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Regionalized Management of Medicine

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Translational Bioinformatics

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Series Editor

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Translational bioinformatics is defined as the development of storage-related, analytic, and interpretive methods to optimize the transformation of increasingly voluminous biomedical data, and genomic data in particular, into proactive, predictive, preventive, and participatory health. Translational bioinformatics includes research on the development of novel techniques for the integration of biological and clinical data and the evolution of clinical informatics methodology to encompass biological observations. The end product of translational bioinformatics is the newly found knowledge from these integrative efforts that can be disseminated to a variety of stakeholders including biomedical scientists, clinicians, and patients. Issues related to database management, administration, or policy will be coordinated through the clinical research informatics domain. Analytic, storage-related, and interpretive methods should be used to improve predictions, early diagnostics, severity monitoring, therapeutic effects, and the prognosis of human diseases.

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Regionalized Management of Medicine

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Preface

This book with a high focus on "Regionalized Management of Medicine" for this understanding originally stemmed from our improvement of understanding and vision in the importance and significance of "regionalization" during our medical practice, hospital management, and information sharing. The meaning of regionalization does not tell us to "limit" our knowledge and experience or make issues more confidential. In opposite, we highly encourage that data collection, storage, and preservation should be more open to reachable collaborators, partners, and societies. We highly encourage that the members of the regionalized alliance have the right to access legacy materials created with outdated technology. It is our passions to call the special attentions from researchers, clinicians, managers, and leaders on regionalized collaborations and development.

I also would like to express my deep appreciations to all co-editors, Hui Shen who is the president of Jinshan Hospital of Fudan University, Yiming Zeng who is the president of The Second Hospital of Fujian Medical University, and Li Li who is the director of Scientific Research and Education of Henan Province People's Hospital of Zhengzhou University, China, to all assistant editors, Feiyu Yang and Dongli, Song, and to all authors of chapters, for their efforts and supports as well as hard works. I also appreciate colleagues from Nature Springer for the great and unwavering efforts and supports.

"Regionalized Management of Medicine" is a new strategy to optimally perform medical practice and management. I expect more advances in regionalized management of medicine, especially in update of new biotechnology, application of therapeutic strategy, and understanding of disease-associated molecular mechanisms. I expect more developing in medical informatics, systems analysis, database sharing, and artificial intelligent for improving the quality of hospital managements, disease therapies, regional collaborations, and medical services in future.

Shanghai, China
October 20, 2021

Xiangdong Wang

Contents

About the Editors

Hui Shen, MD is the dean of Jinshan Hospital Affiliated to Fudan University and president of Yangtze River Delta Integration Gene Testing Alliance, Shanghai, China. His research focus on studying hospital human resource management, cultural construction, and hospital operation process. He is also the standing director of Shanghai Hospital Association and vice president of Shanghai Health Education Association (president of Hospital Branch).

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Xiangdong Wang, MD, PhD is a distinguished professor of medicine at Fudan University, director of Shanghai Institute of Clinical Bioinformatics, director of Fudan University Center of Clinical Bioinformatics, director of Shanghai Shanghai Engineering Research Center for AI Technology of Cardiopulmonary Diseases, deputy director of Shanghai Respiratory Research Institute, executive director of Clinical Science Institute of Fudan University Zhongshan Hospital, and visiting professor of King's College of London. He serves as the president of Chinese Society of Gene Technology and deputy president of National Committee of Clinical Precision Medicine, Chinese Medical Doctor Association. His main research is focused on single cell sequencing, clinical bioinformatics, disease-specific biomarkers, lung chronic diseases, cancer immunology, and molecular and cellular therapies. He is the author of more than 300 scientific publications with the impact factor about 1100, citation number about 9923, h-index 51, and i10-index 256.

Chapter 1
The Importance of Regionalized Management of Medicine

Hui Shen, Yiming Zeng, Qinqi Ling, Li Li, and Xiangdong Wang

Abstract The present book presents the new and international understanding, vision, and experience on regionalized management of medicine, including clinical practice, knowledge, methods, and effectiveness. The regionalized management is a new approach to gather all strengths, resources, and facilities and improve the effectiveness, efficiency, and outcome of medical services and clinical therapies.

Keywords Regionalized management · Clinical · Hospitals · Medicine

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Regionalized management of medicine is defined as the management of case, care, patient, disease, and therapy-associated activities that is regionalized according to geographical locations, culture-associated living, and collaboration-based regions. Regionalized management of medicine also includes the share of medical information, resource, transport/delivery, Internet medication, and new technologies. For example, fucoidan from brown seaweed was suggested to have various biological and pharmacological activities, especially anticancer/antitumor, anti-proliferation, and anti-inflammatory and immune-modulatory functions (Hsu and Hwang 2019). As a complementary therapy, fucoidan was applied to patients with cancer after operation or in severe condition in the scientific collaboration-based regions. Regionalized management of medicine plays an important role in clinical and translational medicine from bench to patient, from patient to bench, and from patient to policy, to improve the quality of life in patients as suggested (Cheng et al. 2020). Regionalized management of medicine is also a critical approach to face the unexpected challenge like COVID-19, since the current status of infection management lacks the regionalized management system and organization, dependent upon either the government or hospital itself. Clinical laboratory features to distinguish COVID-19 from community-acquired pneumonia were identified by a group/hospital (Pan et al. 2020), while those characters of routine laboratory tests failed to be shared among regional hospitals and be an efficient tool for clinical diagnosis and therapy.

Regionalized management of medicine is a shortcut to introduce and develop a new therapeutic strategy among hospitals. The "multidisciplinary therapy strategy of precision medicine" was proposed as a new approach for clinical practice, decision-making, and therapies for complicated cancer (Qian et al. 2020). The strategy provides optimal and precise therapy for the individual patient by integrating multidisciplinary experts and developing real-time therapeutic strategy based on clinical phenomes, gene sequencing of tissue DNA, and circulating DNA. In order to extend such strategy into regional hospitals, the Yangtze River Delta integration alliance of gene test was used as a platform to educate clinical nurses and physicians, train techniques and operations, and organize clinical practice of multidisciplinary therapy strategy of precision medicine. This can be an example of regionalized management in clinical application of gene sequencing for tumor therapy. Yan et al. shared the experience of regional alliance to measure gene sequencing to support clinical decision-making for target therapy and efficacy evaluation (Yan et al. 2021).

The aim of this book entitled *Regionalized Management of Medicine* is to share the understanding of regionalized management scope and definition, the experience of regionalized management of medicine in practice, and the knowledge of scientific and clinical research in molecular medicine. Hwang and Williams described the importance of medical informatics in management of patients with alcohol use disorder by using hospital system-wide solutions, managing patient populations, and supporting public health efforts (Hwang and Williams 2021). Regionalized management of medical information, informatics, clinical phenomes, and therapies can be an efficient approach to dynamically control and follow-up patients.

Precision medicine is an emerging approach for doctors to select individual treatments based on a genetic understanding of the disease. One of the most important issues in performance and regionalization of clinical precision medicine is to standardize management, technology, and standards of precision medicine. Tan et al. described the development and advancement in gene sequencing technologies, next-generation sequencing in clinic (Tan et al. 2021). Qian et al. emphasized the importance of precision medicine and headlined the understanding of "Clinical Precision Medicine" as an up-to-date resource on precision medicine and pathways toward clinical performance for clinicians and researchers (Qian et al. 2021). It is the first time to share their own typical workflow and experience of metagenomic gene sequencing in details, e.g., sample collection, nucleic acid extraction, library construction, sequencing, data analysis, and report writing. It is also the first time to introduce the standardization of clinical practice in metagenomic gene sequencing, interpretation of positive and negative results, and potential of regional application.

Artificial intelligence can be an important tool of regionalized management of medicine and is considered as the predictive and prognostic power of molecular biomarkers in clinical and translational medicine. For example, the DNp73 expression was identified as a predictive marker for the 5-year prediction and prognosis of the rectal cancer patients in aid of artificial intelligence management (Pham et al. 2020). Artificial intelligence was also found to be valuable to monitor the occurrence of acute lung injury in patients with COVID-19 infection and clinical phenomes of patients with COVID-19 infection (Li et al. 2020; Zhang et al. 2020). In this book, Briganti overviewed the importance of artificial intelligence as a tool to improve the quality of medical care, design of development studies, and models and testing the effectiveness (Briganti 2021). It is necessary to evaluate the strengths of regional medical resources and build bridges between the industrial and healthcare sectors. In addition to medical care, the artificial intelligent single cell was proposed as a single-cell-like system with computerized databases, digitalized informatics of biological elements, and programmed function and signals (Zeng et al. 2018). The artificial intelligent single cell can act not only as an optimal system with a full understanding of cell molecular profiles, intelligent capacity of functioning and deep learning, and precise interpretation of measurements but also as a decision-making assistant and a powerful tool to monitor clinical phenotypes and molecular networks in patient response to therapies, especially for regionalized management of medicine.

One of the most exciting issues here is that the book also combines new sights of understanding about deep science with frontline bioanalysis, to offer an example how to promote the advanced disciplines and talent development during hospital management. Huang et al. described the importance to translate the synthetic lethality to therapy by the synthesis of genetic interaction data from model organisms, tumor genomes, and human cell lines, and to identify nonintuitive targets for improving drug resistance (Huang et al. 2021). Tang et al. headlined the new understanding of epigenetics and DNA methylation in regulating gene expression throughout the genome, linking environmental factors with genetic susceptibility factors in lung diseases (Tang et al. 2021). With the rapid development of bioinformatics, clinical bioinformatics become more important and applicable for clinical

practice in the identification and development of disease diagnosis and prognosis prediction. Liu et al. addressed the important role of clinical bioinformatics in the understanding of pathogenesis, in the discovery of disease-specific biomarkers and therapeutic targets, and in the prediction of patient prognosis (Liu et al. 2021). This will benefit clinical mangers and leaders to understand the techniques of clinical bioinformatics and to solve clinical problems.

The experience of regionalized management from various locations is shared in the book. Ferna´ndez et al. demonstrated that the inventory management as an essential task was performed at the pharmacy department in Spain and presented different and contradictory optimization criteria, more challenges to be overcome, and advanced demand estimation methods and control techniques (Fernández et al. 2021). Dogan shared the experience and understanding of symptom and life quality management in patients with cancers in Turkey (Dogan 2021). Ling et al. shared a mode of the "Fudan-Minhang Medical Alliance" in China to develop a healthcare system for regionalized management on medical, educational, and research aspects of healthcare services (Ling et al. 2021). This is an approach to strengthen the regional medical management and improve the service quality and ability to reform the medical and health system. Belciuga discussed potential factors associated with bed-occupancy management and hospital planning in Romania, including diseases, patients' characteristics, cultural background, budget, local and national political considerations, and others (Belciuga 2021). This provides a management mechanism by which the efficacy of bed utilization can be improved. Jahan shared Japanese experience on management of severe childhood pneumonia in low resource setting, especially when clinic beds were limited in developing countries (Jahan 2021). This strategy on the basis of WHO guidelines can be realistic and applicable for developing and other developed and/or underdeveloped countries with cost-effectiveness. Pires et al. emphasized the importance and effectiveness of the mission in the management, which should be realistic, acceptable, implementable, and motivative (Pires et al. 2021).

In conclusion, the present book presents the new understanding, vision, and experience on regionalized management of medicine, including clinical practice, knowledge, methods, and effectiveness. The regionalized management is a new approach to gather all strengths, resources, and facilities and improve the effectiveness, efficiency, and outcome of medical services and clinical therapies.

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Chapter 2
Alcohol Use Disorders: Leveraging Informatics to Improve Patient Care

Calvin Hwang and Lyncan Williams

Abstract Alcohol use disorders (AUDs) is a worldwide public health problem. Incidence and severity may vary based on geography, culture, and individual genetics. Pharmacogenomics offers the potential for personalized medicine of patients with specific genetic profiles. Informatics may help clinicians better identify patients with have or are at-risk for AUD. It may also offer better, more standardized in-hospital and ambulatory treatments. Lastly, integrated informatics efforts may better inform decision makers of more effective public health approaches.

Keywords Alcohol use disorders · CIWA · SBI · Public health · EHR

2.1 Introduction

The use of electronic health records (EHRs) in clinical medicine has improved the detection, treatment, and prevention of alcohol use disorders in multiple settings. This chapter explores the various ways in which medical informatics has impacted laboratory research, clinical medicine, and finally, public health systems.

Worldwide, alcohol is the seventh leading risk factor for poor health. In 2016, it was estimated that alcohol was associated with three million deaths (5.3% of all deaths) and 132.6 million disability-adjusted life years (5.1% of all DALYs) (Fig. 2.1). Harmful alcohol use contributed to more than 200 diseases and injury-related health conditions, most notably DSM-IV alcohol dependence, liver cirrhosis, cancers, and injuries (WHO Alcohol Fact Sheet 2021).

According to the WHO, the European region continues to have the heaviest alcohol consumption in the world. It is estimated that of the 70% of Europeans

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Fig. 2.1 Total alcohol per capita consumption (APC) (15+ years; in liters of pure alcohol), 2016 Source: WHO. Global status report on alcohol and health 2018

who drink, 31.5% of men and 12.6% of women report heavy episodic drinking. On average, Europeans consume 10.7 L of pure alcohol each year. Average consumption of alcoholic beverages varies widely between WHO European Region member countries, from an average of 3.9% in the Southeast European subregion (Anon n.d.-a) to as high as 14.4% in the Eastern European subregion (Anon n.d.-b; WHO Regional Office for Europe, Alcohol Use 2021).

