance services. However, OHIP may not cover prescription drugs which are not provided by hospital setting, dental services which are provided by dental clinic or cosmetic surgery. Moreover, Ontario has OHIP plus to provide the drugs.

In 2011, 70.5% of total health expenditure came from taxation, 14.7% from out-of-pocket payment, and 12.8% from private insurance (185) There are no caps on out-of-pocket payment.

2.1.3 Singapore

The Republic of Singapore is a city-state in Southeast Asia. The territory of Singapore consists of one main island and 62 islets. Singapore has a total area of 725.1 square kilometres, with 5.63 million population (186). It has GNI with a value of $339,548.34 in 2018 (187). In 2016, the total health expenditure was 4.6 % of GDP, and the public health expenditure was 39.8% of total health expenditure (188).

Singapore has a philosophy of healthcare system with three pillars. The first, creates healthy population with preventative health care and promotes a healthy lifestyle. The second, health care is a personal responsibility. The last, the government can control the supply of healthcare services and provide some subsidies in public sector. (189) Thus, the Singapore's healthcare system consisted of 3M plus E, including MediSave, MediShield and Medifund, plus ElderShield. The details of 3M plus E are shown in Table 4 below.

CPF	Eligibility	How to get	Benefits
MediSave	An individual's Central Provident Fund account for Singaporean employees and permanent residents	7-9% of salary	Subsidized for basic healthcare needs.
MediShield	- Singaporean with Medisave account	paid from your Medisave account	Premium for OPD-IPD service, surgery, and medicines
Medifund	Difficulties paying for your healthcare bills after Government subsidies	The endowment fund set up by the Government	Hospitalization expenses and OPD services after Medisave and MediShield.
ElderShield	Have Medisave account when reach the age of 40	Automatically enrolled when reach the age of 40	There are no exclusions of existing illnesses at the time.

Reference: Government of Singapore (190)

Table 4 Characteristics of 3Ms – Singapore's Healthcare system

2.1.4 United Kingdom

The United Kingdom, known in full as, The United Kingdom of Great Britain and Northern Ireland, is located off the northwest coast of Europe. Great Britain comprises three countries which are England, Scotland and Wales. The population of the United Kingdom is estimated at 66.44 million people (191). The United Kingdom is a high-income country and the sixth-largest economy of the world. It has GNI per capita with a value of $41,680 in 2014 (22).

The United Kingdom offers public healthcare for all permanent residents. The National Health Service (NHS) is a publicly funded national healthcare system in United Kingdom which is supported by the government. The public health services are independently managed by its own government under the name of National Health Service in England, NHS Scotland, NHS Wales, and Health and Social Care in Northern Ireland (192).

Source of healthcare funding includes 81% of general taxation, 18% of National Insurance Contributions (NICs) and out-of-pocket payments. In 2006, 2009, 2010, 2011, and 2014, trends of total healthcare expenditure were increased by 6.0%, 9.3%, 8.8%, 9.5% and 9.9% of GDP, respectively.

The NHS in UK provides many benefits including preventive services, hospital services for in- and out-patients, medication prescribed by public hospital, mental health care, palliative care, home visits, and rehabilitation, but these funds do not cover for some prescriptions, optical services and non-necessary dental services (192).

Patients are required to pay for these healthcare costs including prescriptions, dental care, eye care, and wigs and fabric supports. In contrast, the NHS provides Prescription Prepayment Certificates (PPC) to save money. According to the NHS statistics in 2017, patients have to pay 11.70 U.S. dollars per item for current prescription charge. If patient needs medicine more than 3 prescribed items for 3 months or more than 12 prescribed items per 12 months, they will require to pay 38.70 and 138.30 U.S. dollars for three-month PPC and 12-month PPC, respectively (193).

2.1.5 United States

The United States of America comprises 50 States and located in the central part of North America. It is the fourth largest country in the world, after Russia, Canada, and China. The US Capitol is Washington DC. It has GNI per capita with a value of $60,200 in 2018 (187).

In the United States, federal government do not provide universal healthcare coverage for all citizens. The U.S. health insurance system is based on employment, mainly in the private sector, which is more than a half of American people. The public healthcare insurance system is provided by the federal government through Medicare and Medicaid. These are managed by the Centers for Medicare and Medicaid Services (CMS) and are under the Department of Health and Human Services (166).

Medicare is provided for Americans who are over 65 years old, certain young people with disabilities, and End-Stage Renal Disease (ESRD) patients with kidney transplant or dialysis. Furthermore, Medicare is divided into 4 parts which cover specific services.

- **Medicare part A** is a hospital insurance that covers for in-patient services, care with skilled nursing facilities and some home health care.
- **Medicare part B** is a medical insurance that covers certain doctors' services, out-patient care, medical supplies, and preventive care services.
- **Medicare part C** is an additional insurance plan for part A and part B called Medicare Advantage Plans which is offered by contracted private company with Medicare. The patients can pay a premium for voluntary enrolment in this part. The additional benefits provide coverage for vision care, hearing care, dental care, and, most of plans also provide prescription drug coverage.
- **Medicare part D** is prescription drug coverage, an additional coverage to Original Medicare, some Medicare Cost Plans, some Medicare Private-Fee-for-Service Plans and Medicare Medical Savings Account Plans because they do not cover for the medicine received outside hospital (194).

Medicaid is a joint policy between state and federal government which offers the benefits for low income person, defined by statute which are children whose parents are below a certain wage, pregnant women, seniors and disabled people. The definition varies from state to state, although Medicaid covers broader healthcare services than Medicare.

Another healthcare system in United States is Veterans Health Administration (VHA). VHA is operated by the U.S. Department of Veterans Affairs. These provide healthcare services for 6 million military veterans through 153 hospitals medical centers and almost 1,000 ambulatory clinics across the country (166, 195)

The U.S. healthcare insurance covers approximately 84 percent of population, which can be broken down to private insurance (54%) Medicare (12%), Medicaid (16%), VHA (1%), and uninsured (16%). In March 2010, Affordable Care Act or “Obamacare” was signed by President Obama, to enact legislation which covers health insurance for almost everyone. As a result, all Americans can access to a good-quality health insurance and affordable coverage. They should have the right to select the healthcare coverage which meets their unique needs.

2.2 Upper-middle-income country

2.2.1 China

China, known in full as, the People's Republic of China (PRC) is the most populous country with nearly 1.4 billion residents. located in the geographical region of East Asia. It has GNI per capita with a value of $18,140 in 2018 (187).

Healthcare reform was introduced in 2009. The central government of the People's Republic of China provides basic healthcare services for their citizens under three basic medical insurance schemes, which include:

1. **Urban Employee Basic Medical Insurance Scheme (UEBMI)**

This benefits scheme covers employees and retirees in urban areas. This scheme covers about 98.7 percent of China's population. Most premiums are mainly financed by taxation (from 2 percent of employees and 6 percent of employers) and individual medical savings accounts including government funding. A report by E. Deiaco (2013), showed that UEMBI expenditure was 85.02 billion U.S. dollars.

2. **Urban Resident Basic Medical Insurance Scheme (URBMI)**

Funding for URBMI mainly comes from the government. Unemployed residents including students in urban areas are covered under this scheme. The total healthcare expenditures accounted for 8.30 billion U.S. dollars in 2011. The UEBMI and URBMI are both working under the management of the Ministry of Human Resource and Social Security (MOHRSS).

3. **New Rural Cooperative Medical System (NRCMS)**

Residents in rural areas were enrolled in the NRCMS as families, which is also a subsidized voluntary health insurance scheme. RCMS is managed by the administration of National Health and Family Planning Commission (NHFPC). These three-health insurance schemes provide funds for in-patient and out-patient services. Cost-sharing is used in all these basic health insurance schemes by deductible, co-payment and the coverage ceiling. For medical expense, there are two major reimbursements lists which called National Reimbursement Drug List (NRDL) and Essential Drug List (EDL). The NRDL, an older and larger reimbursement list, was created in 2000 which is managed by the Ministry of Human Resources and Social Security. In 2009, an updated version of

NRDL claimed that they it comprised 1,140 western medicines and 987 traditional medications. The EDL has been supporting the purpose of healthcare reform since 2009 and is managed by the NHFPC. From 2009, 307 medicine items in EDL (205 western medicines and 102 traditional medicines) has increased to 520 medical items (317 western medicines and 203 traditional medicines) in 2012 (168). However, the medical prescription is not on the NRDL and EDL must be paid for out-of-pocket payment. In 2011, the total health expenditure was 279.7 U.S. dollars of GDP per capita (167).

2.2.2 Malaysia

Malaysia is located in Southeast Asia, and consists of two parts which are Peninsular Malaysia (west) and East Malaysia (East). Malaysian people are separated into four major races 53% of Malay-born bumiputras (called Malay), 10% of Borneo Earths, 27% of Chinese and 10% of Indians. Referring to the statistical data of Malaysia, the life year expectancy has increased from 2011 to 2017, 72.1 years to 72.7 years for male and 76.8 years to 77.4 years for woman, respectively. From this can be seen that Malaysian people live slightly longer.

Since 1970s, Malaysia has been operating a two-tier health care system, including a tax-funded and government-run universal services and a fast-growing private sector (196). The Ministry of Health takes responsibility for central management. The proportions of the public and private sectors are shown in Table 5 below.

	In-patient services	Ambulatory services
The public sector	82%	35%
The private sector	18%	62%

Reference: The World Bank Group, 2010 (197)

Table 5 The proportions of the public and private healthcare sectors in Malaysia

For healthcare services, it includes health promotion, disease prevention, curative and rehabilitative care delivered through clinics and hospitals. Source of financing mainly comes from the Ministry of Health (MOH) which accounts for 82.4

percent of total public health expenditure. Goods and services fees are subsidized or with some minor co-payments in the public sector. However, Malaysia residents also have to pay with out-of-pocket payment which has been raised up to 2,650 million U.S. dollars for the private sector in 2009. These examples of public healthcare service charges are set by the government and is shown in Table 6. The total health expenditure of Malaysia was 5.5 million U.S. dollars in 2015 (198).

	Malaysian citizens RM (U.S. dollars)	Non-citizens RM (U.S. dollars)
General out-patient services	RM 1 (0.30)	RM 5 (1.50)
Specialist consultation	RM 15 (4.50)	RM 60 (18.00)

Reference: Jaafar, and et. Al., 2013 (196)

Table 6 The public healthcare service charges in Malaysia

2.2.3 Thailand

Thailand is a country located in Southeast Asian, and covers 514,000 square kilometres which comprises of 77 provinces. The Thai population is estimated at 69 million people. Life expectancy at birth was 77.74 years (199). Percentage of total health expenditure was 4.1 of GDP in 2014 (200).

The population of Thailand are cover under three public health insurance schemes including Civil Servant Medical Benefit Scheme (CSMBS), Social Security Insurance Scheme (SSS) and Universal Coverage Scheme (UC). The differences of each health insurance scheme is shown in Table 7 below.

Health insurance schemes	CSMBS		SSS	UC
Types of populations	- Government employees and their dependents (including spouses, three children under 20 years and parents) - Pensioners (9%)		Private sector employees (16%)	The rest of the population (75%)
Organization	The Ministry of Finance Comptroller General Department		The Social Security Office of the Ministry of Labour	National Health Security Office (NHSO)
Source of financing	General tax, non-contributory scheme		Consisting of three parts from employee, employer and the government	General tax
Method of payment	Services		Services	
	out-patient	in-patient	out-patient	in-patient
	Fee for service	DRG	Capitation	global budget plus DRG
Health service utilization	The public hospital		A registered contractor hospital	A contracting unit of primary care (CUP) both public and private
Pharmaceutical services	Essential drugs (ED) and non-essential drugs (NED) with approval by three doctors		only ED	only ED

List of abbreviation: CSMBS; Civil Servant Medical Benefit Scheme, SSS; Social Security Insurance Scheme, UC; Universal Coverage Scheme, DRG; Diagnosis-related group

Adapted from: Health Systems in Transition Vol. 5 No.5 2015 (201)

Table 7 Characteristics of three public health insurance schemes in Thailand

In 2012, the total health expenditure of Thailand was 15.57 billion U.S. dollars (202). All health insurance schemes cover, are different with certain conditions, for hospital services (in- and out-patient), delivery services, pharmaceutical services, renal replacement therapy, organ transplantation, antiretroviral therapy for HIV/AIDS, Organ transplantation and medical devices.

CHAPTER III METHODOLOGY

This descriptive-comparative study intended to discover the health insurance coverage policy and implementation of precision medicine especially the diagnostic tests which have never been disclosed elsewhere. Targeted review was used to answer the research questions by using selected precision medicine and selected countries as a scope of searching. (Figure 4)

Based on studies from Meckley L.M. (86) and Chong H.Y. (87), six factors were used as a framework to describe precision medicine reimbursement decisions. The six primary factors included; national drug regulatory authority recommendations, clinical guideline recommendations, carrier gene frequency among ethnic groups, economic evaluation evidence, strength of evidences, and healthcare environment.

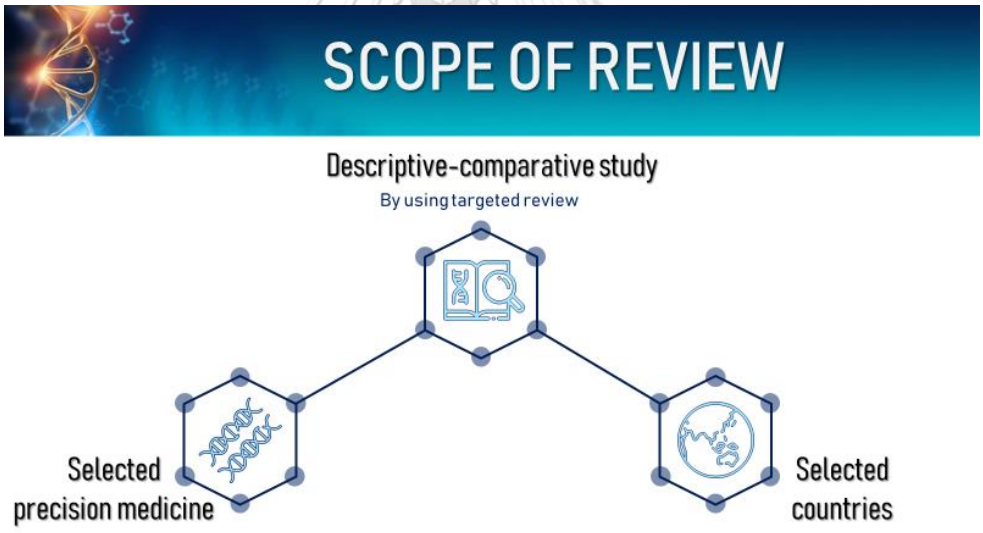


Figure 4 Research methodology

1. SELECTION VARIABLES AND SEARCH STRATEGY

1.1 Precision medicine selections

Thirteen precision medicines with their biomarkers were selected based on purpose of precision medicine, variety of therapeutic areas, high global incidence and high severity of illness. Moreover, the precision medicine tests might available in Thailand. The general information of precision medicine tests was provided in Appendix. Details of selected precision medicines are show in Table 8 below.

Precision medicine tests	Drug	Therapeutic areas	Incidences or reason supported selections
1. Targeted cancer therapies			
HER2/neu gene	Trastuzumab	Breast cancer	5.03 for breast cancer (203)*
BCR-ABL gene	Nilotinib	Chronic myeloid Leukaemia	5.2 for leukaemia (203)*
EGFR gene	Gefitinib	Lung cancer	22.5 for lung cancer (203)*
2. Pharmacogenetics testing			
2.1) Genotyping of HLA alleles predisposition for screening patients at risk of drug-induced SCARs			
*HLA-B*15:02*	Carbamazepine	Epilepsy, Mania/Bipolar Disorder, neuropathic pain	564 cases from carbamazepine in FDA AERS (204)**
*HLA-A*31:01*	Carbamazepine	Epilepsy, Mania/Bipolar Disorder, neuropathic pain	564 cases from carbamazepine in FDA AERS (204)**

*HLA-B*57:01*	Abacavir	HIV infectious	193 cases from abacavir in EuroSIDA study (205) †
*HLA-B*58:01*	Allopurinol	Hyperuricemia agents	685 cases from allopurinol in FDA AERS (204)**
2.2) Genetic polymorphisms on drug metabolizing enzymes to monitor drug response‡			
TPMT	Azathioprine	Immunosuppressant	Selected based on variety of disease within this sub groupp
UGT1A1	Irinotecan	Colorectal cancer	
CYP2C19	Clopidogrel	Antiplatelet agents	
CYP2C9/VKORC1	Warfarin	Anticoagulant agents	
CYP2D6	Tamoxifen	Breast cancer	
3. Genetic risk predictors for determining the development of disease			
BRCA1/2	-	Breast and ovarian cancer	5.03 for breast cancer (203)*

* Reported estimated new cases of cancer by ASRs; Age standardised rates (per 1000,000).

** Reported number of SJS/TEN cases in Food and Drug Administration Adverse Event Reporting System.

†Reported number of abacavir induced hypersensitivity reaction in 93 centres across Europe, Israel and Argentina.

‡Selection based on variety of therapeutic areas.

Table 8 Description of thirteen precision medicines included in this study

1.2 Country selections

This study focused on the upper-middle-income and high-income countries as defined by the World Bank (179). Eight countries which have national health insurance systems were included in this study. All countries must be Three countries; China, Malaysia and Thailand, were selected to be the representatives of upper-middle income countries. These three countries are located in ASIAN region. Australia, Canada, Singapore, United States and United Kingdom were selected as representatives of high-income countries. All eight selected countries have some kind of health insurance system. The general information for countries was provided in Appendix. Representative

of the national health insurance program had to cover the majority of nation's population, except the United States used Medicare because the health insurance programs were provided by private health insurance plans and Medicaid were different in each companies and states, respectively. Moreover, Singapore's healthcare system had different systems due to Central Provident Fund (CPF) which allowed the citizens to collect the money themselves. While the government would help keeping the healthcare costs down and providing heavy subsidies. Details of selected countries are show in Table 9 below.

Countries	Income level	Location	Health insurance program* (% of beneficiary population)
China	UMI	East Asia	Public sector (95%) (206)
Malaysia	UMI	Southeast Asia	Public sector (82% of IPD, 35% of OPD) (196)
Thailand	UMI	Southeast Asia	Universal coverage (72%) (207)
Australia	HI	Australia	Medicare (91.2%) (208)
Canada (Ontario)†	HI	North America	OHIP (87%) (209)
Singapore	HI	Southeast Asia	MediSave‡ (210)
United Kingdom	HI	Europe	NHS England (88.9%) (211)
United States	HI	North America	Medicare (17.7%) (212)

List of abbreviation; UMI; upper-middle-income, HI; high-income, OHIP; Ontario health insurance plan, IPD; In-patient, OPD; Out-patient

*Representative of health insurance system of each countries.