Use of alcohol in the USA mirrors that of Europe, with 55.3% reporting use in the past month and 26.5% reporting heavy episodic drinking (Substance Abuse and Mental Health Services Administration (SAMSA) 2021). In 2010, alcohol misuse cost the USA $249 billion with three-quarters of the total cost related to heavy episodic drinking (Sacks et al. 2015).

Though the prevalence of alcohol consumption in China is lower than most Western populations, it has increased more than 50-fold from 0.4 L in 1952 to 4.9 L in 2009 of pure alcohol (Cochrane et al. 2003). The China Kadoorie Biobank cohort found that 33% of Chinese men drink regularly (compared to 2% of women) with an increase in the proportion engaging in heavy episodic drinking increasing from 30 to 35% between 2004 and 2008 (Im et al. 2019). Left unchecked, this will have profound systemic health impacts in the future.

Much of the variation in alcohol use behavior may be due to cultural norms. Unlike many diseases, AUDs are often described in qualitative terms. For instance, in the ICD-10 diagnosis of alcohol dependence, one criterion includes "difficulties in controlling substance-taking behaviors in terms of its onset, termination, or levels of use." But loss of control may depend on normalization of culturally acceptable behavior (Marques et al. 2019). Without absolute benchmarks, it may be difficult to compare national perceptions of alcohol use (Rehm and Room 2017).

Some have recommended using Europeans as the standard or benchmark for alcohol consumption. Yet even in Europe, acceptable behavior may be contextual (e.g., permissible during festivals or weekends) or evolve over time (Rehm et al.

2005). Similar findings have been found worldwide in Switzerland (Haug and Schaub 2016), China (3), and Australian Aborigines (Haroon et al. 2018).

Furthermore, the quantity of alcohol consumed may not directly correlate with observed injuries or costs. Self-report population surveys may underdetect AUDs based on acceptable normalized behavior (Gmel et al. 2013; Probst and Rehm 2018). Populations which consider loss-of-control behavior unacceptable may have less tolerance for aggressive behavior, translating into lower rates of injury and death (Norström 2001).

The overwhelming fact is that excessive consumption of alcohol affects the economy of all countries or regions due to potentially preventable harm, lost revenues and productivity. Informatics may help in the early identification of at-risk individuals, provide cost-effective preventative strategies to mitigate use, provide targeted treatment for AUD, and support public health initiatives.

2.2 Use of Informatics in Laboratory Research

Alcohol use disorders (AUDs) arise from a combination of chronic response to alcohol exposure, individual genetic makeup, and environmental disturbances over time. In many people, alcohol use disorder behavior patterns are established during adolescence, which are modulated by genetically influenced individual risk profiles (Blomeyer et al. 2013). Known as candidate gene and environment interaction studies (cGxE), these studies have identified potential candidate genes that influence the development of alcohol addiction and maladaptive behavior. These candidate genes typically influence reward seeking, inhibition, systemic stress response, or alcohol metabolism (Kim and Park 2018).

Current research has shown that the genetic component of vulnerability to alcohol addiction is complex, does not follow clear Mendelian inheritance, and is not linked to a single gene. Widespread availability of genomic mapping and analysis now allows genome-wide association studies (GWASs) to identify candidate genes for multiple diseases, including alcoholism. GWASs of European populations identified alcohol dehydrogenase cluster variants associated with alcohol use disorders (Treutlein et al. 2009; Schumann et al. 2011; Stacey et al. 2012; Frank et al. 2012; Biernacka et al. 2013; Kapoor et al. 2013).

Advances in pharmacogenomics have also identified potential epigenetic mechanisms influencing the onset of addictive behavior. Genomic DNA methylation mapping (Zhang et al. 2014) and hypermethylation (Taqi et al. 2011) of alcohol-dependent patients support the theory that such changes arise as a consequence of, rather than a cause of, the disorder (Nieratschker et al. 2014). Reversal of such methylation may be examples for potential future pharmacologic treatment of alcohol use disorders.

Pharmacogenomics can be used to predict treatment response. Some studies have suggested that functional single nucleotide polymorphism (SNP) in the μ-opioid receptor gene may predict clinical response to naltrexone (Oslin et al. 2003; Anton

et al. 2008; Kranzler et al. 2013; Chamorro et al. 2012). Similarly, genetic variations in GAT-binding protein 4 may influence treatment response to acamprosate (Kiefer et al. 2011; Mann et al. 2013). Other potential treatment candidates identified using genomic analysis of SNPs include topiramate and ondansetron, as well as sensitivity to benzodiazepines (Zastrozhin et al. 2019). Pharmacogenomics offers the potential for personalized treatment of AUDs.

2.3 Use of Informatics in Clinical Medicine

During the past decade, informatics has begun to positively impact the treatment and prevention of AUDs in several clinical settings: emergency departments, hospitalized inpatients, ambulatory practice, and adolescent medicine.

2.3.1 Emergency Medicine

In 2018, US motor vehicle drivers with blood alcohol concentrations (BAC) above 0.08 accounted for nearly one-third of all traffic-related deaths, or 10,511 (Thomas et al. 2019). This resulted in an estimated economic cost in 2010 (the most recent year that cost data is available) of $44 billion including direct and indirect costs. The impact of elevated BAC on driving has been well described. Effects include impaired coordination, judgment, self-control, loss of balance, concentration, and situational awareness (Anon 2020).

Among 25 European Union members, the number of traffic fatalities officially attributed to alcohol declined by nearly 50% between 2006 and 2016 from 4950 to 2630 (Fig. 2.2) (European Transport Safety Council 12th Annual Road Safety Performance Index (PIN) Report 2020). But there is widespread consensus that the real number of alcohol-related deaths may be as high as twice the reported rate due to several factors. These include inconsistent national definitions of deaths attributed to drunk driving, lack of systematic testing of all drivers involved in collisions, and use of police records as the sole data source (World Health Organization (WHO) 2012). Thus, international comparisons of the impact of drunk driving may not be possible.

Studies have not conclusively found direct associations between elevated BAC and clinical outcomes such as injury severity scores, in-hospital mortality, or discharge disposition in survivors (Ahmed and Greenberg 2019; Demetriades et al. 2004; Stübig et al. 2012; Lowenfels and Miller 1984; Maier 2001). Thus, the benefit of alcohol screening in trauma patients may be more impactful with the potential reduction of future harm rather than at the time of the incident.

In the USA, alcohol screening in emergency departments is performed by hospitals voluntarily participating in the National Trauma Data Bank. Similar collaboratives exist elsewhere, such as in Germany (German In-Depth Accident Study) and Canada (British Columbia Trauma Registry).

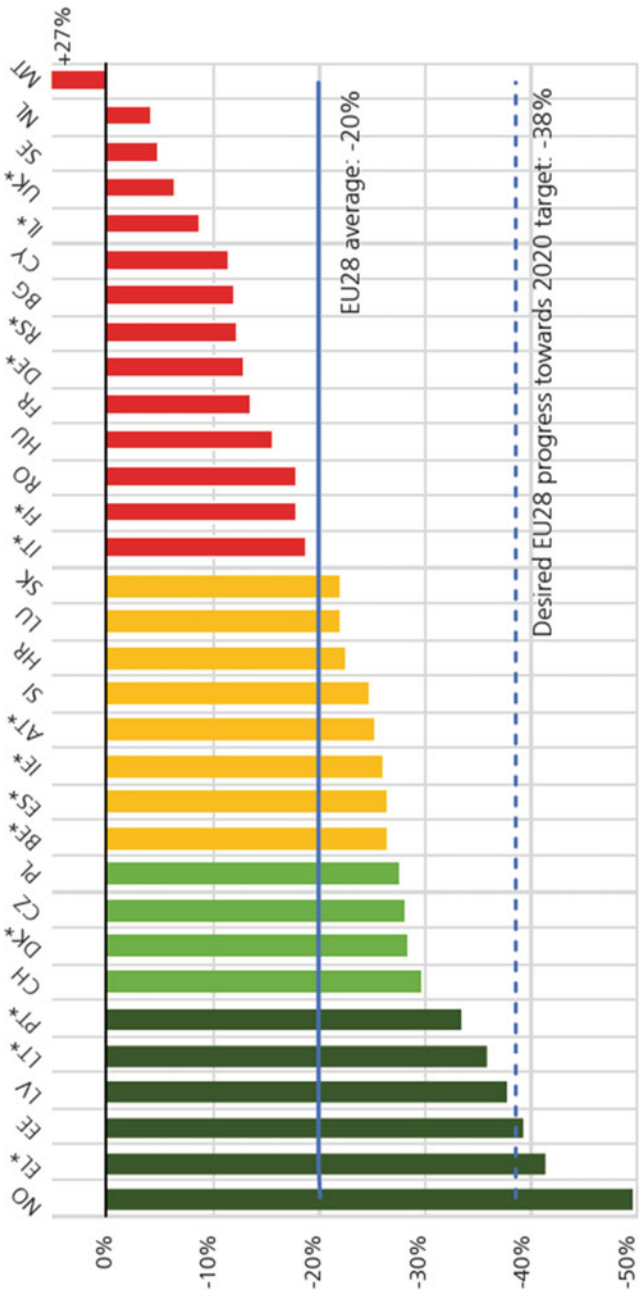

Fig. 2.2 Relative change (%) in European traffic fatalities between 2010 and 2017
Source: European Transport Safety Council 12th Annual Road Safety Performance Index (PIN) Report, accessed Aug 4, 2020

The American College of Surgeons Committee on Trauma (ACS/COT) began focusing on alcohol screening and brief intervention in 2006. Participating level 1 and level 2 trauma hospitals were required to develop protocols for alcohol screening and brief intervention (SBI). This mandate, however, did not specify which patients to screen, leading many centers to screen a limited subset of patients (Schermer 2005; Cunningham et al. 2010; Schermer et al. 2003; Terrell et al. 2008).

Some studies found that having an elevated BAC was the best blood test for detecting hazardous alcohol use (Savola et al. 2004). Not surprisingly, 71% of trauma centers used BAC as their sole method for alcohol screening (Schermer 2005). However, as much as 40% of trauma patients with hazardous alcohol behavior may be undetected based on BAC alone (Ewing et al. 2012).

A few studies of ED-based SBI programs have found positive results. One meta-analysis demonstrated that ED-based SBIs were correlated with fewer alcohol-related injuries at 6 or 12 months without an impact on ED visits or admissions (Landy et al. 2016).

A Scottish government medical informatics project linking anonymized personal healthcare records with core datasets found slightly different results. These datasets included medical outpatient attendance, inpatient admission, psychiatric inpatient admissions, emergency department visits, and pharmacy dispensing records. Targeted SBI of emergency department patients was associated with a reduction of emergency department visits for 2 years, while outpatient and inpatient usage returned to baseline by the end of the study period (Baldacchino et al. 2018).

Despite encouraging evidence of the effectiveness of ED-based SBIs, significant barriers exist. Factors include EHR system heterogeneity, lack of IT support and resources, funding, and resistance among clinical staff (Van Eaton et al. 2014). Studies examining the potential financial benefits of a coordinated SBI on a community-wide or national scale have yet to be published.

2.3.2 Adult Inpatient Medicine

The use of medical informatics in the inpatient hospital setting has focused primarily on treatments of alcohol withdrawal syndrome (AWS). Shaw first described the use of an objective alcohol withdrawal symptom scale, known as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A), in 38 chronic alcoholics admitted for AWS (Shaw et al. 1981). Foy et al. used the CIWA-A scale to guide treatment for AWS and found that higher scores were correlated with higher risk of severe withdrawal (Foy et al. 1988). Sullivan et al. later demonstrated that a pure symptom-based CIWA scale (CIWA-Ar) without the use of traditional clinical vital signs – such as tachycardia or elevated blood pressure – resulted in similar reliability as the original scale (Sullivan et al. 1989). The CIWA scale and its variants have been validated in several countries outside of the USA including Australia (51), Germany (Stuppaeck et al. 1994), and India (Sachdeva et al. 2014) (Fig. 2.3).

PHARMACOLOGICAL TREATMENT AND REASSESSMENT PARAMETERS

CIWA-Ar Score	Orders		
≤7	No treatment necessary. Reassess CIWA score every four (4) hours. If score remains ≤7 for 24 hours, contact provider to discontinue the protocol.		
8-10	Chlordiazepoxide 50mg PO every one (1) hour PRN. Reassess CIWA score every hour and re-dose as needed to achieve CIWA < 8.		
11-12	Diazepam 5 mg IV every ten (10) minutes PRN for CIWA score of 11-12. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <11.	OR	LORazepam 1 mg IV every twenty (20) minutes PRN for CIWA score of 11-12. Reassess CIWA score every 20 minutes and re-dose as needed to achieve CIWA <11.
13-15	Diazepam 10 mg IV every ten (10) minutes PRN for CIWA score of 13-15. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <13.	OR	LORazepam 2 mg IV every twenty (20) minutes PRN for CIWA score of 13-15. Reassess CIWA score every twenty (20) minutes and re-dose as needed to achieve CIWA <13.
≥16	Diazepam 10 mg IV every ten (10) minutes PRN for **Obtain ICU consult. Reassess CIWA score every ten (10) minutes and re-dose as needed to achieve CIWA <16.	OR	LORazepam 2 mg IV every twenty (20) minutes **Obtain ICU consult. Reassess CIWA score every twenty (20) minutes and re-dose as needed to achieve CIWA <16.

Fig. 2.3 Example of CIWA-Ar protocol used for EHR implementation
Source: Melkonian et al. (2019)

Since then, CIWA-Ar-based protocols have been incorporated into the EHRs of many individual hospitals. Most use benzodiazepines as the main treatment medication. Results have demonstrated significant clinical and operational improvements. Use of a symptom-triggered approach to AWS treatment has resulted in significant reductions in average medication dosage (Foy et al. 1988; Saitz et al. 1994; Reoux and Miller 2000; Eberly et al. 2016; Melkonian et al. 2019), duration of treatment in inpatient detox units (Shaw et al. 1981; Foy et al. 1988), inpatient length of stay (LOS) (Foy et al. 1988; Saitz et al. 1994), delirium tremens (Jaeger et al. 2001), and incidence of mechanical ventilation (Saitz et al. 1994; Sen et al. 2017). One study found no difference in outcomes including harm but was limited by a high exclusion rate and significant variation in protocol adherence (Waye et al. 2015).

Pope demonstrated that by linking nutritional supplements to the CIWA-Ar order set, more patients received appropriate doses of multivitamins, thiamine, and folate (Pope et al. 2016).

Other medications have been used as well with CIWA-Ar-based protocols. These include barbiturates (Askgaard et al. 2016; Tidwell et al. 2018), baclofen (Girish et al. 2016), and dexmedetomidine (Woods et al. 2015) but with mixed results.

Some critics of CIWA-Ar-based protocols argue that these protocols are often implemented after symptom onset, thus missing an opportunity for AWS prophylaxis. The Alcohol Use Disorders Identification Test (AUDIT) has been studied as a predictive tool for the development of AWS (Bohn et al. 1995; Dolman and Hawkes 2005). Another tool is the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) (Maldonado et al. 2015). Further research is required to determine if use of a predictive AWS tool prior to implementation of an AWS treatment protocol (such as CIWA-Ar) improves clinical outcomes.

SBIs have also been attempted in the hospitalized medical inpatient setting. A Cochrane review showed that SBI may result in a non-sustainable decrease in alcohol intake (6–9 months) and a significant reduction in death at 6 months and 1 year (McQueen et al. 2011). However, the quality of included studies was mixed.

2.3.3 Adult Ambulatory Medicine

In the outpatient setting, much of the focus has been primarily on implementation and effectiveness of SBI (Fig. 2.4). Theoretically, the intimacy of the patient-provider relationship should facilitate screening and interventions. One study found that an overwhelming majority of surveyed patients agreed that doctors should screen for alcohol use (92%) and that the overwhelming majority (93%) would want their doctor to perform an SBI if indicated (Miller et al. 2006). They also expressed a willingness (89%) to undergo blood testing for harmful alcohol use if one was available.

However, in the USA, few patients with AUD received SBIs. According to the 2013 US National Survey on Drug Use and Health (NSDUH), though over 80% of subjects who reported heavy episodic drinking, alcohol abuse, or alcohol dependence were screened for potentially harmful alcohol use, less than one-fourth recalled receiving some form of SBI with 15.5% seeking alcohol treatment services (Anon n.d.-d). Among those with alcohol abuse, only 10.2% received some sort of SBI (Glass et al. 2016). A similar effect was observed among US veterans (Bachrach et al. 2018).

QUESTIONS	0	1	2	3	4	5	6	Score
1. How often do you have a drink containing alcohol?	Never	Less than Monthly	Monthly	Weekly	2–3 times a week	4–6 times a week	Daily	
2. How many drinks containing alcohol do you have on a typical day you are drinking?	1 drink	2 drinks	3 drinks	4 drinks	5–6 drinks	7–9 drinks	10 or more drinks	
3. How often do you have X (5 for men; 4 for women & men over age 65) or more drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	2–3 times a week	4–6 times a week	Daily	
							Total	

Fig. 2.4 The AUDIT 1–3 (US) example of a brief alcohol use screening tool. Drink sizes were modified for the US standard drink (14 g vs. 10 g in the international version). A score of 7 or more for women and men over age 65, or 8 or more for younger men is positive
Source: CDC. https://www.cdc.gov/ncbddd/fasd/documents/AlcoholSBIImplementationGuide-P.pdf, accessed January 29, 2021

A Cochrane review found that SBIs performed in the primary care setting by general practitioners (GPs) or nurses may have a small reduction in the frequency of binges per week, quantity consumed, and days drinking per week. However, extended interventions were not shown to be superior to SBIs (Kaner et al. 2018). Additionally, SBIs have not been shown to increase treatment or decrease in alcohol intake among adults with alcohol dependence (Saitz 2010; Hepner et al. 2018).

Similar findings have been found in Europe and non-European countries. One meta-analysis found a statistically significant decrease in weekly alcohol consumption after SBI (Elzerbi et al. 2015). While there was a study of population heterogeneity, subgroup analysis of alcohol consumption did not show significant effect variation between Europe and the rest of the world. Geographic bias may exist, however. The majority of studies involving SBI and primary care were conducted in English and Nordic speaking countries in high-income regions. The impact of structural, political, and cultural differences on SBI effectiveness in developing and transitional countries remains unclear (O'Donnell et al. 2014).

Electronic SBIs (e-SBIs) may be an alternative solution to in-person SBIs in selected populations, particularly in resource-limited settings (McCambridge and Cunningham 2014). A computerized SBI with computer-generated feedback letters and integrated therapeutic electronic information provided to patients with at-risk alcohol use but not more severe disorders produced a similar sustained reduction in alcohol intake for up to 24 months as in-person counseling (Freyer-Adam et al. 2018).

A meta-analysis independently assessing adult and college student alcohol misuse found a modest reduction of alcohol consumption at 6 months but not at 1 year (Dedert et al. 2015). Dedert et al. found that the most common e-SBI approach was the use of personalized normative feedback. Personalized normative feedback aims to correct participant misperceptions by showing that their behavior is atypical from the norm.

An alternative solution may be Internet-based SBI (i-SBI). A review of 17 randomized controlled trials with a high proportion of at-risk, heavy, or binge drinkers found a small but significant reduction in alcohol use (White et al. 2010). While another one-stage individual patient data meta-analysis (IPDMA) pooling 19 randomized control trials with 14,198 adult participants found that in-person SBIs were superior to fully automated i-SBI, it found that when compared to controls, i-SBI resulted in a significant reduction in total alcohol consumed and increased treatment response regardless of drinking profile (Riper et al. 2018). The study also found that participants treated with e-SBI using personal normative feedback were significantly less likely to sustain improvements compared to those treated with integrated therapeutic principles.

2.3.4 Pediatrics and Adolescent Medicine

There is a growing interest in the potential use and impact of SBI targeted at the adolescent population. US surveys found that between 28 and 60% of high school students reported binge drinking in the past (Committee on Substance Use and Prevention 2016). Underage drinking was estimated to be responsible for $361 million in total economic costs in the USA in 2006 (Sacks et al. 2013).

In Europe, serial surveys of 15–16-year-old adolescents between 1995 and 2015 found a high rate of alcohol use. Among the over 96,000 students surveyed in 35 European countries, 47% reported alcohol use within the past 30 days. More worrisomely, 35% of adolescents reported recent heavy alcohol use as well (The European School Survey Project on Alcohol and Other Drugs (ESPAD) 2020). The study noted significant differences in the adolescent intoxication rates among the various countries, ranging from as low as 1% up to 36%.

Mirroring ED SBI efforts in the adult trauma population, participating pediatric trauma EDs increased SBI screening from 11 to 73% of eligible patients (Yuma-Guerrero et al. 2012). SBIs at pediatric trauma EDs were easy to complete but subjects tended to question their credibility (Newton et al. 2017). Furthermore, successful completion of 1- and 3-month telephone follow-ups was generally moderate (40.9–53%) (Sacks et al. 2013; Linakis et al. 2013).

One study of e-SBI with normative feedback in adolescent volunteers demonstrated a 3-month reduction in alcohol ingestion (Spijkerman et al. 2010). Another meta-analysis found that three interventions targeted at adolescent health produced multiple positive effects: interpersonal skills training, emotional regulation, and alcohol and drug education (Skeen et al. 2019).

Though research on SBIs in this at-risk age group remains limited, the potential for future harm reduction is promising.

2.4 Use of Public Health Informatics for Alcohol Use Disorders

Modern healthcare has grown increasingly complex outside the traditional boundaries of disease diagnosis and treatment. As seen earlier, use of informatics is now being explored to identify and monitor at-risk individuals for AUD and prevent the development of long-term disease.

Due to the global impact of AUDs, the WHO and individual countries have implemented various responses to reduce alcohol consumption. Common policy responses include legal restrictions on the sale of alcoholic beverages including licensing or advertising, alcohol excise taxes, maximal permissible blood alcohol concentration (BAC) limits to prevent drunk driving, legal age limits for purchase, and disclosing alcohol content on labeling. Some countries have begun implementing national monitoring systems to collect data on alcohol consumption

and related health consequences. Fewer monitor social consequences and response to alcohol policies (WHO 2020). Informatics may play a key role in national monitoring systems.

2.4.1 US Public Health efforts

In the USA, various government agencies and private and public health facilities loosely collaborate in public health functioning. Quality standards established by public agencies such as the National Institutes of Health (NIH) and Agency for Healthcare Research and Quality (AHRQ) are used by public health insurers such as the Centers for Medicare & Medicaid Services (CMS) and Medicaid to establish financial incentives for providers.

But in much of the rest of the world, health systems remain fractured structurally (e.g., privately owned) or financially (e.g., large proportion of self-pay or private insurance). This presents challenges for the implementation of public health initiatives.

Public health relies heavily on information technology to gather and monitor data. Obstacles to overcome include availability of data (real time or delayed) and quality, depending on its source (community health centers, hospitals, clinics, urgent cares, and pharmacies) (Landais et al. 2014). In the USA, this is accomplished via a grid system that involves federal agencies, regional health information organizations (RHIO) or health information exchanges (HIE), state and local public health departments, and providers.

Effective public health informatics must accomplish four pillars: first, utilization of information and technology to improve population health; second, focus on disease prevention over treatment; third, focus on preventative interventions in the steps prior to disease development or injuries; and lastly, work within the government and not the private sectors (O'Carroll et al. 2003). At the core, an informaticist must have consistent, reliable, meaningful data, an understanding of ethics, and knowledge of disease surveillance (Dixon et al. 2015).

Over time, informatics has evolved significantly to improve data collection especially in the inpatient and outpatient settings. With the invention and evolution of the computer, capturing data has rapidly improved. In the USA, collecting data is done via electronic health records (EHRs) which allows for easier aggregation of data from one or more sources. For the inpatient side, the EHR information is collected by providers interviewing and examining patients.

The US 2009 Health Information Technology for Economic and Clinical Health (HITECH) Act promoted the expansion and adoption of electronic health records (EHRs) by hospitals, clinics, and other healthcare-related entities, public and private. These EHRs are meant to serve as building blocks for data collection architecture. The infrastructure would also include event detection, laboratory results, management of contacts and threats, and automation of collecting and disseminating data and the most important provide security (Hanrahan et al. 2006).

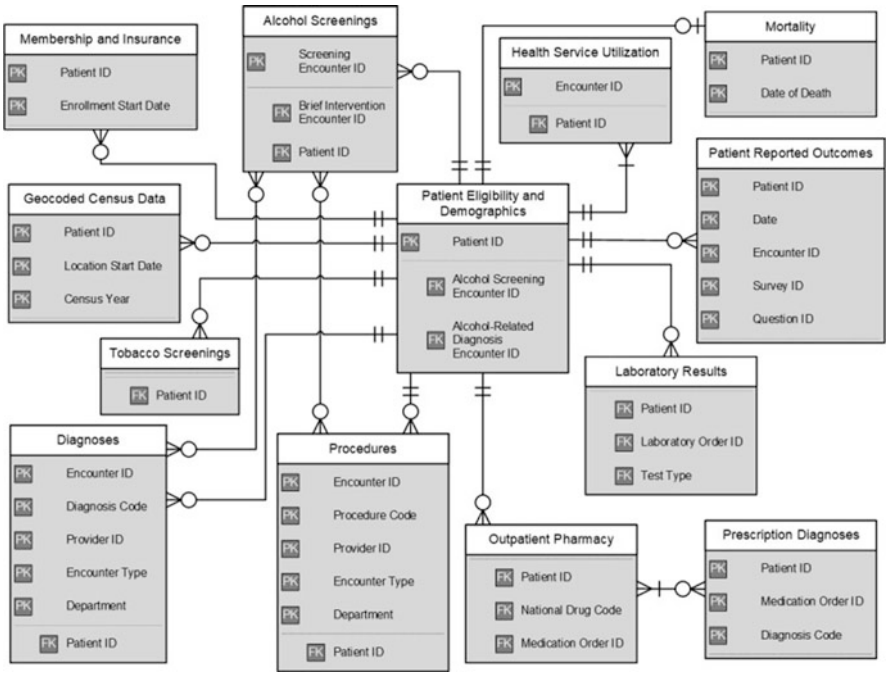

Fig. 2.5 Entity-relationship diagram representing the data structure of core files in the Kaiser Permanente Northern California Adult Alcohol Registry. PK, primary key; FK, foreign key
Source: Palzes et al. (2020a, b)

One example of the private sector creating its own regional health system is the Kaiser Permanente health system. A pioneer in the field of medical informatics, Kaiser Permanente Northern California (KPNC) implemented an alcohol registry within its closed network to monitor adult alcohol use disorders (Palzes et al. 2020a). Conventional national population-based surveys rely on primary data acquired at separate study visits. In contrast, the KPNC approach takes advantage of data collected at the time of healthcare delivery (secondary data) (Fig. 2.5). Similar to the US Veterans Health Administration (VA) alcohol screening protocol in 2004, the EHR approach better reflects the general population and may be a more cost-effective way to monitor population health (Bradley et al. 2006).