†Ontario is the province with the largest population in Canada.

‡MediSave is the national savings scheme which contribute a part of monthly salary to MediSave Account (MA).

Table 9 Description of eight selected countries included in this study

1.3 Search strategy

The literature search was undertaken between July 15, 2018 and August 31, 2019 to explore the health insurance coverage policy and implementation of precision medicine especially the diagnostic tests in different countries. A detailed search strategy was developed and revised appropriately.

1.3.1 Search strategy for reimbursement status

Literature searches included information from official websites of government agencies, payer organizations, national health technology assessment organizations, and professional organizations. The search strategy used combination of keywords including “Biomarker name”, “Reimbursement status” and country to search.

1.3.2 Search strategy for factors possibly related to precision medicine reimbursement policy

Literature searches were performed by using PubMed, MEDLINE, Cochrane Library, and Science Direct conducted via the Chulalongkorn University online library. Google Scholar was also utilized to locate open access articles. The search strategy used combination of keywords including “Biomarker name”, “recommendation”, “genetic frequency”, “strength of evidence”, “economic evaluation”, “health insurance system”, and country to search. This included information from official websites of government agencies, payer organizations, national health technology assessment organizations, and professional organizations. Examples of relevant websites are shown in detail in **Appendix**.

Hand-searching was included in the search strategies to identify the relevant information and complete the non-indexed searching in the databases. The wider search strategy used combination of keywords including “precision medicine”, “genetic”, “test”, “reimbursement”, “coverage”, “policy”, and country to search. The names of specific biomarkers such as ‘*HER2/neu*’, ‘*HLA-B*15:02*’ or ‘*BRCA1/2*’ were used (Full search strategy is provided in detail in **Appendix**.) The reference lists of relevant articles were included in this study.

The detail of inclusion and exclusion criteria for article selection are described below.

Inclusion criteria: The study included:

- Full-text articles from peer-reviewed journals and book chapters. OR
- Information from government official websites and payer official websites. OR
- Information from private sectors which refers to the information of the government and payer official websites.

Exclusion criteria: The articles were excluded if:

- They did not focus on health care policy or reimbursement decision about precision medicine or diagnostic test.
- Articles were unable to identify the specific country.
- Recommended policies that were not implemented in the country at that time of the publication.
- Articles were published in languages other than English or Thai.

2. DATA EXTRACTION AND DATA MANAGEMENT

2.1 Data extraction

The reviewer extracted the following information from included articles.

1) General information of the paper e.g.
   - Name of the first author
   - Year of publication
   - Type of article (original article, review article, case report)
   - Country in the article
   - How PMs are defined in the article

2) Content related to health insurance coverage policy e.g.
   - Strength of evidences (the details of levels of evidence are provided in detail in **Appendix**)
   - Clinical Practice guideline
   - Drug regulatory authority recommendation and labelling
   - Economic evaluation detail
   - Other factors that will be extracted from selected articles

2.2 Data management

Content analysis will be used to summarize policy and decision criteria regarding precision medicine especially for diagnostic testing. Policy and decision criteria will be compared and contrasted across countries and economic levels. The results will be tabulated as summarized table by determining the precision medicine tests/biomarkers as row and determining countries as columns.

CHAPTER IV RESULTS

This chapter presents the results of this study, in order to answer two research questions which were about the reimbursement policy decisions for precision medicine focusing on the diagnostic tests in each country and what were the factors which related to reimbursement decisions of precision medicine focusing on the diagnostic tests in health policy across countries. Thus, the findings of this study were summarised into three parts according to the research question.

In this study, two variables were used to compare reimbursement decisions of precision medicine emphasizing the diagnostic test. This first part begins with the general information which are the characteristics of selected precision medicine and selected country, and the second part was the result for answering the research question what the reimbursement policy decides for the tests. Additionally, the last part was the results of the relationship between primary factors and reimbursement decision of precision medicine focusing on the diagnostic tests in health policy across countries.

PART I: GENERAL INFORMATION

1.1 Precision medicine tests

The precision medicine's selection was based on two criteria. These were purpose of precision medicine tests usage and variety of diseases. Three purposes of precision medicine tests usage included three targeted cancer therapies, one genetic risk predictor for determining the development of disease, and nine pharmacogenetic tests, were divided into two sub-groups. These were genotyping of HLA alleles' predisposition for screening patients at risk of drug-induced severe cutaneous adverse reactions (SCARs) and genetic polymorphisms on drug metabolizing enzymes to monitor drug response. The characteristics of the thirteen-precision medicines were described in Table 10

Precision medicine tests		Test benefits	Disease area
1) Targeted cancer therapies			
	HER2/neu gene	Trastuzumab's candidate	Breast cancer
	BCR-ABL gene	Nilotinib's candidate	Chronic myeloid leukemia
	EGFR gene	Gefitinib's candidate	Non-small cell lung cancer
2) Pharmacogenetics testing			
2.1) Genotyping of HLA alleles' predisposition for screening patients at risk of drug-induced SCARs	*HLA-B*15:02*	Preventing Carbamazepine-induced SJS/TEN	Epilepsy, bipolar-disorder, and Trigeminal neuralgia
	*HLA-A*31:01*	Preventing Carbamazepine-induced SJS/TEN, DRESS	Epilepsy, bipolar-disorder, and Trigeminal neuralgia
	*HLA-B*57:01*	Preventing Abacavir-induced hypersensitivity syndrome	HIV/AIDs
	*HLA-B*58:01*	Preventing Allopurinol-induced SJS/TEN	Hyperuricemia
2.2) Genetic polymorphisms on drug metabolizing enzymes to monitor drug response	*TPMT* gene	Monitoring of bone marrow suppression from Azathioprine	Immunosuppressive medication
	UGT1A1 gene	Monitoring of Irinotecan's ADR such as neutropenia, diarrhoea, anaemia, and thrombocytopenia	Colorectal cancer
	CYP2C19 gene	Monitoring efficacy of Clopidogrel	Antiplatelet medication
	CYP2C9 and *VKORC1* gene	Warfarin's dose adjustment	Anticoagulant medication
	CYP2D6 gene	Tamoxifen's dose adjustment	Breast cancer
3) Genetic risk predictors for determining the development of disease			
	BRCA1 and *BRCA2* gene	Identifying the risk of breast cancer	Breast and ovarian cancer

Table 10 Characteristics of 13 precision medicine tests

1.2 Country classification

There are two groups of country classifications by income levels as defined by the World Bank (179), consisting of high-income countries and upper-middle-income countries. Eight countries were recruited in this study. Five in eight (5/8) of all countries were high-income countries, including Australia, Canada, Singapore, United States, and United Kingdom. The other three countries represented upper-middle-income countries. Those were China, Malaysia, and Thailand. The average of life expectancy among high-income countries was 81.6 years, while the upper-middle-income countries was 74.67 years. The United States had the highest total population among high-income countries, while the highest total population among upper-middle-income countries was China. United States also had the highest current health expenditure was 17.07% of GDP. Conversely, the lowest current health expenditure was Thailand (3.71% of GDP).

Table 11 below illustrates below some of the characteristics of the demographic indicators of national healthcare system in each country.

Countries	World Bank Category	Total population[1] (x1000s)	Per capita total health expenditure[1] (PPP Int $)	GDP/capita[1] ($, 2017)	Current health expenditure[2] (% GDP, 2016)	Current Health expenditure[2] (% of Total, 2016)		Life expectancy[1] (Years)	National policy on HTA of medical device[1]	Performance healthcare system by WHO[3]
						Public	Private			
Australia	HIC	23,343	4068	55,926	9.25	68.31	31.69	83	No	10
Canada	HIC	35,182	4676	51,316	10.53	73.44	26.56	82	Yes (not part of NHP)	23
Singapore	HIC	5,412	2881	55,236	4.47	54.53	45.47	83	Yes	24
United Kingdom	HIC	63,136	3495	42,514	9.76	80.23	19.76	81	No	13
United States	HIC	320,051	8895	53,129	17.07	81.85	18.19	79	No	30
China	UMIC	1,385,567	480	7,329	4.98	58.02	41.98	75	Yes (part of NHP)	46
Malaysia	UMIC	29,717	692	11,521	3.80	50.47	49.51	74	No	34
Thailand	UMIC	67,011	386	6,126	3.71	78.14	21.63	75	Yes	6

List of abbreviations: HIC; high-income country, UMIC; upper-middle-income-country, NHP; National Health plans

[1]: Reference from World Health Organization (22), [2]: Reference from The World Bank Group (28), [3]Ireland, S. (2019) (30)

Table 11 Demographic indicators of national healthcare system

PART II: THE REIMBURSEMENT DECISION COMPARED ACROSS COUNTRIES

The three purposes of using included 13 precision medicine tests which comprised of three targeted cancer therapies (23.08%), nine pharmacogenetics tests (69.23%), and one genetic risk predictor (7.69%). The nine pharmacogenetics tests are divided in two sub-groups, followed by four genotyping of HLA alleles predisposition for screening patients at risk of drug-induced severe cutaneous adverse reactions (SCARs) and five genetic polymorphisms on drug metabolizing enzymes to monitor drug response.

2.1 Targeted cancer therapies

Most biomarker tests of targeted therapies were more likely reimbursed. The results of this subgroup were present in Figure 5 below. Two precision medicine tests, *HER2/neu* gene and *BCR-ABL* gene, can be reimbursed in all countries (100%). Whereas six in eight countries reimburse for EGFR mutation (75%), except China and Thailand.

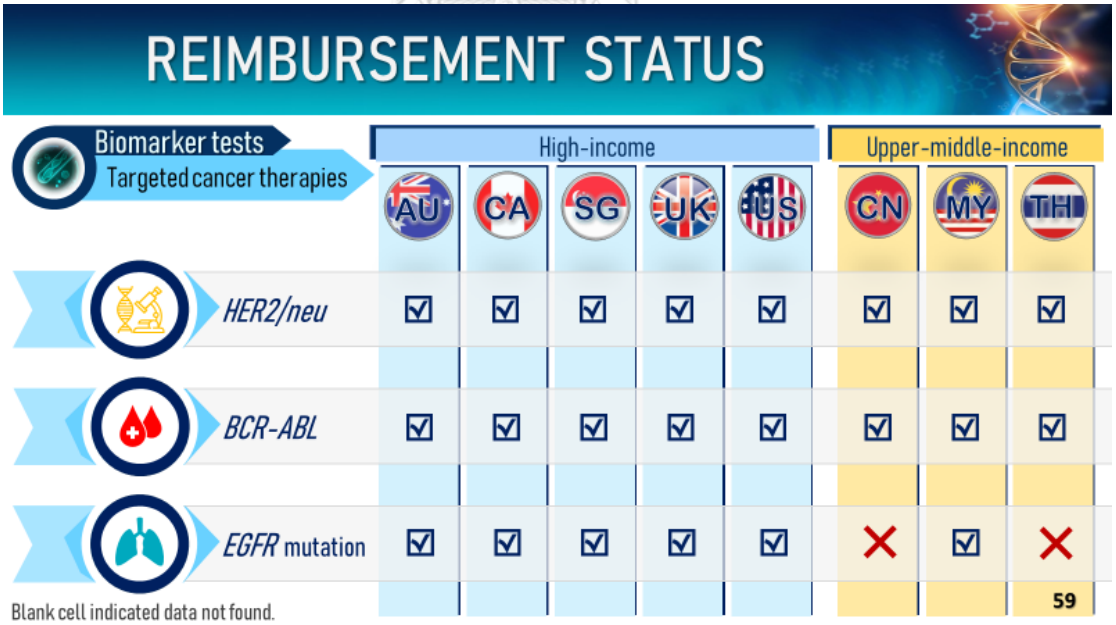


Figure 5 The result of reimbursement status for targeted therapies

2.2 Pharmacogenetics testing (PGx test)

In this study, as shown in Figure 6 and Figure 7, two sub-groups of the PGx testing differ in the reimbursement status of each country.

For the genotyping of HLA alleles predisposition for screening patients at risk of drug-induced SCARs (Figure 6), *HLA-B*15:02* and *HLA-B*57:01* gene test can be reimbursed in four countries and three countries, respectively. Thailand was the only one of upper-middle-income countries which covered for pharmacogenetics testing (*HLA-B*15:02* for preventing carbamazepine induced SJS/TEN). *HLA-B*31:01 g*ene test was only reimbursed in United Kingdom. However, the *HLA-B*58:01* gene test cannot be reimbursed.

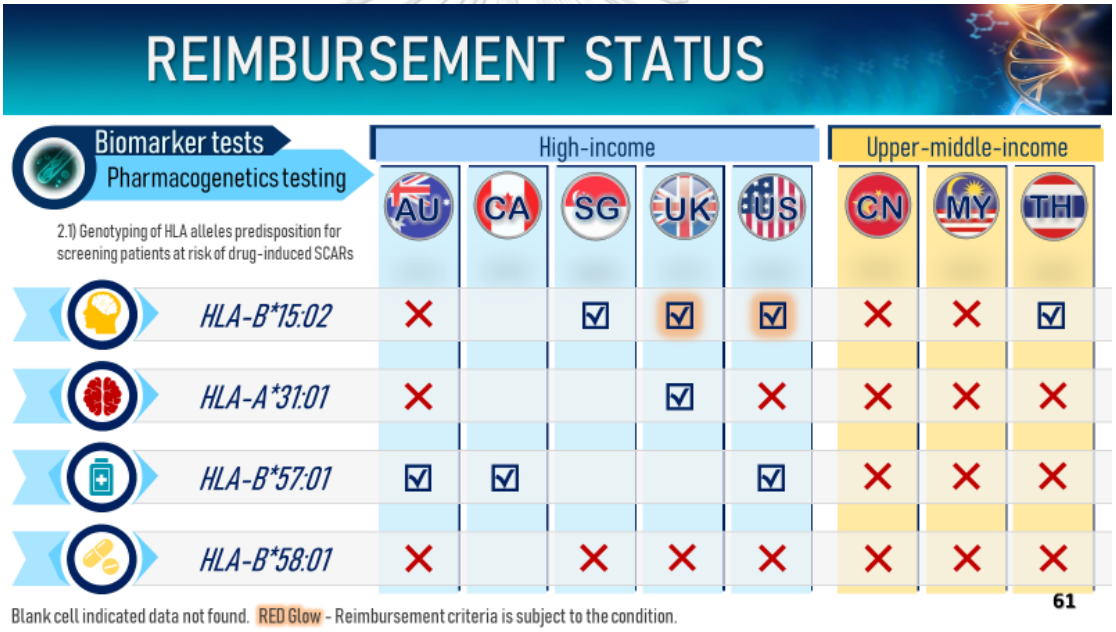


Figure 6 The result of reimbursement status for pharmacogenetics testing (genotyping of HLA alleles predisposition)

As can be seen from Figure 7 (below), There are quite a variety of reimbursement decisions for genetic polymorphisms on drug metabolizing enzymes to monitor drug response. Only three countries that allows to reimburse PGx test in this sub-group are Australia, United Kingdom, and United States which allows for three biomarkers, including *TPMT* gene test used to monitor adverse drug reaction from

azathioprine, *UGT1A1* gene test used to monitor adverse drug reaction from irinotecan, and *CYP2C19* gene test used to monitor efficacy of clopidogrel. The United States could reimburse for three biomarker tests including *TPMT, UGT1A1,* and *CYP2C19* gene testing. In contrast, Australia and United Kingdom were covered only *TPMT* gene testing. While the upper-middle-income countries were not covered for all pharmacogenetics testing in this sub-group.

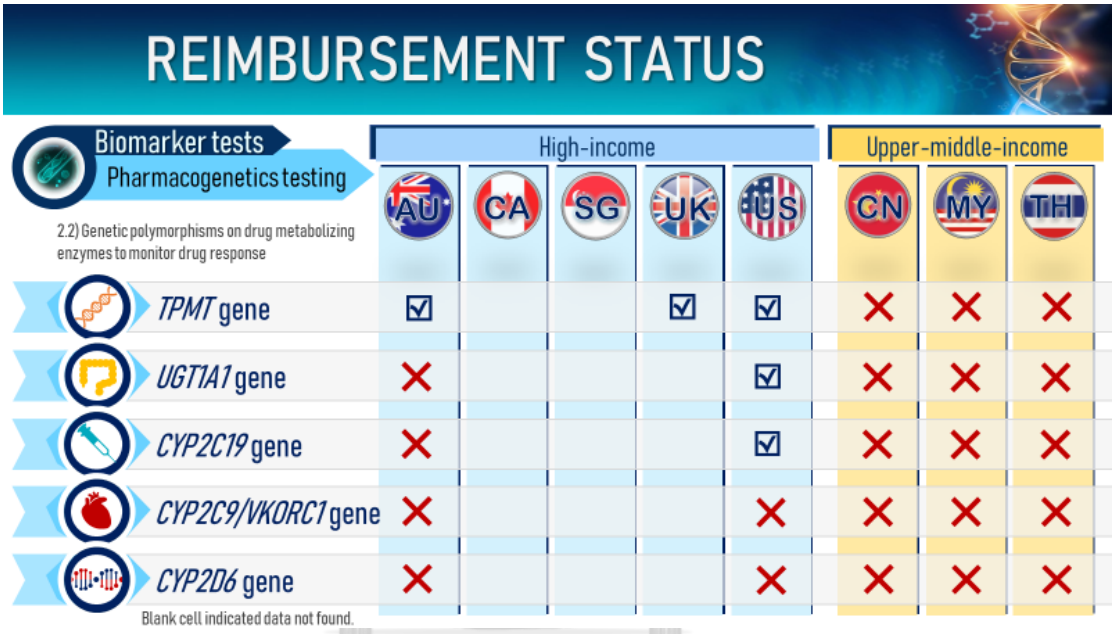


Figure 7 The result of reimbursement status for pharmacogenetics testing (genetic polymorphism on drug metabolizing enzymes)

2.3 Genetic risk predictors

Only one biomarker in this group had been selected to compare in this study, was showed in Figure 8. The finding showed that four countries allowed this precision medicine to reimburse which are Australia, Canada, United Kingdom, and United States, was accounted to 50% of all countries. These countries are classified as high-income countries. Whereas the upper-middle-income countries were not reimbursable.

Figure 8 The result of reimbursement status for genetic risk predictors

The overview results of the reimbursement status of national healthcare system for the precision medicine tests showed in Table 12.