KPNC also found that certain conditions were more prevalent among patients reporting unhealthy drinking than those who were to drink within guidelines. These conditions included diabetes, atrial fibrillation, hypertension, COPD, and several others (Sterling et al. 2020). Informatics helped identify median time to remission from unhealthy drinking and potential factors (Palzes et al. 2020b). These findings may help health providers identify and target patients for earlier harmful alcohol use prevention and intervention. RHIOs may be a cost-effective model for countries with deregulated healthcare markets.

2.4.2 *European Public Health Efforts*

Countries such as Germany and France coordinate public health responses through nationwide collaborations within a highly regulated, universal health insurance system. National health systems such as in the UK implement public health initiatives through publicly owned and operated hospitals with salaried physicians. Single-payer national health insurance systems, as found in Canada, Denmark, Norway, Australia, and Sweden, allow public health policies to be enacted more directly (The Commonwealth Fund 2020).

Germany provides universal healthcare through a mandatory multi-payer system. Public health goals are achieved largely through regulation, legislation, and funding. Earlier informatics attempts relied on primary data: hospitalized patients discharged for AUD were asked to self-report. Not surprisingly, the main challenge was post-discharge treatment adherence due to self-reporting (Freund et al. 2013). In contrast, secondary data from addiction treatment centers fed into the national German Monitoring System allowed AUD screening, treatment, and patient monitoring with relative ease (Ritchie 2018).

Unlike the USA or Germany, Finland relies on decentralized but mainly public-funded universal healthcare system (National Health Insurance). The EHR was developed by the Finnish government and is used in both inpatient and outpatient settings, thus allowing it to be linked concurrently to a registry. Of interest, investigators found that alcohol-related visits to primary care providers were associated with higher mortality rates (Rautiainen et al. 2019), raising the question if Finnish primary care providers have adequate resources to address the care of patients with AUD.

2.5 Use of Personal Devices

Besides traditional population surveys or linking EHRs with RHIOs or national registries, other technology-based approaches on AUD informatics have been explored. These include text-based artificial intelligence-driven conversational agents (aka chatbots) (Crutzen et al. 2011), wearable fitness trackers (Abrantes et al. 2017), printable biosensors (Khan et al. 2019), and mobile phone apps (You et al. 2017; Gustafson et al. 2014; Bertholet et al. 2017). Other sources include alcohol ignition interlock devices (Marques et al. 2003) with geolocation tracking capabilities (Voas 2014).

2.6 Conclusion

Medical informatics now plays an increasing role for the prevention, diagnosis, and management of alcohol use disorders. While informatics offers the promise of personalized medicine, we believe that it is most impactful when used to implement hospital system-wide solutions, to manage patient populations, or to support public health efforts.

Some barriers to widespread adoption of informatics in AUDs include patient privacy concerns, proprietary EHR/databases/registries with limited external support, multiple regional private and public entities, regulatory agencies, and lack of familiarity among clinical providers. It remains to be seen how future leaders will navigate the tension between individual patient data privacy concerns and the public health needs of the community.

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Anon (n.d.-a) Southeast European subregion is defined as Armenia, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Tajikistan, Turkey, Turkmenistan and Uzbekistan.

Anon (n.d.-b) Eastern European subregion is defined as Russian Federation, Belarus, Republic of Moldova and Ukraine.

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Chapter 3
Regionalized Management of Clinical Gene Sequencing in Application: An Example and Proposal of Haixi Economic Zone

Furong Yan, Erdong Yang, Linlin Guo, You Yang, Xiangdong Wang, Hongzhi Gao, and Yiming Zeng

Abstract The economic zone on the west side of the Straits (Haixi economic zone) refers to the west bank of the Taiwan Strait. It is located in Fujian Province and includes some cities in Zhejiang, Guangdong, and Jiangxi. Haixi economic zone is a comprehensive region covering economy, politics, culture, society, and other fields. With the rise of national strategy, Healthy China, a series of policies has been urgently issued to support the development of health industry, and the genetic testing industry has shown a vigorous development trend. An organization is required to promote the research and application of new technologies and the development of

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the genetic testing industry. By forming a genetic testing alliance and establishing a big gene data center, the regional management can be realized, data sharing can be promoted, and a large database of pathogenic mutations can be improved.

Keywords Haixi economic zone · Genetic testing · Regional management · The west coast of the Taiwan Strait · Precision medicine

3.1 Regional Introduction

3.1.1 Geographical Location of the Haixi Economic Zone

The Haixi economic zone locates in the west bank of the Taiwan Strait, with Fujian as the main part and covering Zhejiang, Jiangxi, and Guangdong provinces. In addition to covering all prefecture-level cities in Fujian Province, it also includes Wenzhou, Lishui, and Quzhou in Zhejiang Province; Shantou, Meizhou, Chaozhou, and Jieyang in Guangdong Province; and Shangrao, Yingtan, Fuzhou, and Ganzhou in Jiangxi Province (Fig. 3.1). The Haixi economic zone is a comprehensive area covering economic, political, cultural, social, and other fields. Its overall goal and task is to basically realize economic integration, investment and trade liberalization,

Fig. 3.1 Geographical location of the Haixi economic zone. The Haixi economic zone is located on the west bank of the Taiwan Strait, with Fujian as the main body, covering parts of Zhejiang, Jiangxi, and Guangdong Province. It is an economic complex

unification of macro policies, advanced industrialization, regional urbanization, and social civilization through "opening to outside world, coordinated development, and overall prosperity."

The history of constructing urban agglomerations on the Haixi economic zone can be traced back to the concept of the "Southern Fujian Golden Triangle" proposed by Fujian in the late 1980s. In 2004, Fujian Province formally put forward the strategic concept of "The Economic Zone on the West Side of the Straits." In 2009, the State Council issued the *Several Opinions of the State Council on Supporting Fujian Province to Accelerate the Construction of the Haixi Economic Zone*. In 2011, the National Development and Reform Commission issued the full text of *The Development Plan of Haixi Economic Zone*; the plan pointed out that the Haixi economic zone will be built into a scientific development zone, a reform and opening up zone, a civilized and peaceful zone, and an ecologically beautiful zone and become a new economic growth zone in China.

3.1.2 Cultural Characteristics of the Haixi Economic Zone

As the largest urban agglomeration across provinces, Haixi is facing a sense of fragmentation that is difficult to reconcile. Cities in Zhejiang and Guangdong are more inclined to the Yangtze River Delta and the Pearl River Delta. Cities in Jiangxi are also in the planning of the Poyang Lake City Cluster. The main force of the Haixi urban agglomeration is the coastal cities in Fujian. The Haixi economic zone has strong characteristics of marine culture, presenting a diversified structure and regional distribution characteristics, mainly including the Minnan culture, Shipping culture, Mazu culture, Hakka culture, Tea culture, Zhuzi culture. and She nationality culture. These cultural brands represent image of Fujian and highlight Fujian people.

The Minnan region locates in the southern part of Fujian Province. Because of the special geographical location, the Minnan culture has a pivotal significance in the entire Haixi culture. Minnan culture is a derivative of Heluo culture. It is the fusion of Central Plains culture and local culture, which gives Minnan culture the characteristics of mainland culture. At the same time, Minnan culture has the characteristics of Marine culture, and it exports culture and materials to the outside world, and it also receives input in exchanges. Minnan people have a strong concept of clan, which originated from the migration of the Central Plains to Fujian, where they lived in the form of clan. So far, there is still the consciousness of cultivating genealogy, building ancestral temples, and spreading customs. This makes Minnan people have unusual cohesion when they develop abroad (Liang and Song 2018).

3.1.3 Public Health Development in the Haixi Economic Zone

The *Outline of the Eleventh Five-Year Plan for National Economic and Social Development of Fujian Province* clearly requires that the urban and rural public health service system should be improved and perfected to be compatible with the growth of the Haixi. However, current regional government is inconsistent and uncoordinated in public health needs and provision, public health awareness and knowledge, and social development and economic development: firstly, severe situation of prevention and control of public health emergencies; secondly, most primary medical institutions do not have advanced equipment and timely emergency response and comprehensive service capabilities; and finally, lacking public health knowledge of urban and rural residents. The term "public health" is simply understood by many people as clean environment, and urban and rural residents lack basic knowledge of public health.

3.1.4 Economic Development in the Haixi Economic Zone

At present, the economic development of the Haixi economic zone is still uneven. The economic development of the entire economic zone mainly depends on Fujian, and most of economic data of the nine cities in Fujian is in a leading position. Among Haixi area, the economic development of coastal cities has limited capacity to cover inland hinterland and mountainous cities. Except for some cities in Jiangxi Province, which all locate inland, the economic development level of coastal cities in other provinces is higher than that of inland. From view of the Haixi cities, the basic situation of strong coastal areas and weak inland areas has not been effectively improved. Xiamen, Fuzhou, Wenzhou, and Quanzhou have kept their positions as the central cities on the Haixi. Zhangzhou is catching up with Shantou with a faster economic growth rate, and it is expected to become one of the central cities in the future.

Comparing the main economic data of the Haixi economic zone with three major urban agglomerations in the eastern coastal area, the Yangtze River Delta, Greater Bay Area, and Beijing-Tianjin-Hebei, a gap exists in the main economic data. At present, Haixi cannot be compared with other economic zones. But its foundation and relevant development does help to the economic growth rate which far exceeds that of the other three economic zones. This shows that the economic structure of the Haixi economic zone is reasonable and healthy, with strong vitality, and has embarked on the fast track of rapid development.

3.2 Genetic Testing

Before the molecular structure of double-stranded DNA was verified, human knew nothing about genes, but had a rough understanding of heredity. An old saying in China which basically means "you reap what you saw" shows ancestors' insight into the "genetics." The Human Genome Project has been launched over 30 years, which marks the beginning of this achievement to catalogue every human gene and identify each of their genomic function patterns. Novel features of this program include the capacity to automatically predict multiple genes by sequencing technology, and nowadays, researchers have a deeper understanding of these genes (Kirkpatrick and Rashkin 2017).

The advancement of gene technology has brought an unprecedented innovative revolution (Katsanis and Katsanis 2013). Genetic testing as a basic screening and testing tool has also played an important role in the advanced service and manufacturing industries and refilled the context of public health strategies in various countries. The *Bio-industry Development Plan* issued by the State Council at the end of 2012 pointed out that the bio-industry is a strategic emerging industry identified by the state and is expected to become a pillar industry of country's economy by 2020. The major breakthroughs made in genomics-related advances in the past few decades have brought great reformations to diagnosis of diseases. The genetic testing helps doctors to make recommendations for treatment or monitoring, give the patients or consumers more information for making decisions about their health, and identify genetic disorders early in life so treatment can be started as soon as possible.

3.2.1 The Epidemiological Statistics of Genetic Diseases and Tumors in Haixi Economic Zone

Tumors have become one of the main burdens to the growing economy worldwide. According to *the 2014 Fujian Malignant Tumor Report* published by the Fujian Cancer Prevention and Treatment Office, out of every 100,000 people, nearly 279 people have tumor, and 164 people die of cancer. It can be seen that cancer has become the main cause of mortality in Fujian residents. More specifically, according to the data from the Second Affiliated Hospital of Fujian Medical University in Quanzhou, the most economically active region on the Haixi economic zone, of the 20,000 malignant tumor patients, lung cancer, colorectal cancer, esophageal cancer, thyroid cancer, breast cancer, gastric cancer, liver cancer, oral and pharyngeal malignancies (of which nasopharyngeal cancer accounts for a quarter), lymphoid hematopoietic system tumors, and cervical cancer, are the highest incidence cancer types in this area (Fig. 3.2). Chaozhou-Shantou area also has several so-called Cancer Town with high incidences of certain cancer types, which by virtue of being surrounded by chemical or coal-fired power plants. According to the Cancer

Fig. 3.2 Cancers with high incidence in Haixi economic zone. According to the data of cancer patients at the Second Affiliated Hospital of Fujian Medical University in Quanzhou, the top ten high-incidence cancers in this region are lung cancer, colorectal cancer, esophageal cancer, thyroid cancer, breast cancer, gastric cancer, liver cancer, oral and pharyngeal malignancies (of which nasopharyngeal cancer accounts for a quarter), lymphoid hematopoietic system tumors, and cervical cancer, which are related to many factors such as climate, living habits, pollution and dietary habits

Hospital of Shantou University Medical College, the major cancer in Chaozhou-Shantou area was esophageal cancer, followed by bronchial lung cancer, breast cancer, and gastric cancer over the years.

Together, the cancer types in the Haixi region have regional specificities. Among them, esophageal cancer, thyroid cancer, nasopharyngeal cancer, gastric cancer, and liver cancer are regionally high, which is related to many factors such as climate and living habits. The subtropical climate in coastal areas will give rise to more cancer risks through exposure to carcinogens after extreme weather events like hurricanes and wildfires (Hiatt and Beyeler 2020). Besides, a few epidemiological studies have addressed the link between the association of esophageal cancers with tea consumption regarding frequency, amount consumed, and temperature (Yu et al. 2018; Islami et al. 2020). The results are conflicting but in general highlight the importance of abstaining from hot tea drinking habits in excessive alcohol and cigarette consumers. However, the influential tea culture has a strong effect on eating habit. They like eating hot foods and drinking hot tea, which will easily cause damage to the esophageal mucosa, creating conditions for the growth of carcinogen aflatoxin,

thus increasing the risk of esophageal cancer and liver cancer. In addition, the crisscrossing distribution of rivers in this area is more likely to worsen water pollution with heavy metal and a relatively high infection rate of viral hepatitis in coastal areas. Moreover, it's said that thyroid cancer is often related to high-iodine dietary habits such as seafood and kelp. Residents in coastal areas like pickled foods, which contain high levels of carcinogens or pre-carcinogens such as nitrites, mycotoxins, and polycyclic aromatic hydrocarbon compounds, leading to a gradual increase in the incidence of gastric cancer. In the meantime, *Helicobacter pylori* has been proved to have a role in promoting the conversion of nitrate into nitrite and nitrosamine, and it can also cause chronic inflammation in gastric mucosa, accelerating the excessive proliferation of mucosal epithelial cells, leading to aberrations and carcinogenesis.

The gene testing technology is an important tool that will promote clinical genomics development and realize personalized precision medicine (Slomski 2016). It can be used not only to screen the population for high risk of certain hereditary cancers but also to clarify the characteristics of genetic mutations in cancer patients. It enables patients to benefit from cancer target therapy. From above, the occurrence and development of tumors in the Haixi economic zone have obvious characteristics of "clustering and regional." In-depth studies such as gene sequencing of these cases are urgently needed to help prevent tumor occurrence at the genetic level and promote the development of oncology. Thus, it is necessary to widely popularize gene testing in the Haixi economic zone.

3.2.2 Current Genetic Testing in the Haixi Economic Zone

Although genetic testing technology helps to achieve the goal of personalized medicine, especially for promoting the development of oncology, it still hasn't been extensively spread among the people. At present, in the clinical field, genetic testing is usually used to assist clinical diagnosis, which is mainly reflected in the detection of genetic defect diseases and tumor mutation. The most mature and representative genetic testing service is noninvasive prenatal genetic testing. The advantages of genetic testing are listed as follows: (1) predictive medicine, (2) disease prevention, (3) health management, and (4) personalized medical services. The specific application directions of genetic testing include (1) tumor diagnosis and treatment, including blood system tumor diagnosis and typing, targeted drug gene detection, tumor susceptibility gene detection, and early tumor screening; (2) birth defect prevention and control, mainly including prenatal screening and diagnosis, screening of neonatal metabolic diseases, etc.; (3) diagnosis of genetic diseases; (4) diagnosis of pathogenic microorganisms; and (5) detection of chemical drug sensitive genes such as anticoagulant drugs.

On June 26, 2000, the United States, China, Japan, Britain, France, and Germany jointly announced that the "work map" of the Human Genome Project was completed. This marks the human life sciences entering the era of gene applications. The

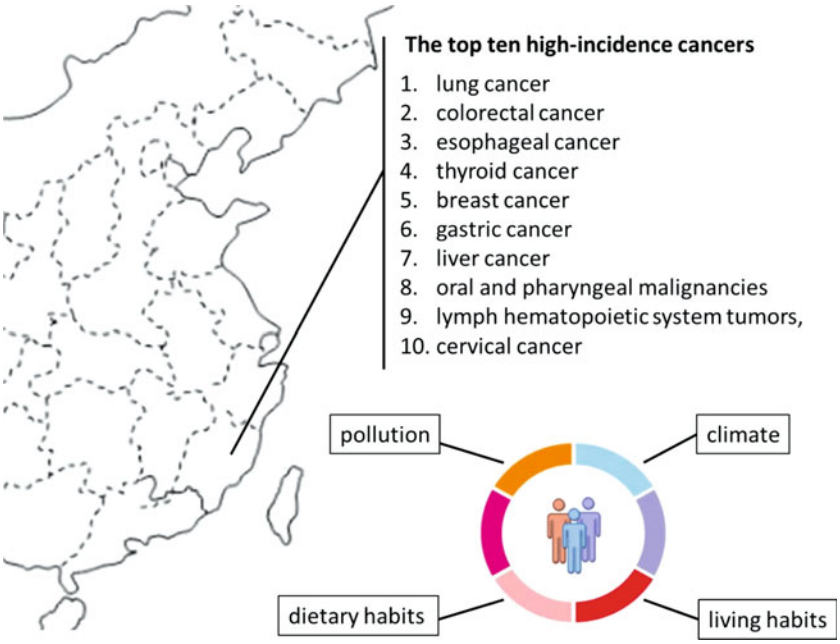

Fig. 3.3 Genetic testing in the Fujian Province. In Fujian Province, there are few genetic testing companies. They are mainly concentrated in Xiamen (preliminary statistics of 12) and Fuzhou (preliminary statistics of 10). In Quanzhou, only HiQ Biomedical Clinic Laboratory undertakes part of the testing projects

gene sequencing enterprises in China are mainly concentrated in the downstream sequencing service industry of the industrial chain, while the upstream gene sequencing equipment suppliers have a high technical threshold, which is basically monopolized by foreign enterprises. The development of genetic testing industry in Beijing, Guangdong, and Shanghai has a leading position in this industry. In addition to the advantages of local talents and capital resources, local industrial policies also play a vital role. Unfortunately, there are few big genetic testing companies in the Haixi region. Most biological companies are concentrated in Xiamen (preliminary statistics of 12) and Fuzhou (preliminary statistics of 10) (Fig. 3.3). In Quanzhou, only the Gaopin Medical Testing Center undertakes part of the testing projects, which covered the tumor mutation detection and defected genetic disease testing. Relatively fewer gene testing companies in other regions have been established. This third-party testing currently uses multi-platform sequencing technology to conduct a full range of research on diseases at the DNA level, RNA level, epigenetic level, and metagenomic level, and combines mass spectrometry technology to carry out proteome level research. The massive data obtained from the research platform, combined with various information related to the phenotype (environment, age, disease treatment history, family history, susceptibility, etc.), have a potential to fully reveal the mechanism of human genetics that

laid an important foundation. Genetic testing also involves single-cell research, immune repertoire research, and liquid biopsy.

Although the Haixi economic zone has a prosperous economic growth, the genetic testing platform in the region has not yet been well established; thus, it is hard to fully use the implementation of genetic testing, as said before. To better serve and reduce diseases, we should gradually improve the framework and rules of the Haixi genetic testing platform; maintain efficient communication with the government, medical insurance, outsourcing service agencies, and other stakeholders to form a gene sequencing plan in the region; and explore the data sharing incentive mechanism, participation in the implementation of clinical trials, and systematic data collection issues to overcome clinical application difficulties.

3.2.3 Opportunities and Challenges for Genetic Testing

The current genetic testing business is in a dilemma in Haixi areas (Ramos and Haidle 2018). In general, medical management strategies in Fujian Province are too strict to fully delegate to process all professional inquires or customer-focused solutions. Also, various product qualifications and prices restrict the application of many innovative products. A large number of challenges should be overcome, for example, there is no integrity professionalism service model. The business cooperation model for now is mainly to directly sell test kits to consumers through online or offline, like in pharmacy. After customers done the sample collection according to the instructions, the company collected samples to do test and issued a personal genetic test report. Also for the medical-grade genetic testing, the operation team collect blood samples in clinics sporadically and sent it back to the company to finish the process. Without corresponding standard protocols, it may pose many risks, such as sample loss, destruction, and information errors.

There is a lack of a supervision platform. Regarding the perspective of detection capabilities, each third-party service company may differ from each other. In an era where gene testing needs are skyrocketing, the efficient allocation of resources is paramount. These not well-qualified companies may take the market share by adopting layer-to-layer subcontracting methods, which could directly affect the authenticity and reliability of the results. From the perspective of industry structure, due to the lack of corresponding industry standards, product price and qualities and other issues involved in genetic testing have not been clearly regulated, which may lead to vicious price competition and hinder the development of the entire genetic testing industry.

To ensure the security of data information is a challenge. Each individual has unique genetic information that should be adequately protected within the scope of personal privacy. Under the current business cooperation model, patients cannot fully protect their vital interests and rights, which results in a lack of trust and recognition in the industry psychologically. There are few services that can be carried out. Most tumor-related gene test kits and microbiological test reagents

have not obtained its clinical testing licenses, so the genetic testing projects carried out in hospitals of Haixi economic zone only include a few testing projects such as prenatal screening NIPT testing and tumor-targeting gene EGFR.

With low customer awareness and lack of trust, people still hold the opposite view that genetic testing was only the high-tech product that has no close connection to their health. Most service teams in genetic testing market does not have professional knowledge and cannot provide professional preventive guidance services or genetic counseling services on the results. There is a greedy need for relevant organizations to promote the application and research of new technologies. As the most important institute to protect life and health, the hospital contains various favorable conditions for carrying out genetic testing, including health professionals, well-equipped technology settings, and an original source of patients. It can ensure that patients or customers not only get the best care over a continuum of time to achieve positive clinical outcomes, but also that appropriate utilization for optimal patient care is being followed. At the same time, by setting up a genetic sequencing laboratory, the hospital can greatly reduce the cost of testing and shorten the turnaround time. However, there are still the following difficulties in carrying out in-hospital genetic testing. There is a lack of hardware platforms (data centers) within hospital, although currently few hospitals have established large-scale genetic data centers. It can be hard to keep up with the digital age when data is rapidly being processed and transferred. Few institutes have administrative staff or technical support. It is also difficult to make full use of data sharing.

Thus, a bigger genetic testing consortium should be formed in Haixi economic zone. And a combined hardware and software company should also be included in the consortium to ensure that data gathering and statistical reporting processes meet essential guidelines, as well as fulfill data sharing systems to benefit more researchers.

3.3 Regional Management

Regional management is an important way for the Haixi economic zone to carry out genetic testing projects (Gatellier et al. 2020; Sarcone and Kimmel 2021). The regional consortium will break the original barriers to a certain extent, unblock genetic testing channels, and realize the sharing of high-quality resources.

Regional management firstly requires the establishment of regional organizations: strategic team, management team, and executive team. The strategic team is in charge of the regional health units. The health committee officers and organizations directly under the jurisdiction form a leading group that is responsible for formulating policies and guidelines and also setting the strategic goals. The management team was founded by the leading group and its subordinate permanent office, and the management department within the consortium. The management department is responsible for authenticating and authorizing third-party service, and carrying out technical management and security level assessment of medical

institutions in the jurisdiction. The executive team is composed of various units in the consortium, and is responsible for the implementation of sample collection, data collection, and data integrity.

In order to effectively carry out the program to the highest quality gene testing service, the pre-work can be mainly divided into the following steps: First, conduct surveys and market forecasts and analyze the demand and feasibility of genetic testing cores according to the disease epidemiology. Second, a necessary market promotion is needed in the beginning. Advertising, paper news, and other marketing methods help expand the visibility and recognition of genetic testing. Third, organize investment promotion activities at designated locations. According to the distribution of hospitals and testing institutions, establish genetic testing stations and substations to seize market shares in key regions. Fourth, provide training and technical support. Technical personnel and franchising organizations should be given corresponding skills training to improve their vocational skills and professionalism.

In the process of project development, it is necessary to first strengthen marker supervision to ensure every team adheres to strict regulatory guidelines by setting up a special team to conduct yearly or monthly inspection to solve the difficulties when doing the project timely. Second, increasing the propaganda methods like social media, online app, or welfare TV shows to derive the most value of the gene testing results and improve the identification, recruitment, and engagement of patients eligible for clinical trial. Finally, enough funding should be guaranteed. With the rise in the awareness of public health, more capitals should be induced to implement the genetic testing industries.

In the context of medical big data, the awareness of ensuring data security should run through the entire process. After each genetic testing project has been completed, medical records should be well recorded into a case database and big data files, and well protected from the entire life of data like during generation, collection, and transmission process. Attention should be paid to all links such as storage, processing, analysis, release, use, and destruction. This requires a centralization of management, with regional coordinate operating mechanism. There are several details included: First, the information management department of health organization can set up a data security and maturity level evaluation system to conduct data security evaluation on the subregions under its jurisdiction and medical institutions under its management. With this system, basis guidelines can be formulated to guide the security plan and set up a threshold to the accessibility to secured data. Second, define data ownership and privacy protection content around the entire life cycle of data from generation to destruction. Third, conduct data security management from three dimensions of guideline: organization, management, and technology. For example, in terms of technology, a complete safe operation platform, data security system, and data security services are required to enable faster clinical transformation of gene sequencing results.