Biomarker testing		Drug	High-income country					Upper-middle-income country		
			AU	CA (Ontario)	SG	UK	US (Medicare)	CN	MY	TH (UCS)
1) Targeted cancer therapies										
HER2/neu gene		Trastuzumab	Yes (14)	Yes (23)	Yes (29)	Yes (31)	Yes (32)	Yes	Yes (33)	Yes (34)
BCR-ABL gene		Nilotinib	Yes (14)	Yes (35)	Yes (36)	Yes (37)	Yes (39)	Yes	Yes (44)	Yes (34)
EGFR mutation		Gefitinib	Yes (14)	Yes (35)	Yes (47)	Yes (50)	Yes (52)	No (53)	Yes (33)	No (67)
2) Pharmacogenetics testing										
2.1) Genotyping of HLA alleles predisposition for screening patients at risk of drug-induced SCARs	*HLA-B*15:02*	Carbamazepine	No (70)		Yes (79)	Yes* (80)	Yes* (82)	No (84)	No (85)	Yes (88)
	*HLA-A*31:01*	Carbamazepine	No			Yes (80)	No (82)	No (84)	No (85)	No (90)
	*HLA-B*57:01*	Abacavir	Yes (14)	Yes (94)			Yes (82)	No (84)	No (85)	No (90)
	*HLA-B*58:01*	Allopurinol	No (98)		No (100)	No (101)	No (82)	No (84)	No (85)	No (90)
2.2) Genetic polymorphisms on drug metabolizing enzymes to monitor drug response	*TPMT* gene	Azathioprine	Yes (14)			Yes (68)	Yes (108)	No (84)	No (85)	No
	UGT1A1 gene	Irinotecan	No (112)				Yes (108)	No (84)	No (85)	No
	CYP2C19 gene	Clopidogrel	No (114)				Yes (115)	No (84)	No (85)	No
	CYP2C9/*VKORC1*	Warfarin	No (114)				No (115)	No (84)	No (85)	No
	CYP2D6 gene	Tamoxifen	No (114)				No (115)	No (84)	No (85)	No
3) Genetic risk predictors for determining the development of disease										
BRCA1 and *BRCA2* gene		-	Yes (14)	Yes (123)	No (124)	Yes (126)	Yes (128)		No	No
Blank cell indicated data not found. *Reimbursement criteria is subject to the condition.										

Table 12 The results of the reimbursement decision across countries

PART III: THE PRIMARY FACTORS AND REIMBURSEMENT POLICY FOR PRECISION MEDICINE TEST COMPARED ACROSS COUNTRIES

Six primary factors were included in this study which are drug regulatory authority (DRA) recommendation, clinical guideline recommendation, carrier gene frequency in ethnics, strength of evidence, economic evaluation data, and healthcare environment. The results of primary factor and reimbursement policy for precision medicine test is shown in Table 13.

3.1 DRA recommendation

All three precision medicine tests for targeted cancer therapies were at the required level from drug regulatory authorities of Canada, United Kingdom, United States, and Thailand. However, the precision medicine test which is used for PGx testing were undecided.

For genotyping of *HLA* alleles predispositions, only two biomarker tests were recommended by DRA at required level, which are *HLA-B*15:02* and gene testing was indicated as required level in United States, but was the recommended level in Canada, Thailand, and Singapore. Meanwhile, *HLA-B*57:01* was indicated as required level in United Kingdom and United States but was recommended level in Thailand. On the other hand, *HLA-B*58:01* was indicated as recommended level in United States and Singapore.

For genetic polymorphisms on drug metabolism, only *TPMT* gene testing was indicated as recommended level in United States. While the other biomarker tests in this sub-group were indicated as actionable level including *UGT1A1*, *CYP2C19*, *CYP2C9* and *VKORC1*, and *CYP2D6*. The information of DRA recommendation in this sub-group could only collected from Canada, United Kingdom, and United States.

For the purpose of genetic risk predictors for determining the development of disease, *BRCA1* and *BRCA2* gene testing was not recommended by any DRA recommendation.

3.2 Clinical guideline recommendation

100% of precision medicine tests (13 biomarkers) had guideline recommendation which varied according to the specific institution. First, three precision medicine tests for targeted therapies were recommended by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO). Second, most PGx tests were recommended by Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), and Dutch Pharmacogenetics Working Group (DPWG), depending on specific biomarkers. Finally, *BRCA1* and *BRCA2* gene testing which is used to predict the development of breast cancer and ovarian cancer, is recommended by institute of cancer specialists such as NCCN and the American Society of Clinical Oncology (ASCO).

3.3 Carrier gene frequency in ethnics

This study investigated the frequency of gene carriers in Caucasians, Asians, and Black (including Africans and African Americans). The Gene frequencies of the 13 biomarkers in the three ethnic groups are shown in Table 13. The gene frequency of *HLA-B*15:02* among Asians (4.64-6.88%) was much higher than Caucasians (0.04-0.16%). *HLA-A*31:01* gene was found higher frequency among Caucasians (2.84-6.43%). The *HLA-B*58:01* was high frequency in Asians (4.54-6.13%) and Blacks (3.89-5.54%). While the gene frequencies of HLA-B*57:01 were not much different among Caucasians (1.55-3.23%) and Asians (0.90-4.49%). Referring to the results were seen that the other gene variations were not quite different among each ethnic.

3.4 Strength of evidence

Most precision medicines were confirmed by many evidences including randomized controlled trial, cohort study, cases-control, systematic review, and meta-analysis. The targeted cancer therapies had strong level of evidence to confirm their relationship by randomized controlled trials, including two studies of each biomarker to confirm the relationship (100% of this group was indicated as strong level). The level of evidences confirmed the relationship of pharmacogenetics testing at the strong and medium level. The *HLA-B*15:02*, *HLA-B*57:01, HLA-B*58:01*, *CYP2C19*, *CYP2C9 /VKORC1*, and *CYP2D6* gene tests were confirmed by strong level accounting for 66.66% (six in nine biomarkers). In contrast, the *HLA-A*31:01*, *TPMT*, and *UGT1A1* gene tests were confirmed by medium level accounting for 25% (three in nine biomarkers). Lastly, the genetic risk predictor for determining of the development of breast and ovarian cancer was confirmed by strong level of evidences.

3.5 Economic evaluation

The study of the economic evaluation that were created to measure the cost effectiveness, cost saving or cost benefit to compare included genetic test and no test in the context of each country. For the purpose of targeted cancer therapies, there were done in all countries by comparing between standard treatment or chemotherapy and targeted cancer drug. Therefore, '*Not applicable'* was defined as result in those groups.

For the genotyping of *HLA* alleles predisposition for screening patients at risk of drug-induced SCARs in pharmacogenetic testing found 17 studies which studied for this sub-group which accounted for 53.125% of all counties (17 in 32 studies). Moreover, the group of genetic polymorphisms on drug metabolism were 37.5% which accounted for 15 in 40 which were performed in 8 countries. The genetic risk predictor was done by 4 in 8 countries which accounted for 50% of all studies.

Biomarker testing		Recommendation		Carrier gene frequency in ethnic groups (%)		Strength of Evidence	Economic evaluation		Reimbursement policy	
		DRA	Guideline				Yes	No	Yes	No
1) Targeted cancer therapies										
HER2/neu gene		Required (US, UK, CA, TH)	NCCN, ESMO, ASCO	Not applicable		Strong (1, 2)*	Not applicable		AU, CA, SG, UK, US, CN, MY, TH	
BCR-ABL gene		Required (US, UK, CA, TH)	NCCN, ESMO	Not applicable		Strong (4, 5)*	Not applicable		AU, CA, SG, UK, US, CN, MY, TH	
EGFR gene		Required (US, UK, CA, TH)	NCCN, ESMO	Not applicable		Strong (6, 7)*	Not applicable		AU, CA, SG, UK, US, MY	CN, TH
2) Pharmacogenetics testing										
2.1) Genotyping of HLA alleles predisposition for screening patients at risk of drug-induced SCARs	*HLA-B*15:02*	Required (US) Recommended (CA, TH, SG)	EMA, CPIC, CPNDS	Caucasian (0.04-0.16) Asians (4.64-6.88)		Strong (12, 13)	AU, SG, TH, US	MY	SG, UK, US, TH	AU, CN, MY
	*HLA-A*31:01*	Recommended (US, CA)	CPIC, CPNDS	Caucasian (2.84-6.43) Asian (2.20-3.34)		Medium (12, 15)	UK		UK	AU, CN, MY, TH
	*HLA-B*57:01*	Required (US, UK) Recommended (TH)	EMA, CPIC, DPWG	Caucasian (1.55-3.23) Asian (0.90-4.49)		Strong (18)	US, CA	CN, SG, TH	AU, CA, US	CN, MY, TH
	*HLA-B*58:01*	Actionable (US, SG)	EMA, CPIC	Asian (4.54-6.13) Black (3.89-5.54)		Strong (19-21)	CN, US, TH	MY, SG, UK		AU, SG, UK, US, CN, MY, TH
2.2) Genetic polymorphisms on drug metabolizing enzymes to monitor drug response	*TPMT*	Recommended (US) Actionable (CA)	CPIC, DPWG	IM	Caucasians (0.11) Blacks (0.09-0.14)	Medium (24, 25)	CA, UK, US		AU, UK, US	
				PM	Caucasians (0.43-0.44) Blacks (0.29-0.73)					
	UGT1A1	Actionable (US, CA)	DPWG	PM (UGT1A1*28)	Caucasians (0.31-0.40) Blacks (0.39-0.40)	Medium (26, 27)	CN, UK, US		US	AU, CN, MY, TH
				PM	Caucasians (0.2) Asians (0.12-0.14) Blacks (0.04)					

Table 13 The primary factor and reimbursement policy for precision medicine test

Biomarker testing		Recommendation		Carrier gene frequency In ethnic groups (%)			Strength of Evidence	Economic evaluation		Reimbursement policy	
		DRA	Guideline					Yes	No	Yes	No
2) Pharmacogenetics testing											
2.2) Genetic polymorphisms on drug metabolizing enzymes to monitor drug response	*CYP2C19*	Actionable (US, UK)	CPIC, DPWG	IM		Caucasians (0.25-0.26) Asians (0.45-0.47) Blacks (0.24-32)	Strong (3)	AU, UK, US		US	AU, CN, MY, TH
				PM		Caucasians (0.2) Asians (0.12-0.14) Blacks (0.04)					
	CYP2C9 /VKORC1	Actionable (US, CA)	EMA, CPIC, CPNDS	IM *(CYP2C9)*		Caucasians (0.2-0.32) Asian (0.07-0.33) Black (0.23)	Strong (8-10)	AU, CA, UK, US	TH		AU, US, CN, MY, TH
				VKORC1		Caucasians (41.2-46.4) Asians (15.3-88.17) Blacks (10.27-12.9)					
	CYP2D6	Actionable (US, CA)	CPIC, DPWG, CPNDS	PM		Caucasians (0.03-0.06) Asians (0.01-0.02) Blacks (0.02)	Strong (11)	UK			AU, US, CN, MY, TH
3) Genetic risk predictors for determining the development of disease											
BRCA1 and BRCA2 gene		-	NCCN, ASCO	BRCA1	BCCR	Caucasians (36.4) Asians (30.7) Blacks (32.8)	Strong (16, 17)	AU, MY, UK, US		AU, CA, UK, US	SG, MY, TH
					OCCR	Caucasians (12.3) Asians (16.7) Blacks (8.6)					
				BRCA2	BCCR	Caucasians (23.6) Asians (23.2) Blacks (20.0)					
					OCCR	Caucasians (29.5) Asians (30.9) Blacks (33.6)					
Blank cell indicated data not found. *There is no direct evidence for gene testing. List of abbreviations: IM; Intermediate Metabolizer, PM; Poor Metabolizer, BCCR; Breast Cancer Cluster Region, OCCR; Ovarian Cancer Cluster Region.											

Table 13 The primary factor and reimbursement policy for precision medicine test (cont.)

CHAPTER V DISCUSSIONS AND CONCLUSIONS

5.1 DISCUSSIONS

It will be hard to give everyone access to this technology equally. The genetic test reimbursement expense is one of the important variables that can tell whether the patient can actually have access to precision medicine. There are difficulties to decide what factors national health policy should consider to implement in the reimbursement process not only the medicine, but also diagnostic tests. This study attempts to find the relationship of these four primary factors.

5.1.1 Reimbursement decision for precision medicine

Firstly, the finding showed whether comparing the targeted cancer therapies were most likely to reimburse across countries. Nonetheless EGFR mutation test was not reimbursed in China and Thailand because Gefitinib was not listed in the National List of Essential Medicines (NLEM). Therefore, the insurance coverage did not automatically cover the EGFR mutation test. Most countries bundle the companion diagnostic tests with the precision medicine, if the medicine is reimbursed, their diagnostic test expenses are often covered.

Secondly, the pharmacogenetic testing categorized to 2 sub-groups which are guided appropriate drug (genotyping of HLA alleles) and dose (genetic polymorphisms on drug metabolizing enzymes), seems to be different between the two groups for reimbursement policies. HLA-B*15:02 gene test was covered by the national health insurance in Singapore, United Kingdom, United States, and Thailand. However, the patient under the Medicare and NHS must be eligible according to the following criteria in order to be able to reimburse the cost of pharmacogenetic test; be patient of Asian and Oceanian ancestry and initiate with carbamazepine therapy. Another genetic test that is more likely to reimburse in this study is *HLA-B*57:01* which is associated with the risk of hypersensitivity reaction to abacavir, an antiretroviral drug which is approved as a first-line antiretroviral regimen in the treatment of HIV infection. A previous study showed

that abacavir based regimen was providing long term clinical benefits for patients(213). This is probably the reason which most countries reimbursed for this genetic test. However, the reimbursement decision of *HLA-B*58:01* and *HLA-A*31:01* genetic screening for allopurinol induced SJS/TEN and carbamazepine induced SJS/TEN/DRESS, respectively, seems to be unable to reimburse in any country, even though many existing evidences elucidate that the pharmacogenetic test and severe adverse drug reaction had strongly relationship (19, 142). Maybe, the policymakers decide not to cover the cost of *HLA-B*58:01* gene testing, probably because of the hidden reason is febuxostat, the alternative drug for patients who carry *HLA-B*58:01*, which is allowed reimbursement in many countries. Most pharmacogenetic testing, which guided the appropriate dose, were not reimbursable by the national health coverage policy. On the other hand, *TPMT* gene testing, which is used to predict the toxicity of azathioprine (myelosuppression) and guide physicians to select the right dose, was covered in high-income countries like Australia, United Kingdom and United States. The recent cost effectiveness studies showed that the cost of *TPMT* gene testing was less compared to expense used for adverse drug reaction treatment (214). The Medicare also provides coverage for genetic polymorphism of *UGT1A1* test (used to select the appropriate dose for irinotecan) but limited to reasonable and necessary for the diagnosis or treatment by the physician. *CYP2C19* gene testing might be considered to reimburse for medically necessity of patient with ACS undergoing PCI and starting clopidogrel therapy, but cannot be reimbursable for others drugs (115).

Lastly, the reimbursement decision of genetic risk predictor, which is *BRCA1* and *BRCA2* genes screening test, depends on preventive care policy at the national level of healthcare insurance system. The high-income countries are more likely to reimburse for this genetic screening test.

5.1.2 Whether the official recommendations affect precision medicines reimbursement decision

The drug regulatory authority (DRA) and clinical guideline recommendations are important information that policy makers must take into consideration for the reimbursement policy for genetic screening test. Although the recommendations are necessary to support the reimbursement decision of genetic testing expense, they do not affect the reimbursement status.

This study used the pharmacogenomics test level applied from the definition of PharmGKB. Those are defined as (1) “Required” implied that the genetic testing should be conducted before using this drug. (2) “Recommended” implied that the genetic testing should be considered to recommend testing. (3) “Actionable” implied that the genetic testing may reveal contraindication of the drug. However, the label does not itself require or recommend genetic testing. Finally, , “Informative” implied that the label contains information of genetic testing but does not affect the metabolism of drugs (215). According to the results of this study, they presented that all genetic tests for targeted cancer therapies which are labelled as “required” are mostly reimbursable for all countries but the reimbursement in some upper-middle-income countries is constrained in this case, China and Thailand. However, the other purpose of using pharmacogenetic testing and genetic risk predictor, were mostly labelled as “recommended” and “actionable” which might affect the decision making of policy makers. However, the U.S. FDA labels the *HLA-B*15:02* and *HLA-B*57:01* gene tests as ‘required’ for biomarker testing prior to initiation of carbamazepine and abacavir, respectively. The national healthcare system might cover for both of these biomarker tests. Although the biomarker testing was indicated as “recommended” and “actionable”, they were seemingly not reimbursable in upper-middle-income countries. For clinical guideline recommendation, all biomarker tests have been recommended by specialists in each therapeutic area. For example, the biomarker testing related to cancer therapy like *HER2/neu*, *BCR-ABL*, *EGFR* mutation and *BRCA1/2* gene testing, in this study was gathered from National Comprehensive Cancer Network (NCCS) and The

American Cancer Society (ACS). They are well-known and have been used for reference in the practice guideline of each country. Moreover, this study gathered the clinical guideline related to pharmacogenetic testing based on the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG) and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). This study explained that the clinical recommendation might not have much effect on the genetic test expense reimbursement status of each country. However, it is something that is indispensable in making decisions as well.

5.1.3 Whether the carrier gene frequency affects precision medicines reimbursement decision

From the data collected in this study, it can be seen that the different gene variant was found in different ethnic groups. Some genes are more common in Asians, while other genes were found in Caucasians, so it is important to find out whether the frequency of genes in each race influences the genetic test reimbursement decision or not. Therefore, it does not depend on the country's financial status and clinical guideline recommendation only, but it also seems to be related to ethnicity because coverage condition is limited for some ethnic groups. *HLA-B*15:02* and *HLA-A*31:01* are the clear examples that suggest whether gene frequency affects reimbursement decision. The recent studies reported that *HLA-B*15:02* which is a gene marker for carbamazepine induced SJS/TEN, and this allele showed higher frequency in Asians than Caucasians (65, 79, 138, 139, 216-218). Then those who are reimbursed must meet the criteria whichever patient has to start treatment with carbamazepine and has Asian or Oceania ancestry. The Medicare (United States) and NHS of England also set these criteria for coverage as well. Although Thailand and Singapore allow coverage for *HLA-B*15:02* gene test, they did not impose conditions on the races. However, this is reasonable because both countries are located in Asia. Whereas, *HLA-A*31:01* gene showed higher frequency in Caucasians. Therefore, the upper-middle-income countries which located

in Asia, did not perform this genetic testing in their countries and consideration of reimbursement policy might not need for this biomarker.

It is still necessary to find more evidence to confirm the frequency of genes that are related to ethnicity or not. This requires systematic data collection from studies of each country in the future.

5.1.4 Whether the strength of evidence affects precision medicines

Most precision medicines have been studied for a long time. Until now, evidence showing the relationship of genes and treatments is evident, both in terms of education and research. In the past study from Meckley L.M. in 2010 (86), they tried to find the evidence which showed whether there is some relationship between the specific biomarker and adverse drug reaction or an effect on metabolism of the drug. The result explained that it needed more randomized controlled trials or stronger evidences to confirm their relationship. This study found that the level of evidences based on the methodological quality of the study design are higher level and more reliable than in the past. Most evidences were systematic reviews and meta-analyses which included the randomized controlled trials and cohort studies. Those studies also found clear evidence of clinical benefit of the precision therapy and with a higher population than previously studied.

5.1.5 The economic evaluation of the precision medicines

The national reimbursement policy always uses the economic evaluation as one of the basic tools for reimbursement decisions (219-221). According to the result, it can be seen that in countries which covered the precision medicine testing, economic evaluation has been done, even though the results may be cost effective or not. The results from this study showed no economic evaluation of the targeted cancer therapy. The economic evaluation which this study is interested in comparing is between including genetic test into the medical treatment or no genetic test. However, the economic evaluation of targeted cancer therapies, mostly compared the standard

chemotherapy with targeted drug or compared several targeted drugs in the same group. Therefore, the result in this study showed “Not applicable”. In contrast, the results of other purposes like pharmacogenetic test and genetic risk predictor were conducted in many countries. Most high-income countries with cost effective results including Australia, Singapore, United States, and United Kingdom, covered for pharmacogenetic testing e.g. *HLA-B*15:02*, *HLA-B*57:01*, and *TPMT* gene. This is consistent with the cost-effective result of Thailand that covers for *HLA-B*15:02* gene testing. Additionally, these reimbursement decisions were in the same direction as the purpose of genetic risk predisposition. As a result of the economic evaluation, the *BRCA1* and *BRCA2* gene testing in cancer patient are cost effective in Australia, Malaysia, United Kingdom, and United States. These economically justify reimbursement for these genetic tests. Even though the economic evaluation result of Malaysia was cost effective, the *BRCA1* and *BRCA2* gene testing still cannot be reimbursed. From this may be inferred that although there are have the results of economic evaluation to support that gene testing is cost-effective, payers still have to concern about financial burden and the country's financial status.

5.1.6 Whether the other factors affect precision medicines

From this study found that these factors which were price of genetic tests, drug substitution of some precision medicine tests, the implementation of genetic test, and the national health insurance system might affect the reimbursement of the genetic testing at the national level. The detail of these factors provided in **Appendix**.

Price of genetic test – According to the review, they found that the methods used in the genetic testing, were varied and different in each country. Therefore, the price range is very wide, if using the prices in comparison. The price would be in accordance with the techniques and technological progress of each country. In determining whether a gene test should be covered by national healthcare system or not, the policy maker must consider the price of genetic tests, then compared to the severity of illness that might occur to patients. Whether, if the price of genetic test was

too expensive and was not cost effective in context of that country, which makes the test was not reimbursable.

Drug substitution – The pharmacogenetic testing was done to help physicians decide on the appropriate drug and appropriate dosing for patients. In contrast, the alternative drugs might be the right for those patients who had undergone pharmacogenetic test. *HLA-B*58:01* genetic screening should be performed among hyperuricemia patients who initiated with allopurinol. Febuxostat was the alternative for patient with *HLA-B*58:01* positive. On the other hand, some countries which allowed reimbursement for this medicine with certain criteria or controlled drug price. The physician might select the febuxostat as a first choice instead of allopurinol. The novel oral anticoagulants (NOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban, were also alternative of warfarin. In some patient who had higher risk of bleeding, the physicians might select NOACs instead of warfarin and perform *CYP2C9* gene testing for dose adjustment. Therefore, the doctors' opinions about drug selection are important for treatment, which may also affect the reimbursement of precision medicine testing.

Implementation of genetic test – The progress of technology and sciences is essential in the medical laboratory examination. The medical laboratory testing was example of relationships with inexpensive procedure and high total costs. In order to build the diagnostic laboratory to have the potential to analyse specimen at the molecular level for diagnosing patients' illness. The important laboratory quality must have accuracy, reliability and rapidity. Therefore, the accuracy instruments, high competent and knowledgeable staff are needed to ensure the patients will subsequently the hospital's efficient and quality services. These are still the limitation of many countries, especially among upper-middle-income countries, in terms of budgets and technological progress. If the reimbursement policy is readily available but cannot pass the limited availability of the laboratory, the patient may not be able to access the precision therapy.

5.2 CONCLUSIONS

Precision medicine has been initiated and increasingly trends to implement in the healthcare system. Access to precision medicine generally depends on each individual country's reimbursement policy. Most countries mainly facilitate patient access through the list of coverage determinations, but still they struggle to enable all population to access to the precision medicine.

Access to precision medicine is still limited in upper-middle-income countries. This study showed that the pharmacogenetic tests have been widely used in academia and research such as China, Malaysia, and Singapore. In contrast, the implementation of pharmacogenetic tests have been blurred in health care policy at the national level in some countries. Each country also has a variety of reimbursement decisions for precision medicine tests especially for pharmacogenetic tests and genetic risk predictors. In addition, the financial status of the country and technological progress affects the precision medicine reimbursement policies at the national level. To complete this study, disclosure and access to public information of each country is still necessary.

According to review, the other limitations which slowed down the precision medicine implementation due to the shortage of laboratory potential and resources and personnel which must also be trained.

In conclusion, the results recommend that the economic evaluation should be performed in each country. The health care policy makers should establish the obvious criteria for precision medicine reimbursement decision especially diagnostic tests/biomarker tests, so that people can access the precision therapy and receive healthcare properly, effectively, and appropriately.

5.3 LIMITATIONS

- This study could not access to information of reimbursement policy and healthcare system in some countries.
- This study had language limitations other than English and Thai.

5.4 RECOMMENDATION – FROM THIS STUDY

- The health care policy makers should establish the obvious criteria for precision medicine reimbursement decision especially diagnostic tests or biomarker tests.
- The economic evaluation should be performed in each country.
- For Thailand, the data in the health policy system should make it easier to find information.

5.5 RECOMMENDATION – LESSONS LEARNED FOR THAILAND

The consideration of precision medicine reimbursement policy such medicine and their biomarker test, must consider many factors together. Whether the academic evidences, the necessity and the severity of risk if the patient does not receive medication or genetic testing including economic evaluation supports and budget burden in the context of Thailand. The reimbursement policy issue should be the same for all three health benefit schemes to achieve equality. For Thailand situation, access to precision medicine especially diagnostic tests across three health benefit schemes are different. Patients under civil servant medical benefits scheme can access to most diagnostic tests, while patients who are under the social security and universal coverage scheme, only have coverage for some biomarkers which are announced in the Royal Thai Government Gazette. For other tests, the patients have to pay on their own. (The reimbursement status of precision medicine of each scheme in Thailand provided in **Appendix**.)

In order to consider approval of precision medicine reimbursement policy including drug and tests, the number of laboratory service units should be sufficient and cover in all areas to prevent restriction of services. At the present, genetic testing in Thailand are still limited to the tertiary hospitals. Even if there is considered that the genetic testing can be reimbursed, but do not guarantee that the patient will be able to access the genetic testing because of the limitations of laboratories lacking in the rural area.

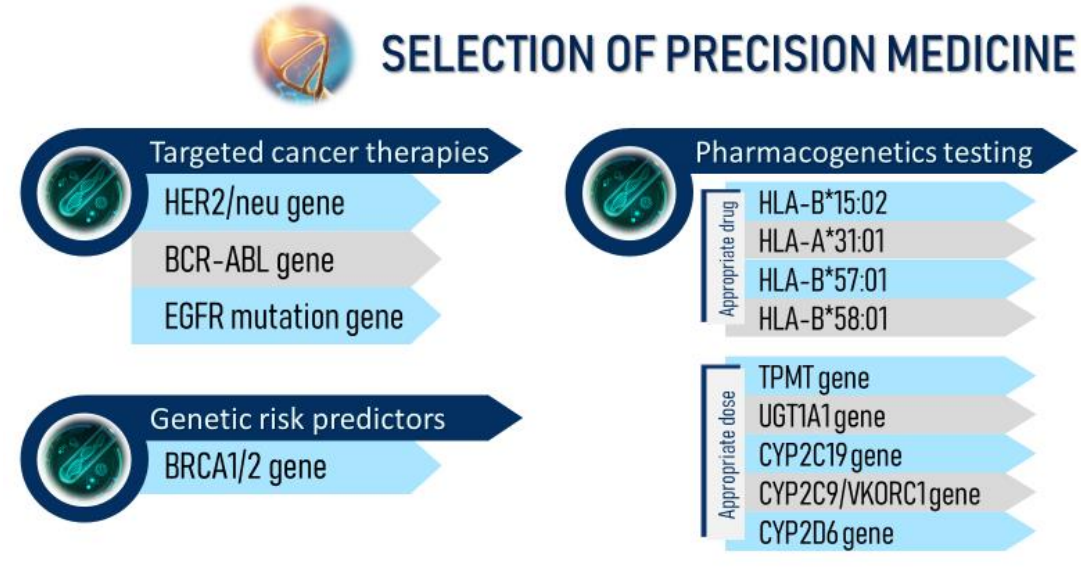
Patient groups and criteria should be defined for prescribing precision medicines or genetic screening tests to provide the same standard of service

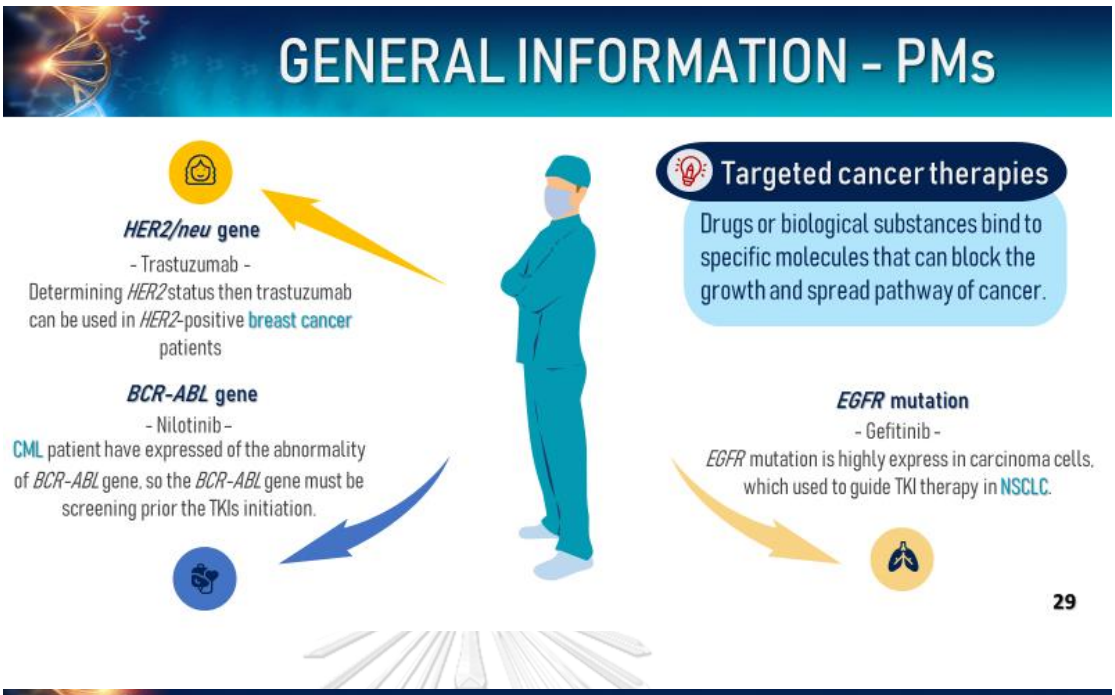
throughout the country. Although precision medicine and some genetic screening tests will reimburse only certain health insurance scheme. But there should be monitored and evaluated the patients who received those benefits, in order to use the information for further consideration of other health insurance schemes in the future.

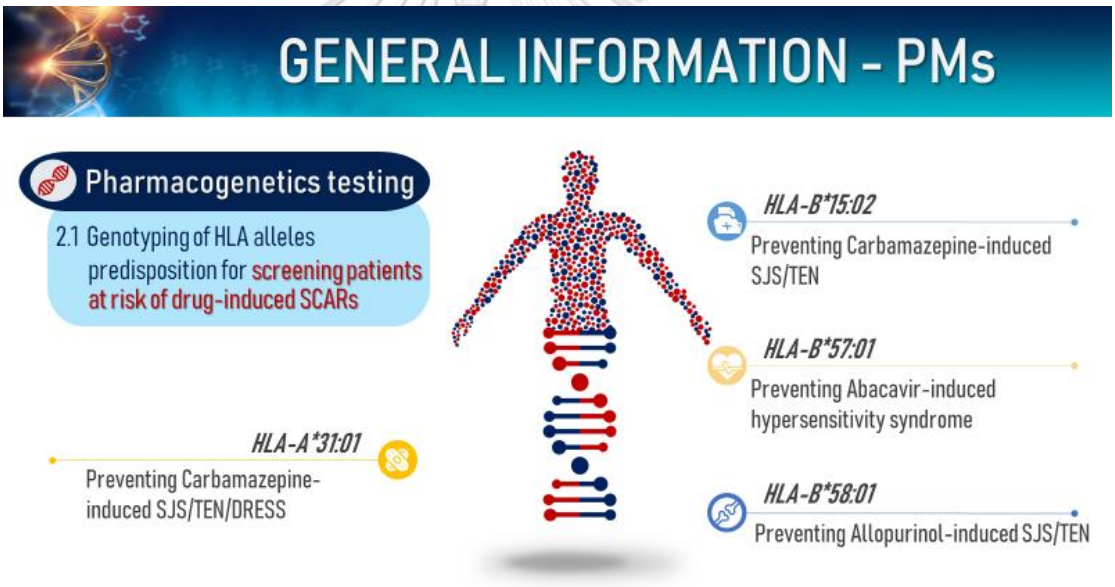
However, the Thailand also need the information management process to make health information systems appear like nervous system that spread throughout the body. which will provide information to the government, the established policies committee various executives and practitioners for learning and analytical thinking. Then, determine to use information to create knowledge and to achieve wisdom which will be used to develop the healthcare system in Thailand.

APPENDIX

1. GENERAL INFORMATION FOR PRECISION MEDICINE TESTS



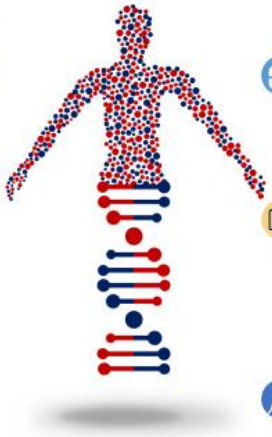

GENERAL INFORMATION - PMs
HER2/neu gene
- Trastuzumab -
Determining HER2 status then trastuzumab can be used in HER2-positive breast cancer patients
BCR-ABL gene
- Nilotinib -
CML patient have expressed of the abnormality of BCR-ABL gene, so the BCR-ABL gene must be screening prior the TKIs initiation.
Targeted cancer therapies
Drugs or biological substances bind to specific molecules that can block the growth and spread pathway of cancer.
EGFR mutation
- Gefitinib -
EGFR mutation is highly express in carcinoma cells, which used to guide TKI therapy in NSCLC.
29


GENERAL INFORMATION - PMs
Pharmacogenetics testing
2.1 Genotyping of HLA alleles predisposition for screening patients at risk of drug-induced SCARs
HLA-A*31:01
Preventing Carbamazepine-induced SJS/TEN/DRESS
HLA-B*15:02
Preventing Carbamazepine-induced SJS/TEN
HLA-B*57:01
Preventing Abacavir-induced hypersensitivity syndrome
HLA-B*58:01
Preventing Allopurinol-induced SJS/TEN

GENERAL INFORMATION - PMs

Pharmacogenetics testing

2.2 Genetic polymorphisms on drug metabolizing enzymes to monitor drug response



***CYP2C9* and *VKORC1* gene**
Warfarin's dose adjustment

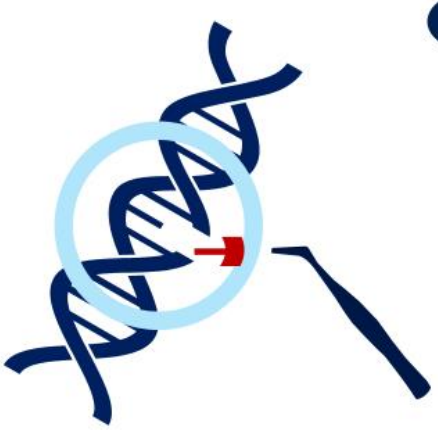
***CYP2D6* gene**
Tamoxifen's dose adjustment

***TPMT* gene**
Monitoring of bone marrow suppression from Azathioprine

***UGT1A1* gene**
Monitoring of Irinotecan's ADR such as neutropenia, diarrhea, anemia, and thrombocytopenia

***CYP2C19* gene**
Monitoring efficacy of Clopidogrel

GENERAL INFORMATION - PMs



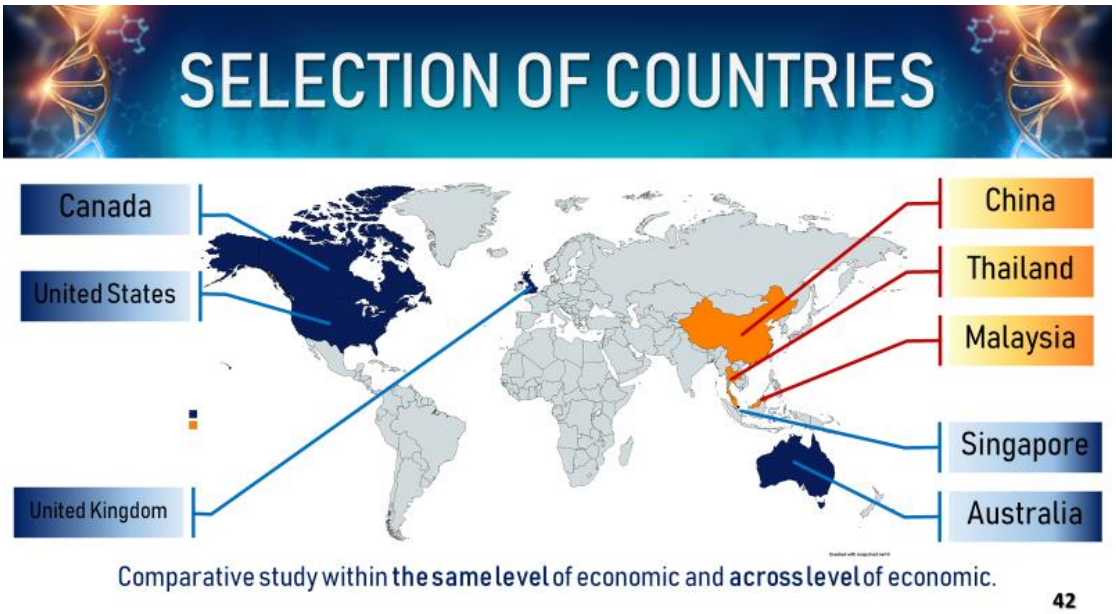
Genetic risk predictors

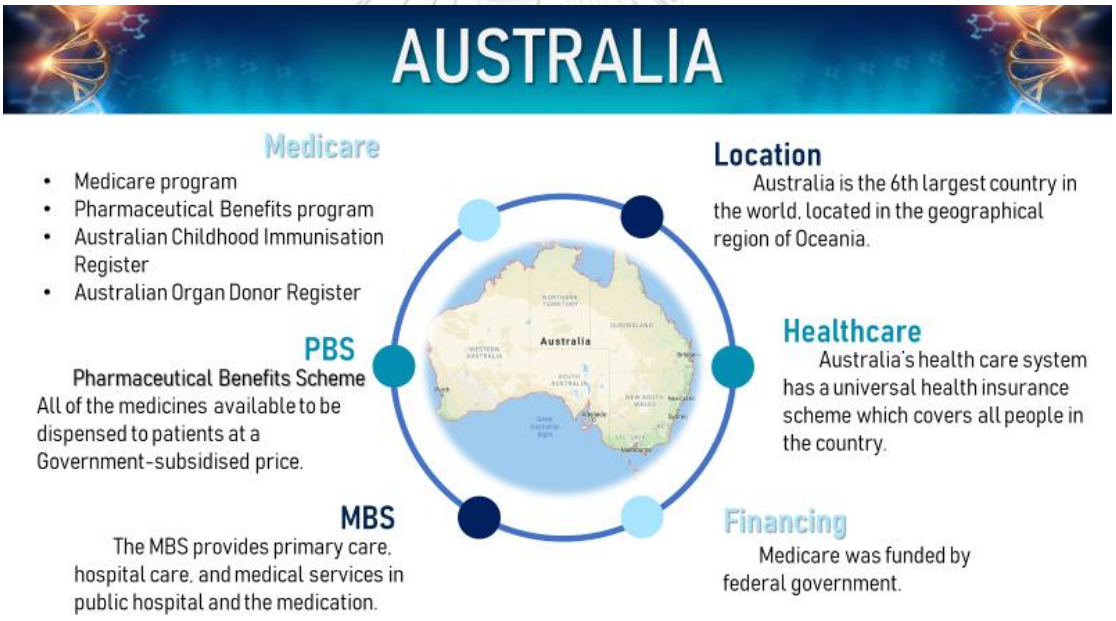
Genetic risk predictors for determining the development of disease.