An important feature of regional management is the establishment of regional cooperation system. Strengthening the cooperation relationship within the zone is an essential way to accelerate the development of genetic testing and also a goal that

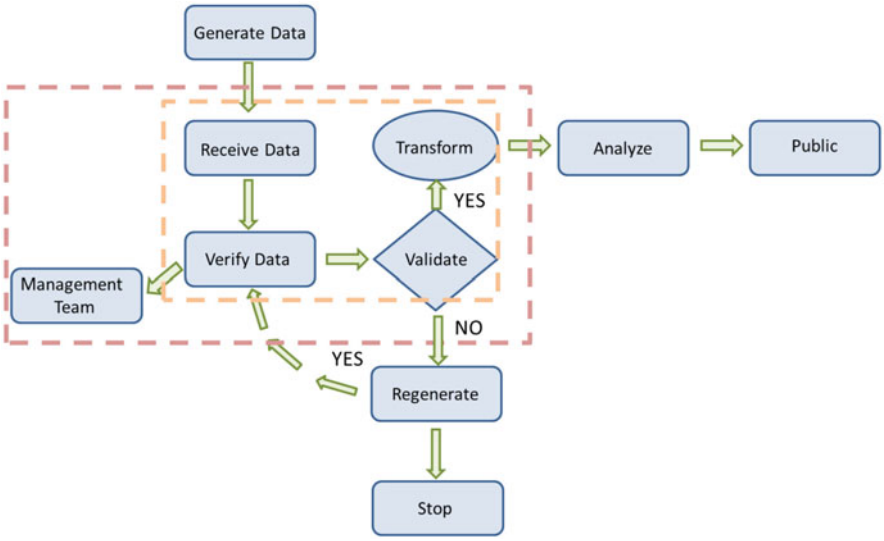

Fig. 3.4 The flowchart of data governance. Through the process of data governance, we can make the results more accurate and reliable

should be well achieved by the consortium. To implement inter-regional cooperation, a mechanism to promote regional interaction and overall development should be established. This mechanism should include the cooperation of city groups involved in the Haixi economic zone and, most importantly, the surrounding region such as Pearl River Delta and Yangtze River Delta economic zone. Annual meetings should be held regularly to exchange the ideas and learn from other regional cooperation systems. By doing this, the consortium could better adjust plan and coordinate major issues in the region as a whole.

On the other hand, the Genetic Testing Professional Society of Haixi economic zone should be formed to connect the government, industry, university, and research groups to serve the integration of technology and economy (Fig. 3.4). The society will establish an expert advisory committee which is composed of experts in related fields to carry out investigations and discussions on major issues in the development of genetic testing technology, guide the development of the society, and enhance independent research and development capabilities. The society will promote the exchange, sharing, and cooperation in different fields related to genetic testing, such as medical and health, life omics, big data, policy research, and financial investment. The society will implement projects, enable the development of genetics, and give full play to the influence of the platform. The platform can also unite workers in multiple industries, such as medical care, life omics, and big data analysis. By closely contacting with government departments, it could also promote collaboration between political officers, business industry, academia, and research group, to urge the industry in the direction of scientific standardization and promote medical research to fully use the advantage of genetic testing.

A strong membership structure of gene test platform covers the entire industry chain of genetic testing. The medical branch is set up with the application of genetic testing as the main line. The society can establish a systematic branch structure based on the three major categories of reproductive health, tumor prevention and control, and pathogen detection. The society should integrate technological alliances and promote the development of the industry with the quality control center as the starting point. The clinical genetic testing quality control center is needed to condense a large number of expert resources in genetic disease testing, tumors, cardiovascular diseases, infectious diseases, genetic counseling, and other disciplines to promote and standardize the quality control of related clinical genetic testing. A consortium of Haixi economic zone genetic testing alliance can serve the development of technological and economic integration. The alliance breaks industry restrictions, field restrictions, and professional restrictions between different institutions. By the integration of basic research, achievement transformation, promotion and application, property rights protection, investment and financing, industry promotion, government support, and other resources in the whole chain, the deep integration of technology and economy will be realized.

3.4 Consortium/Society Benefits

Next-generation sequencing (NGS) has been used for genome sequencing for over 30 years, but their high throughput also makes them popular in the field of functional genomics assays. It has been widely used worldwide for prevention of hereditary gene defect disease, designing precision treatment strategy of malignant tumors, and accelerating breakthroughs – life-changing breakthroughs that enable patient with tumor to live longer and get through pandemics, like the COVID-19. Genetic testing technology is a major revolution in the development of life science and biotechnology. It's one of the most important methods of healthcare service which can help in determining the risk of developing certain kinds of diseases as well as screening and sometimes medical treatment. As the healthcare service is booming, the genetic testing service will also be the industry with the greatest potential and longest acceleration in output.

Currently, only a small scale of well-educated people in Haixi economic zone are aware of the importance of gene test, but very few methods can be approached. As a result, accelerating the establishment of modern health service consortium can be a very powerful method to enhance the comprehensive competitiveness of the cities by expanding the scope of employment, improving people's living standards, and promoting the regional economic structure and the overall development of the institute in the consortium. At the same time, the genetic test consortium will also become one of the main driving forces of the new economic growth. A sound system can reduce sample transaction costs, simplify the workflow, and achieve economic expansion within the consortium. It can also help focusing on the role of industrial upgrading and structural change across the related social gains.

By establishing a diversified, networked, and standardized genetic testing institution, medical organizations, universities, scientific institutions, and research centers can be well qualified for the innovation capabilities in the Haixi economic zone as an alliance. With diversified investment entities and market-oriented operating approach, the society can meet the rapid development of cooperation and genetic testing in the area. Regional centers should be encouraged to gradually form a healthy network and build a public genetic testing service platform. Meanwhile, big data sharing system and analysis platform should also be fully operated by professional personnel. The genetic testing society, in other means, can be a compatible discourse system to communicate with partners and interest alliances outside of the society. The establishment of a diversified, standardized, and well-connected network can also be a good example for the country or even international gene testing industries.

Consortium/society should support the expansion of service category and technological development. The main services can be dispersed to different sections to fully cover the services required by the public and academic research group: reproductive health services, complex disease services, basic scientific research services, and drug research and development services. First of all, encourage qualified cities and counties to carry out prenatal genetic testing and screening projects. Compared with the traditional amniocentesis technique, which is the most commonly used prenatal testing for pregnant women, noninvasive prenatal genetic technology can alleviate the pain of pregnant women and reduce the risk of abortion. However, the quick unpainful test can also determine the risk that the fetus will be born with certain genomic abnormalities. Therefore, the establishment of noninvasive prenatal screening services in local hospitals that can provide regular pregnancy checkups for pregnant women can indeed increase the popularity of the industry. Second, support the establishment of precision medicine centers relying on qualified medical institutions, and use genetic testing technology to carry out precision medicine and individualized medicine to improve the effectiveness and safety of treatment. Encourage qualified medical, medical education, and scientific research institutions to carry out the clinical application of laboratory research and development tests in accordance with laws and regulations, and carry out the prediction, early diagnosis, and individualized treatment of major diseases. Tumor diagnosis and treatment has been currently well studied in research field; thus, cancer genetic testing should become the most power weapon to eliminate cancer burden. Tons of evidence have shown that tumor genetic testing can effectively assist early diagnosis and further guide individual treatment, and extend the life and quality of life of cancer patients. For example, in lung cancer, targeted therapy has greatly improved the 5-year survival rate of patients with lung adenocarcinoma and has become a milestone in the treatment of non-small cell lung cancer. However, to achieve precise targeted therapy requires determination of cancer cell mutations. The pathogenesis of malignant tumors is very complex and the treatment is also highly specialized. So, only certain hospitals (such as tertiary A hospitals) have relatively complete clinical treatment experience. Therefore, with the establishment of a precision medicine center, they can make full use of first-hand data to combine genome technology with the latest scientific research results of clinical medicine to provide references for disease diagnosis, treatment, and clinical decision-making.

Consortium/society aims to improve the changing standard system for genetic testing. Different types of genetic testing projects should have different finance policies. A diversified list of charges to maintain price stability and avoid large fluctuations is needed. By summarizing the experience of various medical institutions in the western Taiwan Strait in carrying out genetic testing pilots, the consortium can explore the establishment of financial subsidies and other genetic testing payment mechanisms. For example, in some areas where high birth defects have been occurring, public health service should provide free newborn screening to test for health disorders that aren't otherwise found at birth.

Consortium/society promotes the R&D and industrialization of genetic testing technology. Priority will be given to gene testing institutions to apply for financial science and technology projects. Support genetic testing institutions to introduce advanced technologies at home and abroad; carry out upstream and downstream businesses such as biochips, genetic testing instruments and consumables and reagents manufacturing, life science services, etc., expand new business formats; and cultivate growth points. Formulate and improve genetic testing data application specifications, promote genetic testing data information to enter the big data application platform of various departments, and realize the integrated development of genetic testing technology application and big data industry. Incorporate the provincial genetic testing technology application promotion demonstration center construction project into the provincial key project management, support genetic testing institutions to create provincial innovative leading enterprises, and open the provincial large-scale scientific instrument facility collaboration network to genetic testing institutions. Give key support to the first (set) of genetic testing technology-related equipment and the application of the first batch of products with independent intellectual property rights. Encourage qualified companies and institutions related to genetic testing to explore in accordance with laws and regulations in terms of operating models and application areas. Technical service platforms such as sequencing and information can serve more scientific researchers and the public, and can also attract more opportunities for cooperation.

Consortium/society needs a talent team. Implement the talent introduction policy and increase support for key projects. Any work cannot be carried out without talents, especially in the current situation, and the development of genetic testing technology requires good technical support. The operation of genetic testing and the improvement of sequencing accuracy can be improved through the improvement of operating procedures and technological advancement, but the implementation of these improvement measures ultimately requires human participation. Genetic testing is developing rapidly, but the bottleneck in data interpretation hinders its further development. Since most diseases are regulated by multiple genes and signaling pathways, genes in different tissues have different functions, and different types of gene mutations and different mutation sites will affect the phenotype and outcome of the disease. In the huge human genome database, about only 2% of the gene functions are known. In addition, the relationship between diseases and genes has not yet been clarified. It requires professional ability and complete knowledge system to correctly explain the relationship between genes and diseases. Therefore,

the training of talents and the recognition of qualifications are particularly important. This breakthrough requires the use of big data, artificial intelligence (AI), and other tools. Therefore, it is necessary to conduct professional training and training of relevant personnel from universities and scientific research institutions to strengthen scientific research on genomics-related technologies. Finally, cooperating with foreign companies and supporting R&D and industrialization of advanced genetic testing technologies will also be of great help.

Consortium/society can promote the high-quality output like publications and testing kits. The research characteristics of gene sequencing make it possible to obtain more results after the initial investment. Gene sequencing mainly relies on sequencing technology and data analysis tools, so a sequencing result can be a scientific research when analyzed completely. Therefore, completed data along with detailed clinical information and scientific research transformation can have very convincing results. High-level research publication, useful testing kit, and successful clinical trial can have an overall influence on research fields as well as public recognition with unique innovation ability, transformation ability, and unlimited development potential. Thus, a professional society for genetic testing and realizing regional management can solve the difficulties and problems in the construction and operation of genetic testing institutions in the Haixi economic zone.

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Chapter 4
Artificial Intelligence in Medical Management

Giovanni Briganti

Abstract This chapter will introduce the reader to the current state of artificial intelligence in medicine and its applications for modifying how healthcare is delivered.

Keywords AI · Digital medicine · Medical management · Hospital innovation

4.1 Introduction

Artificial intelligence (AI) is an innovative field of research that is gaining more and more ground in science and society, because of many possible applications. In medicine, since the approval by the Food and Drug Administration (FDA) of several medical technologies exploiting AI in the last decade, a new field is emerging that tries to integrate these technologies into clinical practice: augmented medicine, which is already revolutionizing the hospital world in developed countries (Briganti and Le Moine 2020).

This development in medicine risks bringing about substantial changes in the very functioning of clinical practice and healthcare, and therefore requires relevant awareness-raising among doctors, hospital managers, and anyone contributing to the healthcare sector, so that we can continue to provide patients with high-quality, cutting-edge healthcare.

In this work, we first review the basic concepts of AI; second, we review the present fields of application as well as the future perspectives of medical AI; and third, we discuss the challenges that this area will have to solve in the short and medium term.

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4.2 AI: Definitions

The origins of AI can be traced back to Alan Turing, a famous English computer scientist who in 1950 invented a test (now known as the Turing Test) in which a certain level of intelligence is required by the machine to trick a human into believing they are having a conversation with another human: this was called the Imitation Game (Turing 1950). Even if this level of intelligence has not yet been reached by machines, a simple conversation with a virtual assistant (e.g., Siri) can serve as an example to show how far research in AI has evolved in recent decades.

AI is commonly understood as the part of computer science that is able to handle complex problems with a large amount of data and relatively little theoretical input. It is a set of computations that are able to perceive, reason, and act. The two most widely used areas of AI in medicine are machine learning and deep learning.