***BRCA1* and *BRCA2* gene**

BRCA1 and *BRCA2* genes were highly strong relationship between chance of breast and ovarian cancer development. The women who had high risk of *BRCA1* and *BRAC2* mutation such as age 50 years diagnosed with breast cancer, have family history was diagnosed with cancer.

2. GENERAL INFORMATION FOR COUNTRIES





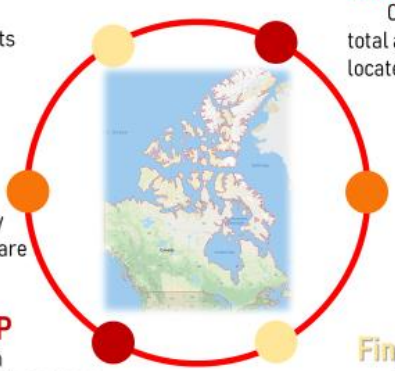
CANADA

Medicare

- Regular benefits
- Special authorization benefits
- Restricted benefits

Location

Canada is the 2nd largest country by total area in the world after Russia, which located in the continent of North America.



Services

Healthcare services are covered all necessary basic care such as basic medications, maternity, basic emergency services, mental health care, palliative care and end-of-life care and rehabilitation

Healthcare

Universal access to publicly funded health services for everyone wherever they live in the country.

OHIP

Ontario's health care plan

Paying for basic healthcare need (full coverage for doctors services, hospital visits and dental surgery, eye- and foot- health and ambulance services).

Financing

Canada was publicly funded by federal, provincial and territorial tax revenue.

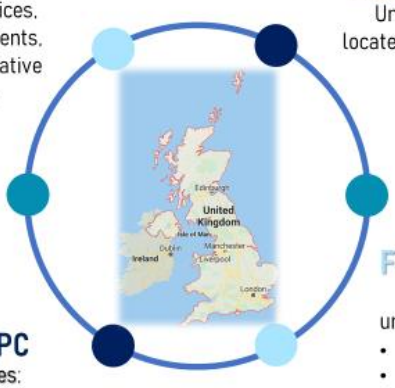
UNITED KINGDOM

NHS

Benefits include preventive services, hospital services for in- and out-patients, medication, mental health care, palliative care, home visits, and rehabilitation.

Location

United Kingdom is an island nation which located off the northwest coast of the Europe.



NICE

- To assess new medicines and treatments.
- To provide clinical guidelines
- Managing and providing health and social care services.

Healthcare

The United Kingdom offers public healthcare for all permanent residents.

Financing

NHS was a government-sponsored universal healthcare system.

- General taxation (80.9%)
- National Insurance Contributions (NICs) (17.9%)
- Out-of-pocket payment in the pattern of co-payments and direct payment (1.2%)

NHS PPC

Prescription Prepayment Certificates:

To pay a set price for prescriptions for 3 or 12 months, no matter how many patient need.

UNITED STATES

Medicaid

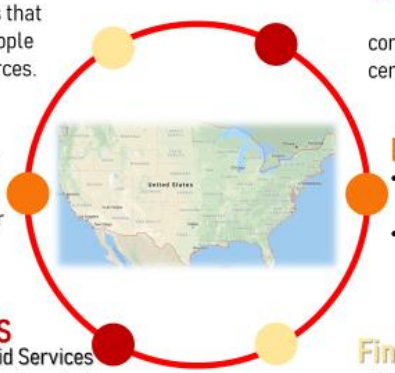
Federal and state programs that provide medical expense for people who limited incomes and resources.

Location

The United States of America is comprising 50 States and located in the central part of North America.

Medicare

- For Americans who is over 65 years old
- Certain young people with disabilities
- ESRD patients with kidney transplant or dialysis.



Healthcare

- Private sector: Based on employment, is more than 50% of population.
- Public sector: The federal government provided Medicare and Medicaid.

CMS

The Centers for Medicare and Medicaid Services

Managing the Medicare program and works in partnership with state governments to manage Medicaid

Financing

- Employer and employee payroll tax
- Federal general revenues
- Federal-state matching general revenues

SINGAPORE

Medisave

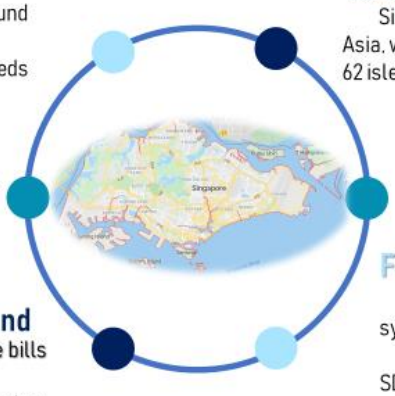
- An individual's Central Provident Fund account for Singaporean
- Subsidized for basic healthcare needs

Location

Singapore is a city-state in Southeast Asia, which consists of one main island and 62 islets.

MediShield

- Singaporean with Medisave account
- Premium for OPD-IPD service, Surgery, medicines



Healthcare

Singapore has a philosophy of healthcare system with three pillars.

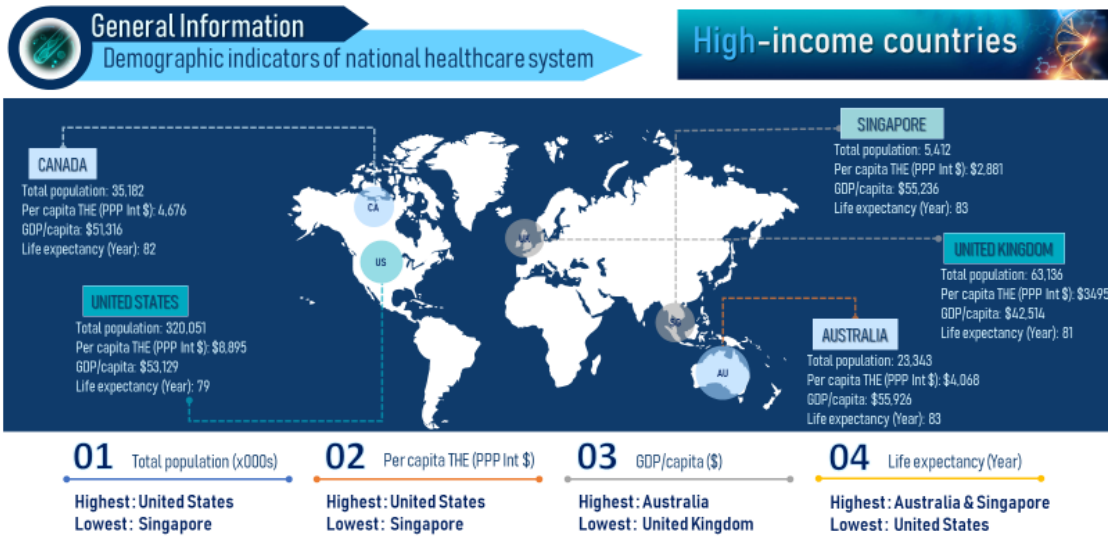
Financing

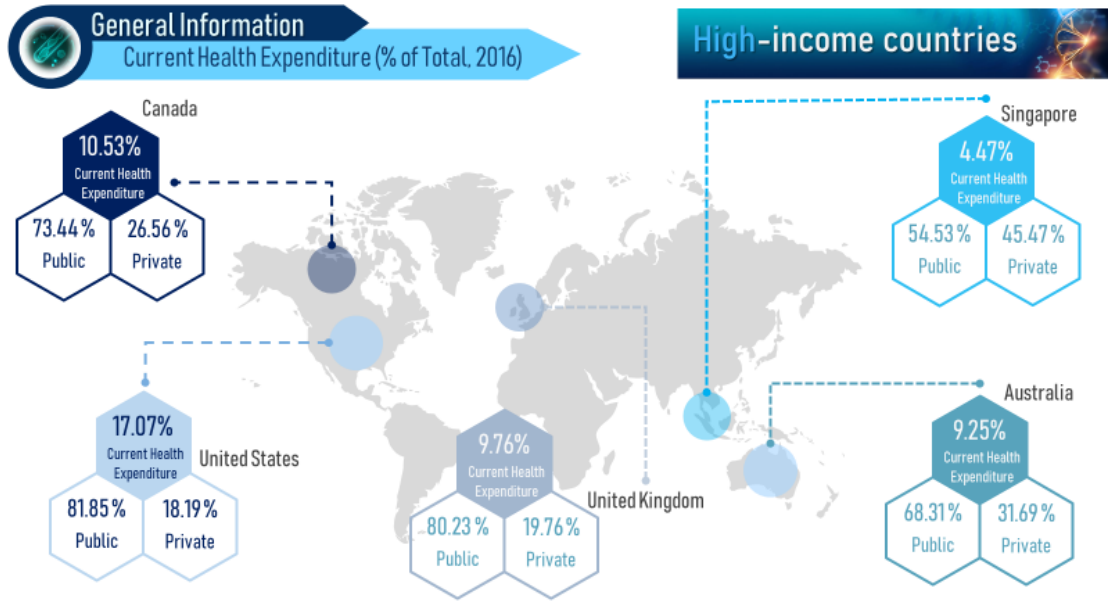
The public financing for Healthcare system consist mainly by "3M".

Subsidised drugs approved under SDL & MAF.

Medifund

- Difficulties paying for your healthcare bills after Government subsidies
- Hospitalization expenses and OPD services after Medisave and MediShield


General Information
Demographic indicators of national healthcare system
High-income countries
CANADA
Total population: 35,182
Per capita THE (PPP Int $): 4,676
GDP/capita: $51,316
Life expectancy (Year): 82
UNITED STATES
Total population: 320,051
Per capita THE (PPP Int $): $8,895
GDP/capita: $53,129
Life expectancy (Year): 79
SINGAPORE
Total population: 5,412
Per capita THE (PPP Int $): $2,881
GDP/capita: $55,236
Life expectancy (Year): 83
UNITED KINGDOM
Total population: 63,136
Per capita THE (PPP Int $): $3495
GDP/capita: $42,514
Life expectancy (Year): 81
AUSTRALIA
Total population: 23,343
Per capita THE (PPP Int $): $4,068
GDP/capita: $55,926
Life expectancy (Year): 83
01 Total population (x000s)
Highest: United States
Lowest: Singapore
02 Per capita THE (PPP Int $)
Highest: United States
Lowest: Singapore
03 GDP/capita ($)
Highest: Australia
Lowest: United Kingdom
04 Life expectancy (Year)
Highest: Australia & Singapore
Lowest: United States

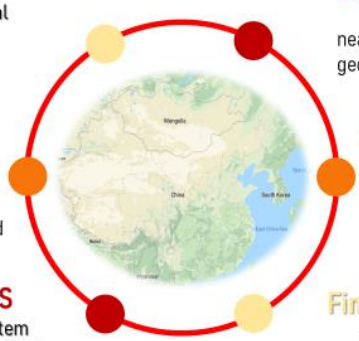

General Information
Current Health Expenditure (% of Total, 2016)
High-income countries
Canada
10.53%
Current Health Expenditure
73.44% Public
26.56% Private
Singapore
4.47%
Current Health Expenditure
54.53% Public
45.47% Private
United States
17.07%
Current Health Expenditure
81.85% Public
18.19% Private
United Kingdom
9.76%
Current Health Expenditure
80.23% Public
19.76% Private
Australia
9.25%
Current Health Expenditure
68.31% Public
31.69% Private

PEOPLE'S REPUBLIC OF CHINA

UEBMI
Urban Employee Basic Medical Insurance Scheme
This covered employees and retirees in urban areas.

URBMI
Urban Resident Basic Medical Insurance Scheme
Unemployed residents including the students in urban areas are covered under this scheme.

NRCMS
New Rural Cooperative Medical System
Residents in rural areas were enrolled in the NRCMS as families.



Location
The most populous country with nearly 1.4 billion residents. located in the geographical region of East Asia.

Healthcare
Providing basic healthcare services for their citizens under three basic medical insurance.

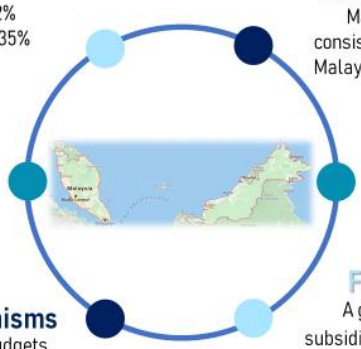
Financing
Cost-sharing is used in all these basic health insurance scheme by deductible, co-payment and the coverage ceiling.

MALAYSIA

The public sector
- In-patient services: 82%
- Ambulatory services: 35%

The private sector
- In-patient services: 18%
- Ambulatory services: 62%

Payment mechanisms
- The public health care: global budgets.
- The private sector funders: fee-for-service



Location
Malaysia is located in Southeast Asia, consisting of two part which are Peninsular Malaysia (west) and East Malaysia (East).

Healthcare
Malaysia has been operating a two-tier health care system with government base and private sector

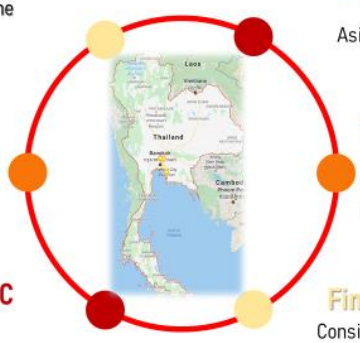
Financing
A goods and services free are subsidized or with some minor co-payments in the public sector.

THAILAND

CSMBS
Civil Servant Medical Benefit Scheme
Government employees and their dependents (9%)

SSI
Social Security Insurance Scheme
Private sector employees (16%)

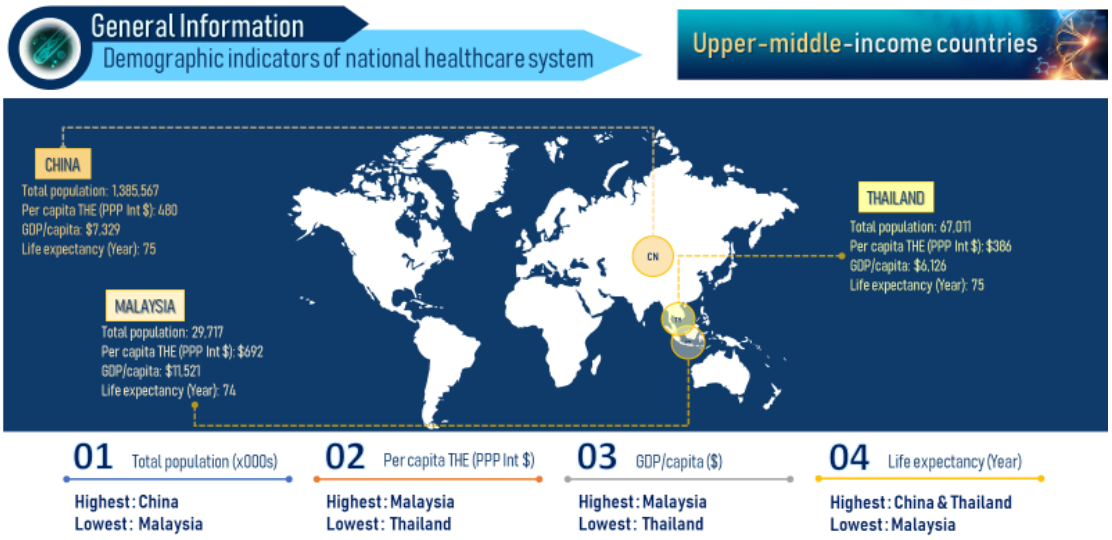
UC
Universal Coverage Scheme
The rest of the population (75%)

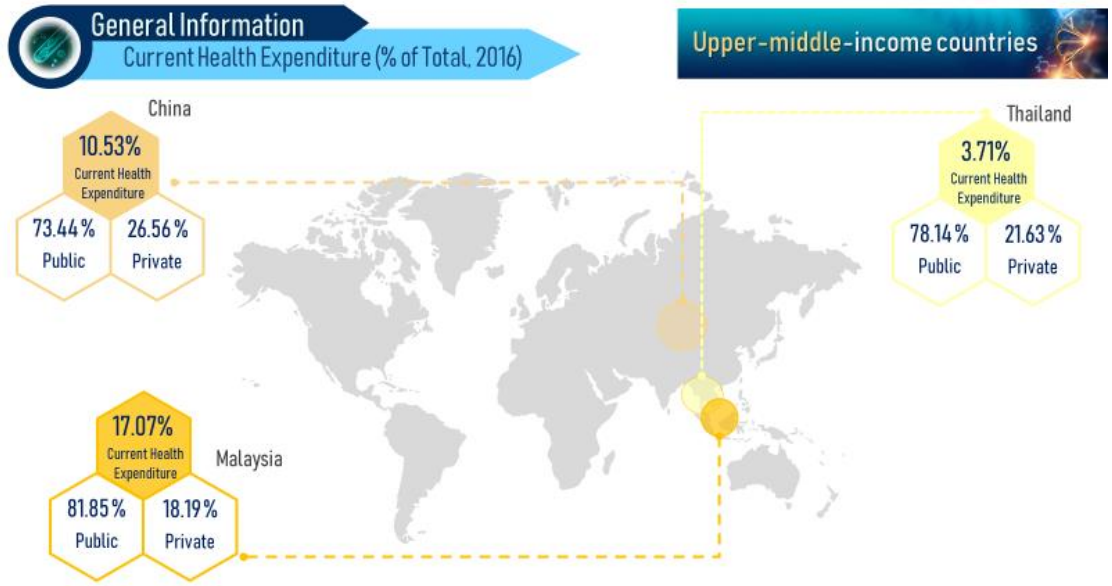


Location
Located in the continent of Southeast Asia, composed of 76 provinces.

Healthcare
Thai Population are cover under three public health insurance schemes including CSMBS, SSS, and UC.

Financing
Consisting of three parts from employee, employer and the government (general tax)


General Information
Demographic indicators of national healthcare system
Upper-middle-income countries
CHINA
Total population: 1,385,567
Per capita THE (PPP Int $): 480
GDP/capita: $7,329
Life expectancy (Year): 75
MALAYSIA
Total population: 29,717
Per capita THE (PPP Int $): $692
GDP/capita: $11,521
Life expectancy (Year): 74
THAILAND
Total population: 67,011
Per capita THE (PPP Int $): $386
GDP/capita: $6,126
Life expectancy (Year): 75
01 Total population (x000s)
Highest: China
Lowest: Malaysia
02 Per capita THE (PPP Int $)
Highest: Malaysia
Lowest: Thailand
03 GDP/capita ($)
Highest: Malaysia
Lowest: Thailand
04 Life expectancy (Year)
Highest: China & Thailand
Lowest: Malaysia


General Information
Current Health Expenditure (% of Total, 2016)
Upper-middle-income countries
China
10.53%
Current Health Expenditure
73.44% Public
26.56% Private
Thailand
3.71%
Current Health Expenditure
78.14% Public
21.63% Private
17.07%
Current Health Expenditure
Malaysia
81.85% Public
18.19% Private

3. FULL SEARCH STRATEGY

3.1 STRUCTURE OF SEARCHING

The search strategy that was used is

[Biomarker name] + [Country] + [Keyword search]

3.1.1 List of Biomarker names

- HER2/neu gene
- BCR-ABL gene
- EGFR gene
- HLA-B*15:02
- HLA-A*31:01
- HLA-B*57:01
- HLA-B*58:01
- TPMT gene
- UGT1A1 gene
- CYP2C19 gene
- CYP2C9 and VKORC1 gene
- CYP2D6 gene
- *BRCA1* and *BRCA2* gene

3.1.2 List of country

- Australia
- Canada
- Singapore
- United Kingdom
- United States
- China
- Malaysia
- Thailand

3.1.3 Description of search strategy

Keyword search	Database
Reimbursement status: Reimbursement or benefits package or reimbursement decision or coverage	PubMed, MEDLINE, Embase, Hand-search via Google search engine Government body website e.g. NHS England, MBS online, Ontario.ca, NHSO Thailand
Recommendation: guideline or recommendation or labeling	PubMed, MEDLINE, Embase, Hand-search via Google search engine DRA and Clinical guideline website e.g. NCCN, ESMO, U.S. FDA, HSA PHARMGKB, CPIC, CPNDS, DPWG
Gene frequency: gene frequency or gene prevalence	PubMed, MEDLINE, Embase, Hand-search via Google search engine
Strength of evidence: efficacy or relationship, association	PubMed, MEDLINE, Embase, COCHRANE, Hand-search via Google search engine
Economic evaluation: cost effectiveness or cost benefit or economic impact or cost saving or economic evaluation	PubMed, MEDLINE, Embase, COCHRANE, Hand-search via Google search engine
Health insurance system: health insurance system or health care system or public health insurance	Government body e.g. MBS, Ontario.ca, NHS England, NHSO, Thai FDA, HAS, Government of Singapore, Ministry of Health (Malaysia)

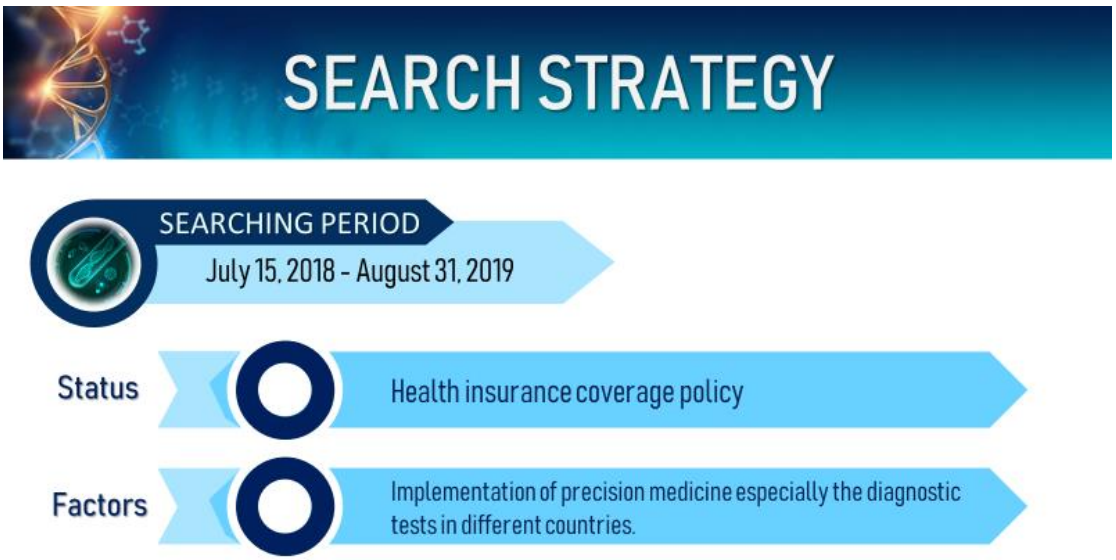


Figure 9 Search strategy (scope of searching)

Figure 10 Search strategy for reimbursement status

Figure 11 Source of information for reimbursement status

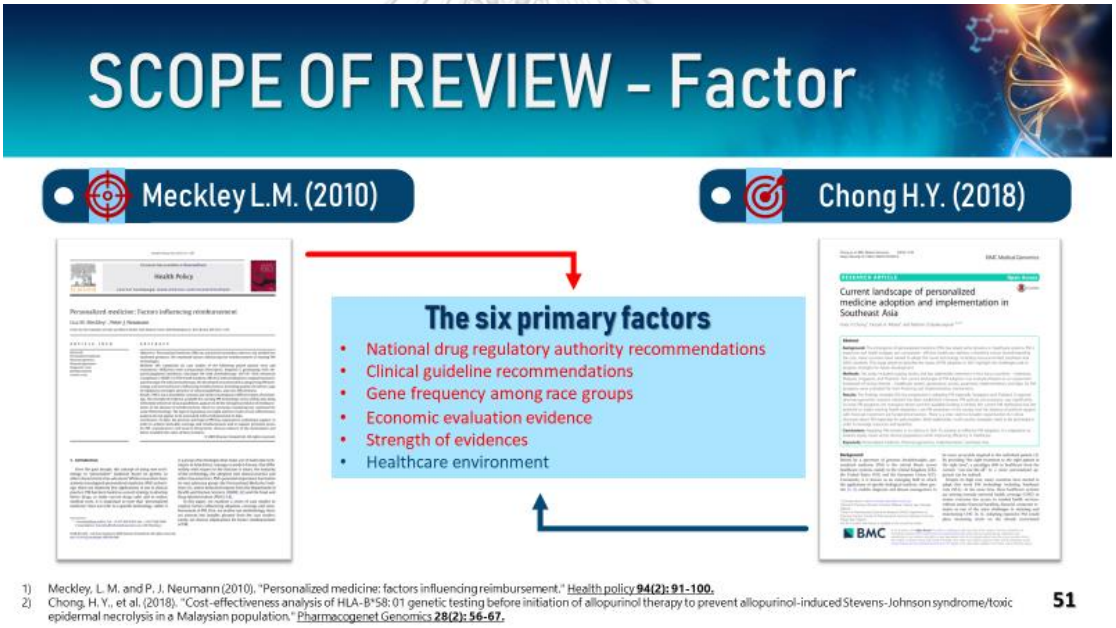


Figure 12 Scope of review for factors possibly related to reimbursement policy

Primary term	Keyword search
Recommendation	**guideline** or **recommendation** or **labeling**
Gene frequency	**gene frequency** or **gene prevalence**
Strength of evidence	**efficacy** or **relationship** or **association**
Economic evaluation	**cost effectiveness** or **cost benefit** or **economic impact** or **cost saving** or **economic evaluation**
Health insurance system	**health insurance system** or **health care system** or **public health insurance**

Figure 13 Search strategy for factors possibly related to reimbursement policy

Figure 14 Source of information for factors possibly related to reimbursement policy

Figure 15 Inclusion and exclusion criteria

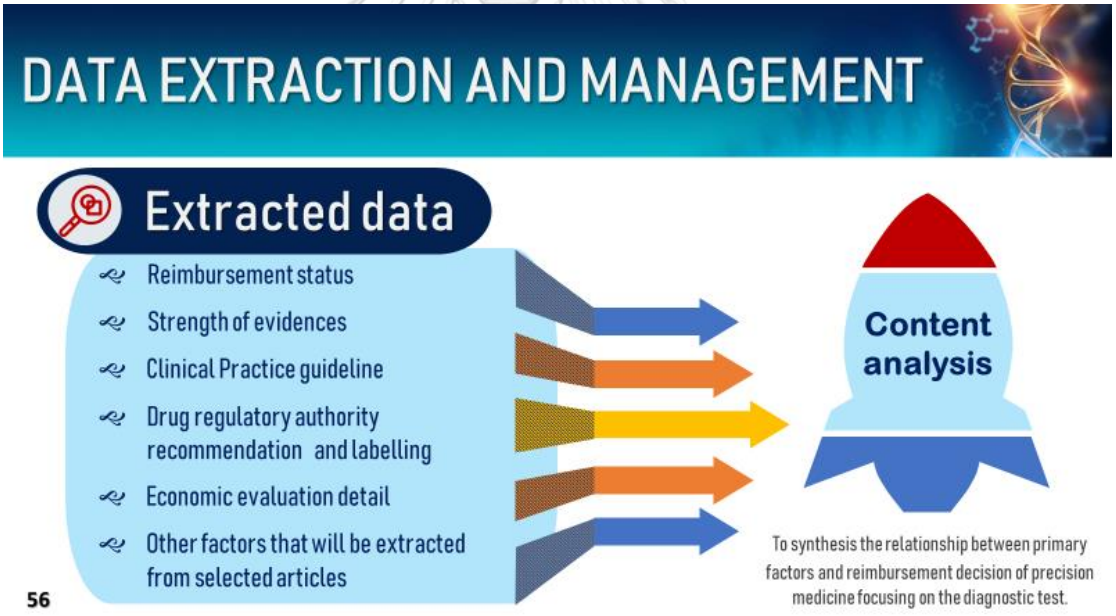


Figure 16 Data extraction and management

3.2 SOURCE OF INFORMATION FOR ADDITIONAL RELEVANT ARTICLES

Country	Organization	URL
Government website: High-income country		
Australia	Medicare services	https://www.humanservices.gov.au/individuals/subjects/medicare-services
	Pharmaceutical Benefits Scheme	http://www.pbs.gov.au/info/healthpro/explanatory-notes
Canada (Ontario)	Government of Canada	https://www.canada.ca/en.html
	Government of Ontario	https://www.ontario.ca/page/government-ontario
Singapore	Singapore Ministry of Health	https://www.moh.gov.sg/
	Health Sciences Authority	https://www.hsa.gov.sg/
United Kingdom	NHS Choices	https://www.nhs.uk/pages/home.asp
	NHS Digital	https://digital.nhs.uk/search/year/2018?query=fee
United States	Medicare	https://www.medicare.gov/
	Medicaid	https://www.medicaid.gov/
	U.S. Centers for Medicare & Medicaid	https://www.cms.gov/
	Veterans Health Administration	https://www.va.gov/health/
Government website: Upper-middle-income country		
China	National Health Commission of the PRC	http://en.nhfpc.gov.cn/
	Ministry of Human Resources and Social Security	http://www.mohrss.gov.cn/
	China Food and Drug Administration	http://eng.sfda.gov.cn/WS03/CL0755

Malaysia	Ministry of Health (MOH)	http://www.moh.gov.my/
	MOH Pharmaceutical Services Programme	https://www.pharmacy.gov.my/v2/ms
	Medical Device Authority (Under MOH)	https://www.mdb.gov.my/mdb/
	Ministry of Finance	http://www.treasury.gov.my/index.php/en/
Thailand	The Comptroller General's Department	https://www.cgd.go.th/cs/internet/internet/Home.html?page_locale=th_TH
	The Comptroller General's Department	http://welcgd.cgd.go.th/wel/checktstmed
	National Health Security Office (NHSO)	https://www.nhso.go.th/frontend/page-about_resolution.aspx
	Social Security Office	https://www.sso.go.th/wpr/
	Royal Thai Government Gazette	http://www.mratchakitcha.soc.go.th/index.php

3.3 DETAILS OF LEVELS OF EVIDENCE

Levels of evidence	Descriptions
Strong	Meta-analysis, systematic reviews, randomized controlled trial
Medium	Cohort studies (prospective), case-control studies (retrospective)
Weak	Case report, case series, expert opinions, editorials, animal and laboratory studies
Adapted from: Petrisor B.A. (2007) (222)	

4. THE REIMBURSEMENT STATUS OF PRECISION MEDICINE IN THAILAND

Precision medicine tests	Range of price* (Baht)	Treatment	CSMBS	SSS	UCS
1) Targeted cancer therapies					
HER2/neu gene	10,000	Trastuzumab	Yes	Yes	Yes
BCR-ABL gene	1,100-6,000	Nilotinib	Yes	Yes	Yes
EGFR gene	7,000-11,000	Gefitinib	Yes	No	No
2) Pharmacogenomics testing					
*HLA-B*15:02*	1,000-2,000	Carbamazepine	Yes	No	Yes
*HLA-A*31:01*	-	Carbamazepine	No	No	No
*HLA-B*57:01*	1,000-2,000	Abacavir	Yes	No	No
*HLA-B*58:01*	1,000-2,000	Allopurinol	Yes	No	No
TPMT gene	1,800-3,400	Azathioprine	Yes	No	No
UGT1A1 gene	1,400-1,700	Irinotecan	No	No	No
CYP2C19 gene	1,800-3,500	Clopidogrel	Yes	No	No
CYP2C9 gene	1,000-2,000	Warfarin	Yes	No	No
VKORC1 gene	2,950	Warfarin	No	No	No
CYP2D6 gene	1,800-4,800	Tamoxifen	No	No	No
3) Genetic risk predictors for determining the development of disease					
BRCA1/2 gene	19,400-50,000	-	Yes	No	No

List of abbreviation: CSMBS; Civil Servant Medical Benefit Scheme, SSS; Social Security Insurance Scheme, UCS; Universal Coverage Scheme

* Price of tests are based on data from university hospitals in Thailand (Chulalongkorn Hospital, Ramathibodi hospital, Siriraj hospital, Srinagarind Hospital).

5. THE REIMBURSEMENT STATUS OF ALTERNATIVE DRUG (PHARMACOGENETIC TESTING)

Precision medicine tests	Alternative drugs	AU	CA	SG	UK	US	CN	MY	TH		
									CSMBS	SSS	UC
*HLA-B*15:02*	-	Not applicable									
*HLA-A*31:01*	-	Not applicable									
*HLA-B*57:01*	-	Not applicable									
*HLA-B*58:01*	Febuxostat	Y*	Y*	N	Y*	N		N	Y*	Y*	Y*
TPMT	-	Not applicable									
UGT1A1	-	Not applicable									
CYP2C19	-	Not applicable									
CYP2C9 /VKORC1	NOACs										
	Apixaban	Y*	Y*	Y*	Y	Y		N	Y*	N	N
	Dabigatran	Y*	Y*		Y	Y		N	Y*	N	N
	Edoxaban		Y*		Y	N		N	Y*	N	N
	Rivaroxaban	Y*	Y*	Y*	Y	Y		N	Y*	N	N
CYP2D6	-	Not applicable									

List of abbreviation: NOACs; Novel oral anticoagulants, Y; Yes, N; No, AU; Australia, CA; Canada, SG; Singapore, UK; United Kingdom, US; United States, CN; the People's Republic of China, MY; Malaysia TH; Thailand, CSMBS; Civil Service Medical Benefits Scheme, SSS; Social Security Insurance Scheme, UC; Universal Coverage Scheme
Blank cell indicated data not found. (-) Dash remark indicated that no specific alternative drugs. (*) Star remark indicated that the medicine can reimbursement under the certain conditions.

REFERENCES

1. Dendukuri N, Khetani K, McIsaac M, Brophy J. Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis. Canadian Medical Association Journal. 2007;176(10):1429-34.
2. Dendukuri N, Khetani K, McIsaac M, Brophy J. Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis. CMAJ. 2007;176(10):1429-34.
3. Holmes MV, Perel P, Shah T, Hingorani AD, Casas JP. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. Jama. 2011;306(24):2704-14.
4. Jabbour E, Cortes J, Kantarjian H. Nilotinib for the treatment of chronic myeloid leukemia: An evidence-based review. Core Evid. 2010;4:207-13.
5. Hochhaus A, Saglio G, Larson RA, Kim D-W, Etienne G, Rosti G, et al. Nilotinib is associated with a reduced incidence of BCR-ABL mutations vs imatinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Blood. 2013;121(18):3703-8.
6. Gaur P, Bhattacharya S, Kant S, Kushwaha RAS, Singh G, Pandey S. EGFR Mutation Detection and Its Association With Clinicopathological Characters of Lung Cancer Patients. World J Oncol. 2018;9(5-6):151-5.
7. Beypinar I, Demir H, Araz M, Uysal M. The relationship between EGFR mutation and metastasis pattern in lung adenocarcinoma. Journal of Oncological Sciences. 2019;5(2):65-9.
8. Jorgensen AL, FitzGerald RJ, Oyee J, Pirmohamed M, Williamson PR. Influence of CYP2C9 and VKORC1 on Patient Response to Warfarin: A Systematic Review and Meta-Analysis. PLOS ONE. 2012;7(8):e44064.
9. Lindh JD, Holm L, Andersson ML, Rane A. Influence of CYP2C9 genotype on warfarin dose requirements—a systematic review and meta-analysis. European Journal of Clinical Pharmacology. 2009;65(4):365-75.