Machine learning is defined as a set of computations that improve through experience: it is divided into supervised learning, where the data used is labeled by the observer, and unsupervised learning, where the data is not labeled (Niel and Bastard 2019). Two techniques frequently used in medical research since the 2000s and deriving from machine learning are random forests (comparable to decision trees) and artificial neural networks (ANN), organized with hidden layers with a number n of neurons per layer, where each neuron plays a particular role in a general reasoning process that has to transform an input (data) into an output. In the last decade, it is rather the techniques of community detection (clustering) that are gaining ground in research, in order to determine congruent groups of patients, symptoms, or treatments in specific situations (Yang and Bang 2019).

Deep learning derives from machine learning but requires less computational power since generally the number of neurons per layer of the neural network decreases over time. Deep learning is optimal for the analysis of temporal data and large databases (big data). In medicine, deep learning is therefore used, for example, for diagnosis based on images in radiology, pathology, and endoscopy (Liu et al. 2019; Campanella et al. 2019).

Along with classical AI, the past few decades have seen the concomitant emergence of Bayesian AI. Bayesian methods and the reasoning on which they are based are less known to the general public: yet Bayesian models in AI directly represent real-world entities and allow their cause-effect relationships to be investigated (Scutari and Denis 2015).

4.3 Applications of AI in Medicine

The medical world is primarily interested in AI in four of its fields of application: monitoring, prediction, diagnosis, and personalized medicine. AI, on the other hand, is only one of the areas of "augmented medicine." For more details on the applications of AI in medicine, the reader is referred to detailed and recent works (Briganti

and Le Moine 2020). All these domains of application have important repercussions on how we imagine and manage healthcare delivery and will therefore greatly impact how healthcare institutions work.

4.3.1 Monitoring

Patient monitoring is a relatively simple but heavy task for the medical and paramedical professions and having great added value in clinical settings. Modern medical technologies allow the emergence of continuous medical monitoring, with the aim of recording certain parameters of the individual and being able to alert the caregiver or relatives when a value considered to be abnormal is recorded. Three medical conditions currently benefit from FDA-approved technologies for continuous medical monitoring: arrhythmia, diabetes, and epilepsy.

The detection of an abnormal heart rhythm by connected device was the first FDA-approved medical device case with AI. Approved devices allow recording of ECGs with an algorithm to recognize, for example, atrial fibrillation (Turakhia et al. 2019). These technologies have great added value in the elderly and/or isolated at risk of developing arrhythmias without anyone being able to alert the emergency services.

Subcutaneous devices connected to an app are able to continuously record blood sugar levels (Christiansen et al. 2017) and report low or high blood sugar levels. By adding AI, these devices are able to predict these adverse events by getting to know the patient. These technologies have a significant impact on a pathology such as diabetes which strongly affects the social life of citizens and which, in addition to improving the quality of life by reducing adverse events, also reduces the stigma associated with these adverse events.

Epilepsy is another example of a disease that strongly affects the quality of life and stigmatizes those who have it, especially children of school age. Connected devices can measure the body's electrical activity to detect acute episodes (e.g., absences) and notify the caregiver, loved one, but also the teacher with the child in their class; in the future, this technology will also be able to predict epileptic episodes (Regalia et al. 2019).

4.3.2 Prediction and Diagnosis

Structured or unstructured information encoded in electronic medical records (EHR) are invaluable for developing models capable of predicting the occurrence of certain disorders: this is the case of cardiovascular risk, renal failure, and digestive disorders (Briganti and Le Moine 2020). The only obstacle encountered for the development of these models is the paucity of solutions for the exploitation of unstructured data, currently constituting a greater proportion of the content in EHR. One potential

solution to restructuring this data is another AI technique, natural language processing (NLP), which automatically analyzes sentences in medical reports to derive structured information. NLP is relatively new in medicine and is enabled in particular by the international coding language SNOMED CT.

Diagnostic AI also extends into a number of areas and is deeply embedded in Bayesian causal reasoning. Thus, it is possible to infer a diagnosis from databases made up of symptoms, parameters (as in the case of ECGs for arrhythmias), medical imaging, endoscopy, and histopathology sections: these last three specialties are not surprisingly the more revolutionized by the wave of new technologies.

4.3.3 Personalized Medicine

AI is particularly effective for high-dimensional data (the number of variables is much greater than that of patients), as in genetics (one patient for thousands of genes) and for temporal data (endoscopy, imaging). This strongly contributes to its innovative and disruptive side since these data were difficult to analyze before. This has resulted in the development of personalized medicine, which is enabled by the collection and analysis of personal data on smartphones. For example, we can denote the clinical trial initiatives relocated on smartphones, as well as applications dedicated to personal parameters (somatic and related to mental health).

4.4 Present and Future Challenges of Integrating AI in Healthcare Delivery

Monitoring technologies, as well as those for prediction and diagnosis, have and will have important repercussions on the way care is provided. For example, reference hospitals for the technologies mentioned in this work have all revised their care process according to the working time saved in the absence of administrative overload and being able to solve easier cases while leaving more complicated ones to experienced physicians, while other institutions delegate part of the diagnostics in imaging or pathological anatomy to the software itself, with subsequent validation by the doctor. Others outsource history taking at home when possible, through applications that automatically provide questions as they might have been asked by a clinician. The field of reinventing hospital care with smart technologies is so vast that it has quickly become a fertile research field in medical management.

Even if initially interested in monitoring in the context of diseases, a larger part of the medical technology industry quickly became interested in the concept of "quantified self," that is to say the measurement of repeated individual parameters without a medical reason: for example, the quantification of physical exercise, diet, and weight. The reason is simple: the quantified self allows for greater market capture

because more people can benefit from it, so the data collection there is exponentially greater and several different types of data are collected. The quantified self, however, introduces a significant bias in the data: many more young people will adopt connected devices, which has the effect of "distorting" the vision of a "healthy" individual. This is all the more important as entire states are beginning to enter into agreements for the mass distribution of connected devices to improve the hygiene of their citizens' lives.

Several challenges relate to diagnostic AI. The first and perhaps most important is the replication crisis of studies aimed at showing the effectiveness of AI in making diagnoses: a meta-analysis (Liu et al. 2019) carried out on the literature shows that most of the results from studies in AI (other than those technologies validated by the FDA) do not have an appropriate design and do not replicate in other source populations: they cannot therefore be translated into clinical practice unless additional studies of primary replication, absent in most cases. To resolve the replication crisis, an obvious path is that of "open science": making public the methods and data leading to the development of the models at hand.

Second, the models developed so far seem to perform too well on training and testing data (i.e., the data that initially feeds the AI so that it can improve) and poorly perform on data from other source populations: this phenomenon is defined as overfitting. Resolving overfitting requires a great deal of effort, since it is only detected after the model has been adopted by a healthcare institution. To resolve overfitting, it is necessary either to recalibrate the models once adopted on the basis of the target population or to develop models from the outset via larger and more diverse populations: this is difficult for companies developing medical technologies because partnerships with hospitals are extremely rare. New partnerships between hospitals and technology companies are therefore needed to develop better diagnostic models.

Third, most studies of diagnostic AI compare its performance to that of physicians: this is not surprising, since companies pushing medical technologies need to demonstrate their effectiveness. However, this does contribute to the resistance of the medical profession against AI, already strong in view of the absence of an ethical, legal framework and the security concerns associated with the technologies. Also, these studies miss the real wish for doctors, patients, and healthcare institutions, that of offering (and receiving) better quality care: in the next decade, we must therefore observe the emergence of studies, combining the two forces to improve the quality of care. Indeed, caregivers are irreplaceable in the care process for reasons that go beyond the simple human guarantee, one of the only principles emerging in the legal- ethical chasm linked to AI and giving the doctor a role of supervisor of the AI.

Regarding personalized medicine, the biggest concern remains that of data security: in fact, most of the time, the data remains on the servers supporting the given application, which is problematic.

We must also consider the capital importance of educating physicians and future physicians in new technologies, so that they are able to use them, co- develop them, and evaluate them (in the same way as the review by peers carried out in the

scientific publication process). For this, courageous initiatives are needed at an international level to allow the emergence of common and effective educational platforms in AI.

4.5 Conclusion

AI must be seen by technology companies as well as caregivers and healthcare institutions as a tool to improve the quality of care. It is necessary to improve the design of development studies, models, and testing their effectiveness so that their implementation is as secure as possible. It is also necessary to study the combined strengths of physicians and RNs before setting up an implementation at the level of healthcare institutions. To do this, we have to build bridges between the industrial and healthcare sectors.

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Chapter 5
Synthetic Lethality and Lung Cancer

Jianan Huang, Tiankui Qiao, and Xiangdong Wang

Abstract Synthetic lethality happens between two genes that the mutation of either gene is feasible but the mutation of both concurrently leads to viability loss. The key to the use of synthetic lethality during cancer therapy is the identification of stable synthetic lethal genetic interactions. The transformation of synthetic lethality to clinical practice will be aided by the integration of genetic interaction data in vitro and in vivo. Lung cancer, especially non-small cell lung cancer (NSCLC), has recently been treated with molecular targeted therapeutic drugs. Despite the development of third-generation inhibitors, dealing with resistance to epidermal growth factor receptor inhibitors (EGFRi) still has an outstanding challenge. Moreover, advances of KRAS-driven lung cancers have been hindered by the diversity in the targetable mechanisms, with unanticipated resistance mechanisms to other effective targeted therapies. Synthetic lethality ensures that targets are identified in this situation to find novel therapeutic targets and address acquired and intrinsic resistance.

Keywords Synthetic lethality · Lung cancer · EGFR · KRAS

5.1 Introduction

Synthetic lethality was first discovered in 1922, when Calvin Bridges found that simultaneous mutations in two genes in a single fruit fly were fatal, but single mutations in each gene did not cause individual death (Bridges 1922). This laboratory finding has also been observed in single cells, where simultaneous loss of

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function of two genes can lead to cell lethality, while cells can survive with loss of function of either gene alone (Novick et al. 1989; Boone et al. 2007). This creates a novel and intriguing concept of tumors, because loss of mutated function of tumor suppressor genes is common, but they are often "undruggable" (Epstein 2013). Targeted targets that are available for drug therapy may lead to drug resistance due to delayed compensation pathways, so it is necessary to search for synthetic lethal genetic interactions for drug resistance.

Recent advances in genome sequencing have made it possible to rapidly identify genetic mutations that distinguish tumor from non-tumor cells (Hyman et al. 2017). Tumor-specific genetic changes reveal the biological changes which drive tumor progression, and reveal targets that can be used selectively to treat tumors. Individualized or precision gene-targeted therapy for tumors is characterized by providing highly specific treatment to reduce adverse reactions and overtreatment. Currently, the frontier of oncology therapy is using this individualized oncogenomic approach to successfully treat patients with tumors that cannot respond to standard therapies (Stockley et al. 2016; Swanton et al. 2016).

Generally, most gene-targeted cancer therapies take advantage of a phenomenon known as "oncogene addiction," in which a tumor relies on an oncogene or its pathway to survive. Unfortunately, although antibody-based or small molecule oncogene inhibitors have been shown to be effective against certain tumor genotypes (Pagliarini et al. 2015), not all tumors have functional acquired targeting of oncogenes, and resistance to treatment is also a common result. In these tumors, oncogenic and non-oncogenic mutations can be exploited to further treat tumors by identifying secondary targets that lead to synthetic lethality (Fig. 5.1).

More than a decade ago, it was discovered that non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutations can respond to EGFR inhibitors (EGFRi) selectively. This great discovery has led to individualized treatment for these difficult-to-treat tumors (Lynch et al. 2004). Although EGFRi have achieved some degree of achievement, most patients who responded to EGFRi treatment initially relapsed within 16 months because of acquired drug resistance (Mok et al. 2009). A deeper research of microcosmic mechanisms of acquired EGFRi resistance could lead to the progress of next-generation medicine to overcome resistance and thus delay tumor recurrence.

KRAS mutations have been discovered in NSCLC tumors for over 20 years (Bos 1989), but we are just starting to recognize the value of identifying KRAS tumor character. Mutations in EGFR and KRAS seem to be mutually exclusive. Recent studies have shown that patients with mutated KRAS genes have difficulty benefiting from traditional or adjuvant chemotherapy and even fail to respond to EGFR inhibitors. Obviously, there is a requirement to develop new therapeutic targets specifically for patients with KRAS-mutated NSCLC.