10. Goulding R, Dawes D, Price M, Wilkie S, Dawes M. Genotype-guided drug prescribing: a systematic review and meta-analysis of randomized control trials. British Journal of Clinical Pharmacology. 2015;80(4):868-77.
11. Province MA, Goetz MP, Brauch H, Flockhart DA, Hebert JM, Whaley R, et al. CYP2D6 Genotype and Adjuvant Tamoxifen: Meta-Analysis of Heterogeneous Study Populations. Clinical Pharmacology & Therapeutics. 2014;95(2):216-27.
12. Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496-506.
13. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship Between the HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Systematic Review and Meta-analysis. JAMA Dermatology. 2013;149(9):1025-32.
14. Australia Co. Medicare Benefits Schedule (MBS). In: Online M, editor. Canberra: Department of Health and Ageing; 2019.
15. Yip VLM, Pirmohamed M. The HLA-A*31:01 allele: influence on carbamazepine treatment. Pharmgenomics Pers Med. 2017;10:29-38.
16. Bhaskaran SP, Chandratre K, Gupta H, Zhang L, Wang X, Cui J, et al. Germline variation in BRCA1/2 is highly ethnic-specific: Evidence from over 30,000 Chinese hereditary breast and ovarian cancer patients. International journal of cancer. 2019;145(4):962-73.
17. Wang F, Fang Q, Ge Z, Yu N, Xu S, Fan X. Common BRCA1 and BRCA2 mutations in breast cancer families: a meta-analysis from systematic review. Molecular Biology Reports. 2012;39(3):2109-18.
18. Tangamornsuksan W, Lohitnavy O, Kongkaew C, Chaiyakunapruk N, Reisfeld B, Scholfield NC, et al. Association of HLA-B*5701 genotypes and abacavir-induced hypersensitivity reaction: a systematic review and meta-analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for

Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2015;18(1):68-76.

19. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenetics and genomics. 2009;19(9):704-9.
20. Saksit N, Nakkam N, Konyoung P, Khunarkornsiri U, Tassaneeyakul W, Chumworathayi P, et al. Comparison between the HLA-B(*)58 : 01 Allele and Single-Nucleotide Polymorphisms in Chromosome 6 for Prediction of Allopurinol-Induced Severe Cutaneous Adverse Reactions. Journal of immunology research. 2017;2017:2738784.
21. Sukasem C, Jantararoungtong T, Kuntawong P, Puangpetch A, Koomdee N, Satapornpong P, et al. HLA-B*58:01 for Allopurinol-Induced Cutaneous Adverse Drug Reactions: Implication for Clinical Interpretation in Thailand. Frontiers in Pharmacology. 2016;7(186).
22. WHO. Essential health technologies. World Health Organization; 2014.
23. Funding of Herceptin® for the treatment of breast cancer. In: Care MoHaL-T, editor. Ontario, CA2001.
24. Liu Y-P, Xu H-Q, Li M, Yang X, Yu S, Fu W-L, et al. Association between Thiopurine S-Methyltransferase Polymorphisms and Azathioprine-Induced Adverse Drug Reactions in Patients with Autoimmune Diseases: A Meta-Analysis. PLOS ONE. 2015;10(12):e0144234.
25. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. Clinical pharmacology and therapeutics. 1989;46(2):149-54.
26. Minmin L, Zhehai W, Jun G, Jie L, Changzheng L, Lin L, et al. Clinical significance of UGT1A1 gene polymorphisms on irinotecan-based regimens as the treatment in metastatic colorectal cancer. OncoTargets & Therapy. 2014;7:1653-61.
27. Liu XH, Lu J, Duan W, Dai ZM, Wang M, Lin S, et al. Predictive Value of UGT1A1*28

Polymorphism In Irinotecan-based Chemotherapy. Journal of Cancer. 2017;8(4):691-703.

28. Current health expenditure (% of GDP) [Internet]. World Health Organization. 2018. Available from: https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?end=2016&start=2016.
29. ACE. Trastuzumab for the treatment of metastatic breast cancer. In: Effectiveness TAfC, editor. Republic of Singapore: Ministry of Health; 2018.
30. Ireland S. Revealed: Countries With The Best Health Care Systems, 2019 New York, NY: CEOWORLD magazine 2019 [Available from: https://ceoworld.biz/2019/08/05/revealed-countries-with-the-best-health-care-systems-2019/.
31. Barnett D. Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. United Kingdom: NICE; 2006. p. 21.
32. Clinical Policy: Her2/neu Testing [press release]. Health Net2018.
33. Salmah binti Bahari KbS, Salbiah binti Mohd. Salleh, Norazlin binti A. Kadir, Saliza binti Ibrahim, Wong Shui Ling, Saidatul Noraishah binti Biden, Liau Siow Yen, Kamarudin bin Ahmad. MEDICINE PRICES MONITORING IN MALAYSIA. In: Division PPaD, editor. Malaysia: Pharmaceutical Services Programme; 2017.
34. FDA. National policy guidelines for the E(2) categorry drug list of the National List of Eessential Medicines (NLEM). In: Control BoD, editor. 2018.
35. Division DaD. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. In: Care MoHaL-T, editor. Ontario, CA2019.
36. Jootar S. CML treatment in Asia–Pacific region. Hematology. 2012;17(sup1):s72-s4.
37. NICE. Final scope for the appraisal of dasatinib, nilotinib and standard-dose imatinib for the first line treatment of chronic myeloid leukaemia (including part-review of TA70). National Institute for Health and Clinical Excellence; 2011. p. 3.
38. Novelli G, Predazzi IM. The genomic era and the new frontiers of medicine. Nature Publishing Group; 2009.
39. CMS. BCR-ABL Coding and Billing Guidelines Update. 2014.

40. Guttmacher AE, Collins FS. Welcome to the genomic era. Mass Medical Soc; 2003.
41. Pavelić K, Martinović T, Pavelić SK. Translational and personalized medicine. Medicine, Law & Society. 2015;8(1):25-33.
42. Movafagh A. Personalised medicine in modern era. Asian Pacific Journal of Cancer Biology. 2016;1(2):31-2.
43. Allison M. Is personalized medicine finally arriving? Nature biotechnology. 2008;26(5):509.
44. Haq ASM. HIGH COST OF MEDICINES: WHAT DO WE DO? Manila, Philippines: World Health Organization Regional Office for the Western Pacific, Pacific WHOROftW; 2016.
45. phgfoundation. Many names for one concept or many concepts in one name. 2015.
46. Xu ASL. Companion Diagnostics for Personalized Medicine Opportunities in an Evolving Landscape. Clinical Laboratory News. 2014.
47. ACE. Tyrosine Kinase Inhibitors for non-small-cell lung cancer (NSCLC). In: (ACE) TAfCE, editor. 2018: Ministry of Health; 2018.
48. FDA. Personalized Medicine and Companion Diagnostics Go Hand-in-Hand. US FDA. 2014.
49. Collins P. Personalized Medicine: From Biomarkers to Companion Diagnostics. Genetic Engineering & Biotechnology News. 2013.
50. Dillon A. Gefitinib for the first-line treatment of locally advanced or metastatic non-smallcell lung cancer. United Kingdom: National Institute for Health and Clinical Excellence; 2010. p. 45.
51. FDA U. Table of Pharmacogenomic Biomarkers in Drug Labeling. Maryland: U.S. Food and Drug Administration; 2017.
52. CMS. FDA-Approved EGFR Tests (CM00092, Vol 2). 2017. p. 1.
53. Cheng Y, Wang Y, Zhao J, Liu Y, Gao H, Ma K, et al. Real-world EGFR testing in patients with stage IIIB/IV non-small-cell lung cancer in North China: A multicenter, non-interventional study. Thorac Cancer. 2018;9(11):1461-9.
54. Patel K. Precision Medicine: Pros & Cons 2015 [Available from:

https://medium.com/@kirtipatelmd/precision-medicine-blessing-or-curse-8722c3ae94cb.

55. FDA U. Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development. In: SERVICES USDOHAH, editor.: U.S. Food and Drug Administration; 2013.
56. Cohen RL. Herceptin®: Breaking new ground. Cancer biotherapy & radiopharmaceuticals. 1999;14(1):1-4.
57. Wilson FR, Coombes ME, Wylie Q, Yurchenko M, Brezden-Masley C, Hutton B, et al. Herceptin® (trastuzumab) in HER2-positive early breast cancer: protocol for a systematic review and cumulative network meta-analysis. Systematic Reviews. 2017;6(1):196.
58. Slamon DJ, Godolphin W, Jones LA, Holt JA, Wong SG, Keith DE, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-12.
59. Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177-82.
60. Hung S-I, Chung W-H, Liou L-B, Chu C-C, Lin M, Huang H-P, et al. HLA-B* 5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(11):4134-9.
61. Somkrua R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B* 5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. BMC medical genetics. 2011;12(1):118.
62. Rattanavipapong W, Koopitakkajorn T, Praditsitthikorn N, Teerawattananon Y, Mahasirimongkol S. Economic Evaluation of HLA-B* 1502 Genotyping in Carbamazepine Induced Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrosis (TEN). Draft report. Draft report. 2012.

63. Mushiroda T, Takahashi Y, Onuma T, et al. Association of hla-a*31:01 screening with the incidence of carbamazepine-induced cutaneous adverse reactions in a japanese population. JAMA Neurology. 2018.

64. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B* 1502 allele in Thai population. Epilepsia. 2008;49(12):2087-91.

65. Ferrell PB, Jr., McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9(10):1543-6.

66. Hung S-I, Chung W-H, Jee S-H, Chen W-C, Chang Y-T, Lee W-R, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenetics and genomics. 2006;16(4):297-306.

67. Hirsch FR, Zaric B, Rabea A, Thongprasert S, Lertprasertsuke N, Dalurzo ML, et al. Biomarker Testing for Personalized Therapy in Lung Cancer in Low- and Middle-Income Countries. American Society of Clinical Oncology Educational Book. 2017(37):403-8.

68. Sanderson JD. TPMT Testing Before Starting Azathioprine or Mercaptopurine: Surely Just Do It? Gastroenterology. 2015;149(4):850-3.

69. Borse MS, Dong OM, Polasek MJ, Farley JF, Stouffer GA, Lee CR. CYP2C19-guided antiplatelet therapy: a cost–effectiveness analysis of 30-day and 1-year outcomes following percutaneous coronary intervention. Pharmacogenomics. 2017;18(12):1155-66.

70. Healthcare S. HLA-B1502 Australia: Sonic Healthcare; 2019 [Available from: https://www.sonicgenetics.com.au/tests/pgx/.

71. Woods B, Veenstra D, Hawkins N. Prioritizing Pharmacogenetic Research: A Value of Information Analysis of CYP2D6 Testing to Guide Breast Cancer Treatment. Value in Health. 2011;14(8):989-1001.

72. Brose MS, Rebbeck TR, Calzone KA, Stopfer JE, Nathanson KL, Weber BL. Cancer

risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. Journal of the National Cancer Institute. 2002;94(18):1365-72.

73. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. Jama. 2017;317(23):2402-16.
74. Butts C, Kamel–Reid S, Batist G, Chia S, Blanke C, Moore M, et al. Benefits, issues, and recommendations for personalized medicine in oncology in Canada. Current Oncology. 2013;20(5):e475.
75. Hapgood R. The potential and limitations of personalised medicine in primary care. The British Journal of General Practice. 2003;53(497):915-6.
76. Hapgood R. The potential and limitations of personalized medicine in the doctor-patient relationship. Pharmacogenomics. 2003;4(6):685-7.
77. McClellan KA, Avard D, Simard J, Knoppers BM. Personalized medicine and access to health care: potential for inequitable access? European Journal Of Human Genetics. 2012;21:143.
78. Tannock IF, Hickman JA. Limits to personalized cancer medicine. N Engl J Med. 2016;375(13):1289-94.
79. Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients, (2013).
80. Agency MaHpR. Carbamazepine, oxcarbazepine and eslicarbazepine: potential risk of serious skin reactions. In: Agency MaHpR, editor. 2012.
81. Merchant M. PRICING AND REIMBURSEMENT STRATEGIES FOR DIAGNOSTICS: Overcoming reimbursement issues and navigating the regulatory environment. USA: Business Insights Ltd; 2010.
82. CMS. SUPERSEDED Local Coverage Determination (LCD): Molecular Pathology Procedures for Human Leukocyte Antigen (HLA) Typing (L34518). Baltimore, MD: U.S. Centers for Medicare & Medicaid; 2018.
83. China Medical Regulations: Reimbursement in China: Pacific Bridge Medical; 2010 [Available from: https://www.pacificbridgemedical.com/publication/reimbursement-

in-china/.

84. Zhao X, Wang P, Tao X, Zhong N. Genetic services and testing in China. J Community Genet. 2013;4(3):379-90.
85. FEES (MEDICAL)(COST OF SERVICES) ORDER 2014. Malaysia: Ministry of Health; 2014.
86. Meckley LM, Neumann PJ. Personalized medicine: factors influencing reimbursement. Health policy. 2010;94(2):91-100.
87. Chong HY, Allotey PA, Chaiyakunapruk N. Current landscape of personalized medicine adoption and implementation in Southeast Asia. BMC medical genomics. 2018;11(1):94.
88. NHSO. Extension of the benefits of screening for HLA-B*15:02 in patients prior to carbamazepine therapy. In: Office NHS, editor. Bangkok, Thailand: National Health Security Office (NHSO); 2019.
89. Pulciani S, Taruscio D. Patient-physician alliance: from Hippocrates to Post-Genomic Era. Annali dell'Istituto superiore di sanita. 2017;53(2):93-5.
90. DMSC. Precision medicine. In: Sciences DoM, editor. Bangkok, Thailand2019.
91. Spoon M. History of Personalized Medicine 2014 [Available from: https://health.howstuffworks.com/medicine/modern-treatments/personalized-medicine1.htm.
92. Sykiotis GP, Kalliolias GD, Papavassiliou AG. Hippocrates and Genomic Medicine. Archives of Medical Research. 2006;37(1):181-3.
93. Arnold RM, Forrow L. Rewarding medicine: good doctors and good behavior. Annals of internal medicine. 1990;113(10):794-8.
94. Laboratory PHO. HIV Genotyping, Resistance, Tropism and HLA-B*57:01 Abacavir Hypersensitivity Testing. 2019. p. 3.
95. Ginsburg GS, McCarthy JJ. Personalized medicine: revolutionizing drug discovery and patient care. Trends in Biotechnology. 2001;19(12):491-6.
96. NCI. NCI Dictionary Of Cancer Terms National Institutes of Health: National Cancer Institute; 2012 [Available from:

https://www.cancer.gov/publications/dictionaries/cancer-terms/def/personalized-medicine.

97. Jameson JL, Longo DL. Precision Medicine — Personalized, Problematic, and Promising. New England Journal of Medicine. 2015;372(23):2229-34.

98. Healthcare S. HLA-B5801 Australia: Sonic Healthcare; 2019 [Available from: https://www.sonicgenetics.com.au/tests/pgx/.

99. PMC. The Age of Personalized Medicine Fact Sheet (PDF): Personalized Medicine Coalition; [Available from: http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_age_of_pmc_factsheet.pdf.

100. Allopurinol-induced serious cutaneous adverse reactions and the role of genotyping, (2016).

101. Plumpton CO, Alfirevic A, Pirmohamed M, Hughes DA. Cost effectiveness analysis of HLA-B*58:01 genotyping prior to initiation of allopurinol for gout. Rheumatology. 2017;56(10):1729-39.

102. Topol Eric J. Individualized Medicine from Prewomb to Tomb. Cell. 2014;157(1):241-53.

103. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. Nature Reviews Drug Discovery. 2007;6:287.

104. Hood L. A Personal Journey of Discovery: Developing Technology and Changing Biology. Annual Review of Analytical Chemistry. 2008;1(1):1-43.

105. Schleidgen S, Klingler C, Bertram T, Rogowski WH, Marckmann G. What is personalized medicine: sharpening a vague term based on a systematic literature review. BMC Medical Ethics. 2013;14:55-.

106. Estape ES, Mays MH, Sternke EA. Translation in Data Mining to Advance Personalized Medicine for Health Equity. Intelligent information management. 2016;8(1):9-16.

107. Im H, Lee H, Castro CM. Challenges influencing next generation technologies for

precision medicine. Expert Review of Precision Medicine and Drug Development. 2016;1(2):121-3.

108. MS Announces 6-Month Period of Enforcement Discretion for Laboratory Date of Service Exception Policy Under the Medicare Clinical Laboratory Fee Schedule (the "14 Day Rule") [press release]. Fort Myers, FL: Neogenomics2018.
109. Kisor D SS. THE PERSONALIZED MEDICINE REPORT 2017: Opportunity, Challenges, and the Future. Washington DC: Personalized Medicine Coalition; 2017.
110. Alliance G. Understanding genetics: a New York, mid-Atlantic guide for patients and health professionals. Washington, Dc: Lulu. com; 2009.
111. What is genetic testing? USA: U.S. National Libraly of Medicine; 2018 [Available from: https://ghr.nlm.nih.gov/primer/testing/genetictesting.
112. Healthcare S. UGT1A1 Screen Australia: Sonic Healthcare; 2019 [Available from: https://www.sonicgenetics.com.au/tests/pgx/.
113. Mulder SD, Heijst JA, Mulder C, Martens F, Hack CE, Scheltens P, et al. CSF levels of PSA and PSA-ACT complexes in Alzheimer's disease. Annals of clinical biochemistry. 2009;46(Pt 6):477-83.
114. Healthcare S. Pharmacogenomic Screen (Sonic PGx Panel) Australia: Sonic Healthcare; 2019 [Available from: https://www.sonicgenetics.com.au/tests/pgx/.
115. CMS. SUPERSEDED Local Coverage Determination (LCD): CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35698). Baltimore, MD: U.S. Centers for Medicare & Medicaid Services; 2019.
116. PhRMA. Therapeutic area distribution of personalized medicine in the U.S. In: Department SR, editor. United States: Statista; 2013.
117. FDA U. Companion Diagnostics: U.S. Food Drug Administration; 2018 [Available from: https://www.fda.gov/medical-devices/vitro-diagnostics/companion-diagnostics.
118. Cancer. In: Organization WH, editor. Cancer Fact sheet N°2972018.
119. What Is Cancer? USA: National Cancer Institute; 2015 [updated February 9, 2015. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
120. Ferlay J SI, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D,

Bray F. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 v1.0. IARC CancerBase. 2012;No. 11.

121. Stein C, Colditz G. Modifiable risk factors for cancer. British Journal of Cancer. 2004;90(2):299.
122. Hristova L, Hakama M. Effect of screening for cancer in the Nordic countries on deaths, cost and quality of life up to the year 2017. Acta Oncologica (Stockholm, Sweden). 2017;36:1-60.
123. Care OMoHaL-T. Ontario Physician's Guide to Referral for Patients with a Family History of Cancer to a Familial Cancer Genetics Clinic or Genetics Clinic. In: Care OMoHaL-T, editor. Kingston, ON: Ministry of Health; 2001. p. 2.
124. Chieng W-S, Lee S-C. Establishing a cancer genetics programme in Asia - the singapore experience. Hered Cancer Clin Pract. 2006;4(3):126-35.
125. Jain KK. Textbook of personalized medicine. 2 ed: Springer; 2016.
126. Grindedal EM, Heramb C, Karsrud I, Ariansen SL, Mæhle L, Undlien DE, et al. Current guidelines for BRCA testing of breast cancer patients are insufficient to detect all mutation carriers. BMC cancer. 2017;17(1):438-.
127. Fleck R, Bach D. Trends in personalized therapies in oncology: the (venture) capitalist's perspective. Journal of personalized medicine. 2012;2(1):15-34.
128. Tuckson RV. Coverage and Reimbursement of Genetic Tests and Services Bethesda, MD: Secretary of Health and Human Services (HHS); 2006.
129. Introduction to Infectious Diseases Houston, Texas: Baylor College of Medicine; 2018 [Available from: https://www.bcm.edu/departments/molecular-virology-and-microbiology/emerging-infections-and-biodefense/introduction-to-infectious-diseases.
130. WHO. Cardiovascular diseases (CVDs): Key Facts: WHO; 2017 [Available from: http://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
131. Risk Factors for Cardiovascular Disease (CVD) Berkshire, UK: HEART UK; 2015 [Available from: https://heartuk.org.uk/files/uploads/documents/huk_fs_mfsl_riskfactorsforchd_v2.pdf.

132. Lee M-S, Flammer AJ, Lerman LO, Lerman A. Personalized Medicine in Cardiovascular Diseases. Korean Circulation Journal. 2012;42(9):583-91.
133. Shahin MHA, Johnson JA. Clopidogrel and warfarin pharmacogenetic tests: what is the evidence for use in clinical practice? Current opinion in cardiology. 2013;28(3):305-14.
134. Mega JL, Simon T, Collet J-P, Anderson JL, Antman EM, Bliden K, et al. Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI: A Meta-Analysis. JAMA : the journal of the American Medical Association. 2010;304(16):1821-30.
135. Moss AJ, Daubert, James P. Congenital long QT syndrome: considerations for primary care physicians. Cleveland Clinic journal of medicine. 2008;75(8):591.
136. Böhm R, Cascorbi I. Pharmacogenetics and Predictive Testing of Drug Hypersensitivity Reactions. Frontiers in pharmacology. 2016;7:396-.
137. Sukasem C, Puangpetch A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. Asian Pacific journal of allergy and immunology. 2014;32(2):111.
138. Chang C-C, Too C-L, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens–Johnson syndrome in the multi-ethnic Malaysian population. International Journal of Dermatology. 2011;50(2):221-4.
139. Lim KS, Kwan P, Tan CT. Association of HLA-B* 1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review. Neurol Asia. 2008;13(6):15-21.
140. Shi Y-W, Min F-L, Qin B, Zou X, Liu X-R, Gao M-M, et al. Association between HLA and Stevens–Johnson Syndrome Induced by Carbamazepine in Southern Han Chinese: Genetic Markers besides B*1502? Basic & Clinical Pharmacology & Toxicology. 2012;111(1):58-64.
141. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B* 1502 and carbamazepine-induced severe cutaneous

adverse drug reactions in a Thai population. Epilepsia. 2010;51(5):926-30.

142. Cheng H, Yan D, Zuo X, Liu J, Liu W, Zhang Y. A retrospective investigation of HLA-B* 5801 in hyperuricemia patients in a Han population of China. Pharmacogenetics and genomics. 2018;28(5):117-24.
143. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Human Molecular Genetics. 2010;20(5):1034-41.
144. Song JS, Kang E-S, Joo EY, Hong SB, Seo D-W, Lee S-Y. Absence of HLA-B* 1502 and HLA-A* 3101 alleles in 9 Korean patients with antiepileptic drug-induced skin rash: a preliminary study. Annals of laboratory medicine. 2014;34(5):372-5.
145. Lucas A, Nolan D, Mallal S. HLA-B*5701 screening for susceptibility to abacavir hypersensitivity. Journal of Antimicrobial Chemotherapy. 2007;59(4):591-3.
146. Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. The Lancet. 2002;359(9308):727-32.
147. Martin AM, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. Proceedings of the National Academy of Sciences. 2004;101(12):4180-5.
148. Saag M, Balu R, Phillips E, Brachman P, Martorell C, Burman W, et al. High Sensitivity of Human Leukocyte Antigen-B*5701 as a Marker for Immunologically Confirmed Abacavir Hypersensitivity in White and Black Patients. Clinical Infectious Diseases. 2008;46(7):1111-8.
149. Institute NC. BRCA Mutations: Cancer Risk and Genetic Testing USA: National Cancer Institute; 2018 [updated January 30, 2018. Available from: https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet.
150. Dinh P, Piccart MJ. HER2-Targeted Therapy. In: Jatoi I, Rody A, editors. Management of Breast Diseases. Cham: Springer International Publishing; 2016. p. 391-410.

151. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. The Lancet. 1999;353(9154):717-9.

152. Marra CA, Esdaile JM, Anis AH. Practical pharmacogenetics: the cost effectiveness of screening for thiopurine s-methyltransferase polymorphisms in patients with rheumatological conditions treated with azathioprine. The Journal of Rheumatology. 2002;29(12):2507.

153. Epidermal Growth Factor Receptor Mutation (EGFR) Testing for Prediction of Response to EGFR-Targeting Tyrosine Kinase Inhibitor (TKI) Drugs in Patients with Advanced Non-Small-Cell Lung Cancer: An Evidence-Based Analysis. Ontario health technology assessment series. 2010;10(24):1-48.

154. de Lima Lopes G. Societal Costs and Benefits of Treatment with Trastuzumab in Patients with Early HER2neu-Overexpressing Breast Cancer in Singapore. BMC Cancer. 2011;11(1):178.

155. Shitara K, Yatabe Y, Matsuo K, Sugano M, Kondo C, Takahari D, et al. Prognosis of patients with advanced gastric cancer by HER2 status and trastuzumab treatment. Gastric Cancer. 2013;16(2):261-7.

156. Allingham-Hawkins D, Lea A, Levine S. KIF6 p.Trp719Arg Testing to Assess Risk of Coronary Artery Disease and/or Statin Response. PLoS Curr. 2010;2:RRN1191-RRN.

157. Allomap: Personalizing Care for Heart Transplant Patients: CareDx; 2005 [Available from: http://www.allomap.com/.

158. Administration USFaD. Step 1: Discovery and Development. Silver Spring, MD: U.S. Food and Drug Administration

2018.

159. Jain K. Personalized medicine. Current opinion in molecular therapeutics. 2002;4(6):548-58.

160. Bumgarner R. DNA microarrays: Types, Applications and their future. Current protocols in molecular biology / edited by Frederick M Ausubel [et al]. 2013;0 22:Unit-22.1.

161. Stebbing J, Copson E, O'Reilly S. Herceptin (trastuzamab) in advanced breast cancer. Cancer treatment reviews. 2000;26(4):287-90.
162. Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359(9312):1121-2.
163. Wang L, McLeod HL, Weinshilboum RM. Genomics and drug response. New England Journal of Medicine. 2011;364(12):1144-53.
164. King M-C, Marks JH, Mandell JB. Breast and Ovarian Cancer Risks Due to Inherited Mutations in BRCA1 and BRCA2. Science. 2003;302(5645):643-6.
165. IA Cree GDB, B Flamion, D Friese, D Haerry, JS Hulot and et al. Personalised Medicine – Opportunities and Challenges for European HealthCare. In: Rosenmüller M, editor. Personalised Medicine – Opportunities and Challenges for European HealthCare2010.
166. Rice T, Rosenau P, Unruh LY, Barnes AJ, Saltman RB, van Ginneken E. Health Systems in Transition. Health. 2013;15(3).
167. Deiaco E. China's Healthcare System – Overview and Quality Improvements. Östersund, Sweden: The Swedish Agency for Growth Policy Analysis (Growth Analysis); 2013.
168. Franck Le Deu LMaJW. An Essential strategy for the Essential Drug List. China: McKinsey & Company 2014.
169. Mossialos E, Ge Y, Hu J, Wang L. Pharmaceutical policy in China: challenges and opportunities for reform. World Health Organization, available at http://www euro who int/__data/assets/pdf_file/0020/320465/Pharmaceutical-policy-China-challengesopportunities-reform pdf. 2016.
170. Fees, Patient Contributions and Safety Net Thresholds. In: Health Do, editor. Commonwealth of Australia2018.
171. Motulsky AG, Holtzman NA, Fullarton JE, Andrews LB. Assessing genetic risks: implications for health and social policy: National Academies Press; 1994.
172. Medicine USNLo. What are the risks and limitations of genetic testing? In: Reference

GH, editor. MD, USA: U.S. National Library of Medicine; 2018.

173. LIMITATIONS OF GENETIC TESTING: Genetic Disease Foundation; [Available from: http://www.knowyourgenes.org/limitations-of-testing.shtml.

174. Kessler L, Collier A, Brewster K, Smith C, Weathers B, Wileyto EP, et al. Attitudes about genetic testing and genetic testing intentions in African American women at increased risk for hereditary breast cancer. Genetics in medicine : official journal of the American College of Medical Genetics. 2005;7(4):230-8.

175. Haga SB, Barry WT, Mills R, Ginsburg GS, Svetkey L, Sullivan J, et al. Public Knowledge of and Attitudes Toward Genetics and Genetic Testing. Genetic Testing and Molecular Biomarkers. 2013;17(4):327-35.

176. Ravine D, Suthers G. Quality standards and samples in genetic testing. Journal of Clinical Pathology. 2012.

177. Bertolotti M. Opportunities, Risks, and Limitations of Genetic Testing: Looking to the Future From Patients' Point of View. Mayo Clinic Proceedings. 2015;90(10):1311-3.

178. Uhlmann WR, Roberts JS. Ethical Issues in Neurogenetics. Handbook of clinical neurology. 2018;147:23-36.

179. Desk WBDH. World Bank Country and Lending Groups 2018 [Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

180. Gross national income per capita 2018, Atlas method and PPP [Internet]. 2018 [cited October 24]. Available from: https://databank.worldbank.org/data/download/GNIPC.pdf.

181. Public Spending on Health: A Closer Look at Global Trends [Internet]. WHO. 2018. Available from: http://apps.who.int/nha/database/Home/Index/en.

182. Pharmaceutical Benefits; Fees, Patient Contributions and Safety Net Thresholds. In: Health Do, editor. Australia2019.

183. Martin D, Miller AP, Quesnel-Vallée A, Caron NR, Vissandjée B, Marchildon GP. Canada's universal health-care system: achieving its potential. The Lancet. 2018;391(10131):1718-35.

184. Canada's Health Care System. In: Canada H, editor. Ottawa, Ontario, CA2019.

185. Marchildon GP. Health systems in transition : Canada. Toronto [Ont.]: University of Toronto Press; 2013. Available from: http://www.deslibris.ca/ID/445959, http://site.ebrary.com/id/10722350, http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&db=nlabk&AN=682998, http://www.jstor.org/stable/10.3138/j.ctt5hjtdh

https://www.overdrive.com/search?q=F77E0B0E-C5FD-4CA9-889B-0B0AF3FA8CE2, http://public.ebookcentral.proquest.com/choice/publicfullrecord.aspx?p=4669222, http://books.scholarsportal.info/viewdoc.html?id=/ebooks/ebooks3/utpress/2013-10-15/1/9781442616417, http://files.deslibris.ca/covers-medium/445/445959.jpg, http://files.deslibris.ca/covers/445/445959.jpg, http://samples.overdrive.com/?crid=f77e0b0e-c5fd-4ca9-889b-0b0af3fa8ce2&.epub-sample.overdrive.com, http://images.contentreserve.com/ImageType-100/5826-1/{F77E0B0E-C5FD-4CA9-889B-0B0AF3FA8CE2}Img100.jpg, http://celarc.ca/covers-medium/445/445959.jpg, http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=e000xna&AN=682998, http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&AN=682998, http://er.llcc.edu:2048/login?url=http://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&AN=682998, http://www.library.yorku.ca/e/resolver/id/2514540, https://search.ebscohost.com/login.aspx?direct=true&scope=site&db=nlebk&AN=682998.

186. Population and Population Structure. In: Statistics SDo, editor. Singapore2018.

187. Group WB. GNI (current US$). World Bank Group; 2018.

188. M. Ramesh ASB. The healthcare system in Singapore. In: Lee kuan Yew School of Public Policy NUoS, editor. Singapore2019.

189. Bai Y, Shi C, Li X, Liu F. Healthcare System in Singapore ACTU4625 Topics: Health

Insurance [online]. 2012 [cited on: June 25 th, 2013 10.10 pm].

190. Healthcare Schemes & Subsidies. In: Website ASGA, editor. Singapore: Government of Singapore; 2019.
191. Infoplease. Countries of the World: Infoplease 2019 [Available from: https://www.infoplease.com/world/countries.
192. Mossialos E, Wenzl M, Osborn R, Sarnak D. 2015 international profiles of health care systems: Canadian Agency for Drugs and Technologies in Health; 2016.
193. Get help with prescription costs. In: England Ni, editor. England: The NHS in England; 2017.
194. Services. USCfMM. What's Medicare? USA: U.S. Centers for Medicare & Medicaid Services.; 2018 [Available from: https://www.medicare.gov/sign-up-change-plans/decide-how-to-get-medicare/whats-medicare/what-is-medicare.html.
195. Shinseki EK. Open Government Plan. In: Affairs USDoV, editor.: U.S. Department of Veterans Affairs; 2010.
196. Jaafar S, Mohamad Noh K, Abd Muttalib K, Nour Hanah Othman M, Judith Healy M. Malaysia Health System Review, Health Systems in Transition" Vol. 3 No. 1 20132013.
197. Group TWB. Health Financing Note: East Asia and Pacific Region. The World Bank Group, Human Development Sector, East Asia and Pacific Region; 2010.
198. Mehmet Yorulmaz NNM. Malaysia Health System Review: Overviews and Opinions. International Health Administration and Education (Sanitas Magisterium). 2019;5(1).
199. World Population Prospects: The 2019 Revision. In: Elaboration of data by United Nations DoEaSA, Population Division, editor. Worldometersinfo: Elaboration of data by United Nations, Department of Economic and Social Affairs, Population Division; 2019.
200. WHO. Thailand Nonthaburi, Thailand: The WHO Representative; 2018 [Available from: https://www.who.int/countries/tha/en/.
201. Tangcharoensathien V, Jongudomsuk P, Srithamrongsawat S, Patcharanarumol W, Limwattananon S, Pannarunothai S. The Kingdom of Thailand Health Systen Review.

Health systems in transition. 2015;5(5).

202. Jongudomsuk P, Srithamrongsawat S, Patcharanarumol W, Limwattananon S, Pannarunothai S, Vapatanavong P, et al. The Kingdom of Thailand health system review (Health Systems in Transition, Vol 5 No 5). Manila: World Health Organization (Asia Pacific Observatory on Health Systems and Policies). 2015.
203. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International journal of cancer. 2019;144(8):1941-53.
204. Papay J, Yuen N, Powell G, Mockenhaupt M, Bogenrieder T. Spontaneous adverse event reports of Stevens–Johnson syndrome/toxic epidermal necrolysis: detecting associations with medications. Pharmacoepidemiology and Drug Safety. 2012;21(3):289-96.
205. Bannister W, Friis-Møller N, Mocroft A, Viard J-P, Van Lunzen J, Kirk O, et al. Incidence of abacavir hypersensitivity reactions in EuroSIDA. Antiviral therapy. 2008;13:687-96.
206. International Profiles of Health Care Systems [press release]. United States: THE COMMONWEALTH FUND2017.
207. Yingpaiboonwong J. Central mechanism for integration of health insurance systems in Thailand. Bangkok: Thailan development research institute; 2019. p. 10.
208. Annual Medicare Statistics. In: Health Tdo, editor. Australia: Department of Health; 2019.
209. Release CBsN. Over 4 Million Canadians Do Not Take Advantage of Prescription Drug Plans Available to Them. Conference Board's News of Canada. 2017.
210. MediSave. In: Board CPF, editor. Singapore: Government of Singapore; 2019.
211. NHS. A – Registrations by GP practice and CCG – Nov 17 to Oct 18. NHS England; 2019.
212. Medicare Beneficiaries at a Glance. Maryland, United Stated: U.S. Centers for Medicare & Medicaid Services; 2019 09/26/2019.
213. Schackman BR, Scott CA, Walensky RP, Losina E, Freedberg KA, Sax PE. The cost-

effectiveness of HLA-B*5701 genetic screening to guide initial antiretroviral therapy for HIV. AIDS. 2008;22(15):2025-33.

214. Thompson AJ, Newman WG, Elliott RA, Roberts SA, Tricker K, Payne K. The cost-effectiveness of a pharmacogenetic test: a trial-based evaluation of TPMT genotyping for azathioprine. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2014;17(1):22-33.
215. M. Whirl-Carrillo EMM, J. M. Hebert, L. Gong, K. Sangkuhl, C.F. Thorn, R.B. Altman and T.E. Klein. Pharmacogenomics Knowledge for Personalized Medicine. Clinical Pharmacology & Therapeutics. 2012;4:92.
216. Chen P, Lin J-J, Lu C-S, Ong C-T, Hsieh PF, Yang C-C, et al. Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan. New England Journal of Medicine. 2011;364(12):1126-33.
217. Khosama H, Budikayanti A, Khor AHP, Lim KS, Ng C-C, Mansyur IG, et al. HLA-B* 1502 and carbamazepine induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Indonesia. Neurology Asia. 2017;22(2).
218. Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Prabmechai N, Vannaprasaht S, et al. HLA-B*1502 Strongly Predicts Carbamazepine-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis in Thai Patients with Neuropathic Pain. Pain Practice. 2012;12(3):202-8.
219. Oliva-Moreno J, Puig-Junoy J, Trapero-Bertran M, Epstein D, Pinyol C, Sacristán JA. Economic Evaluation for Pricing and Reimbursement of New Drugs in Spain: Fable or Desideratum? Value in Health. 2019.
220. Drummond M, Jönsson B, Rutten F. The role of economic evaluation in the pricing and reimbursement of medicines. Health Policy. 1997;40(3):199-215.
221. Simeonidis S, Koutsilieri S, Vozikis A, Cooper DN, Mitropoulou C, Patrinos GP. Application of Economic Evaluation to Assess Feasibility for Reimbursement of Genomic Testing as Part of Personalized Medicine Interventions. Frontiers in pharmacology. 2019;10:830-.
222. Petrisor B, Bhandari M. The hierarchy of evidence: Levels and grades of

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