In this review, we emphasize some of the recent researches and subsequent challenges in using synthetic lethality to find novel potential therapy targets, including its clinical transformation. Then, in view of the latest progress of synthetic lethality in lung cancer, we focus on the mechanism of oncogene signaling network

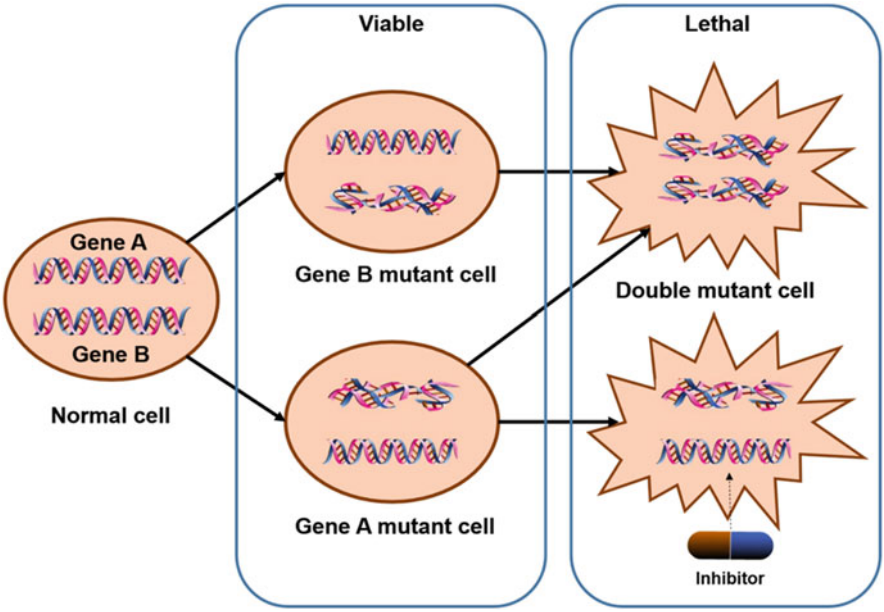

Fig. 5.1 The loss or the inhibition of either of the protein products of gene A or B alone is viable. Mutation or pharmacological inhibition of the protein product of gene B in cells with a mutation of gene A results in synthetic lethality

in EGFRi-resistant NSCLC and the research progress in synthetic lethality related to KRAS-driven lung cancer.

5.2 Expanding Definition of Synthetic Lethality

Theoretically, a synthetic lethal-based approach could be extended beyond the loss of function at the tumor target. Cancer cells often have the characteristics of gene overexpression, which may be due to changes in somatic copy number (Zack et al. 2013) or due to epigenetic changes which can increase gene transcription. Genes that are overexpressed in tumors can be identified by identifying the interaction gene pairs that cause "synthetic dosage lethality" (SDL). SDL is a kind of genetic interaction in which one gene is overexpressed related to the reduction in function of another gene, leading to lethality. The concept of SDL was first reported in yeast (Yan et al. 1991). The overexpression of MAD2 in several types of tumors has been studied extensively in recent years, demonstrating an SDL effect with PP2A inhibition (Bian et al. 2014).

In addition, tumor cells are found to be heterogeneous usually and in different microenvironments, both of which can influence genetic interactions, and most of them are condition dependent. These conditions may be inherent, such as the

metabolic state and genetic background, or they are extrinsic, such as the extracellular microenvironment and therapeutic medication. And some genetic interactions need the mutation of three or more genes to get synthetic lethality (Tong et al. 2004). On the contrary, background mutations can inhibit synthetic lethality and thus generate synthetic viability. Thus, the genetic background of a tumor, such as the activation of an oncogene or the loss of p53, can reveal or inhibit synthetic lethality. It is possible to take advantage of condition-dependent synthetic lethality to exploit tumor-related conditions such as continuous stress, increased mutational load, changed metabolism, and exposure to standard antitumor therapy, to promote the extent of synthetic lethal interactions (O'Neil et al. 2017). For instance, hypoxia reduces the effect of homologous recombination (Bindra et al. 2004), leading to a damaged state of DNA repair, making cells sensitive to suppression of the repair protein PARP1 (Chan et al. 2010). So screening for phenotypes that synthesize lethal interactions under hypoxia or metabolic conditions can reveal the tumor microenvironment, which can discover novel condition-dependent synthetic lethal interactions with higher tumor cell killing specificity.

5.3 Translating Synthetic Lethality into Therapeutics

Clinical treatment based on synthetic lethality is an intriguing concept, but few mature therapeutic strategies have been used clinically to date. One of the main obstacles is the difficulty of finding a stable, clinically useful synthetic lethal interaction.

There are three main challenges to screen for synthetic lethal interactions. First of all, these genetic interactions lead to lethality, so this makes it difficult to recover and identify these mutants. Second, most synthetic lethal interactions are conditional-dependent interactions and may be unstable across all genetic backgrounds or in different conditions. And third, synthetic lethal interaction pairs are relatively rare, and a huge number of mutated gene pairs need to be researched to identify synthetic lethality, which is a huge workload. Considering all above, most synthetic lethal genetic interaction screening is performed only in yeast, as it is easier to obtain techniques that accelerate high-throughput production and analysis of mutated gene pairs under laboratory conditions (O'Neil et al. 2017).

Theoretically, using a treatment strategy based on synthetic lethality also presents three benefits. First, synthetic lethal interactions are selective for tumor-specific genetic mutations, which can easily identify responders in patients. Second, considering there is a large treatment window, treatment side effects based on synthetic lethality are smaller, and lower drug doses are effective. Last, this strategy can be used to any type of tumor mutation, including tumor suppressors and those therapeutic targets that are not thought to be undruggable (O'Neil et al. 2017). Practically, PARP and BRCA1/BRCA2, the only one synthetic lethal interaction, has been successfully transferred from laboratory discovery (Bryant et al. 2005) to the clinical application (Fong et al. 2009). However, synthetic lethality databases, such as

SynlethDB (Guo et al. 2016), contain a huge number of interactions according to the published literature.

In addition, there is a need to evaluate the potential clinical value of synthetic lethal interactions, to include what can be used for tumor prevention (Walcott et al. 2016). Evidence for such chemoprophylaxis strategies based on synthetic lethality is still inchoate, gathered mainly using animal models. Theoretically, a strategy based on synthetic lethality may be more effective if it is implemented before the precancerous lesion becomes highly heterogeneous. It is also necessary to determine whether intermittent administration or lower doses will be effective by this strategy in order to avoid drug toxicity related to continuous high-dose chemotherapy (Wu and Lippman 2011).

5.4 Synthetic Lethality and EGFRi-Resistant NSCLC

In recent years, a lot of studies have been conducted to explore the "oncogene addiction" of EGFRi-resistant NSCLC, based on the notion of synthetic lethality. For EGFR-mutated lung tumor, synthetic lethality is usually used to describe two types of gene interactions: first, genes that are particularly needed in EGFR-mutated cells compared to EGFR wild-type cells, and second, genes that, when damaged, can be combined with EGFRi therapy to cause synergistic death. For the latter, potential targets may focus on the genes that regulate sensitivity to EGFRi. Construction of candidate gene libraries to detect synthetic lethal interactions related to EGFRi resistance can be actuated by hypothesis. For instance, some researches have focused on the analysis of the EGFR "interaction group," which is a network of molecules that interact with EGFR directly or indirectly as a group of possible targets (Fig. 5.2) (Astsaturov et al. 2010; Li et al. 2013; Yoshida et al. 2016; Saafan et al. 2016). Alternatively, phosphorylproteomic analysis of EGFR-mutated signal transduction networks in lung tumor models could afford pathway-specific candidates to be included in targeted screening (Yoshida et al. 2014; Huang and White 2008). In recent years, key pathways associated with EGFRi resistance have been reported, including nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), and Wnt signaling.

Among them, activation of NF-κB pathway is associated with chemotherapy resistance, exhibiting its potential as a clinical candidate (Godwin et al. 2013). Bivona et al. performed a pooled shRNA screening using a library of over 2000 genes in the H1650 cell line. By shRNA screening in the presence of erlotinib, the authors identified genes that promote EGFR dependence and recover EGFR sensitivity when silenced (Bivona et al. 2011). From this screening, 18 genes associated with NF-κB and Fas were revealed as death receptor signaling pathways that sensitized cells to erlotinib. When stimulated with Fas ligand, tumor cells initiated caspase-mediated apoptosis and activates NF-κB pathway (Godwin et al. 2013). Recently, Sudo et al. have shown that the NF-κB pathway is involved in resistance to EGFRi (Sudo et al. 2015). Synthetic lethal screening of genomic shRNA with

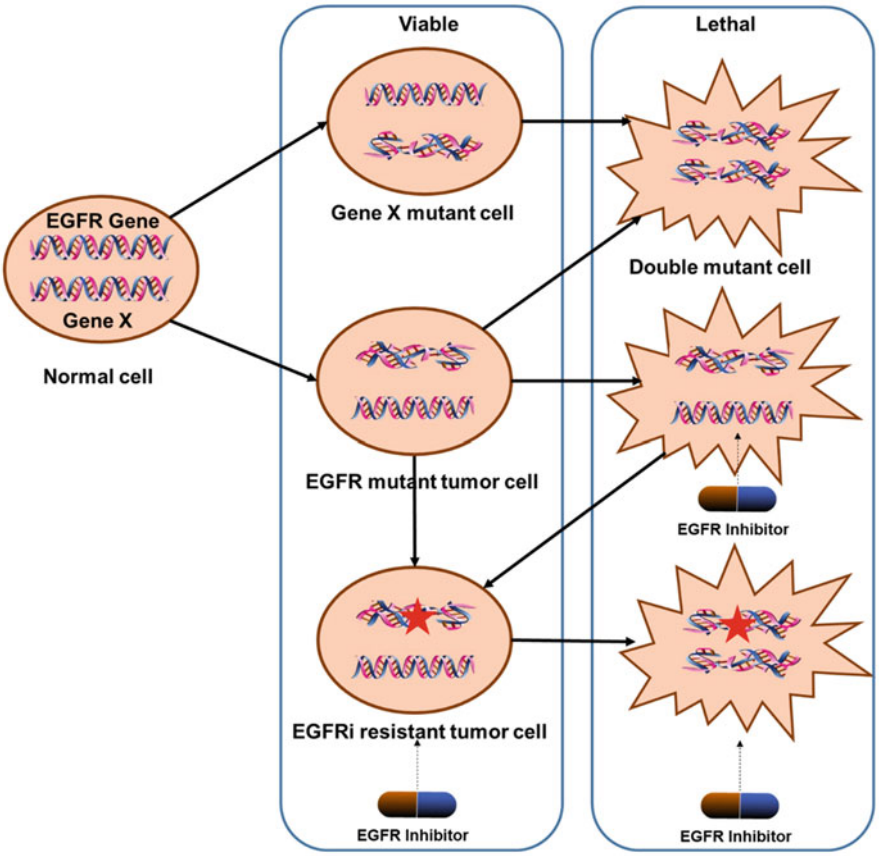

Fig. 5.2 The loss of gene X in normal cell alone is viable, as the mutation of gene X in EGFR mutant tumor cell can result in synthetic lethality. Lung cancer cells that carry mutated EGFR but are insensitive to EGFRi may rely on gene X to survive in the presence of EGFRi

gefitinib combination was performed in NSCLC H1975 cell lines, which contained both L858R and T790M EGFR mutations. In fact, one of the barriers to investigating NF-κB signaling in EGFRi resistance is the shortage of inhibitors that target NF-κB directly (Gilmore and Herscovitch 2006).

The STAT3 is another main driver of cancer signaling and drug resistance in various types of cancer. As portion of the research into the mechanisms why NF-κB promotes EGFRi resistance, Bivona's previous study also observed activation of NF-κB in erlotinib-treated cells leading to the production of IL-6 and follow-up activation of STAT3 pathway (Blakely et al. 2015). Therefore, inhibition of the IL-6-STAT3-NF-κB signaling axis appears to be the key to restoring EGFRi sensitivity in other drug-resistant NSCLC. In the study by Astsaturov et al., STAT3 was considered as a potential synthetic lethal target itself for EGFRi therapy (Astsaturov et al. 2010). The authors constructed a computer network of EGFR-centric proteins by

integrating lots of databases to identify molecules that functionally interact with EGFR. Unfortunately, the lack of STAT3 inhibitors in current clinical trials makes this strategy difficult to carry out in clinical settings.

Ligands in the Wnt signaling family affect a variety of cellular processes, and disorder of the Wnt/β-catenin pathway is also known to occur in different types of cancer, such as colorectal cancer (Zhan et al. 2017). Casas-Selves et al. reported several classic Wnt signaling pathways leading to the regulating factor in EGFR inhibitor can promote cell survival by whole genome synthetic lethal shRNA screening (Casas-Selves et al. 2012). After bioinformatics analysis and second-generation sequencing, they identified multiple shRNA hits associated with the Wnt/Tankyrase/β-catenin signaling pathway, such as genes encoding poly-ADP-Tankyrase1 (TNKS1) and Tankyrase 2 (TNKS2). Mice carrying tumor xenografts showed more growth inhibition significantly in response to gefitinib treatment with shRNA targeting TNKS1 compared with controls.

Although there is an understanding base of synthetic lethality related to first-generation inhibitor resistance, the only agent approved for patients with advanced EGFR mutation is osimertinib. There is still a lack of available remedies for patients who are resistant to first-generation EGFRi but do not have the T790M mutation. There are still significant challenges that limit the transformation the large volume of synthetic lethal interactions described above into an effective treatment for NSCLC patient.

5.5 Synthetic Lethality and KRAS-Driven NSCLC

Mutations of KRAS gene are also usually found in different tumors, such as lung cancer, colorectal cancer, and pancreatic cancer (Bos 1989). Approximately 15–25% of patients with NSCLC are with KRAS mutations meanwhile (Brose et al. 2002). Some researches have illustrated that KRAS and EGFR mutations are mutually exclusive to a certain extent, suggesting that they have functionally identical roles in lung tumor progress (Shigematsu et al. 2005; Kosaka et al. 2004; Taron et al. 2005). However, patients with EGFR mutations responded better to inhibitors (Fukuoka et al. 2011). Although several strategies have been explored to inhibit KRAS, the pursuit of inhibitors for KRAS therapy has fallen to meet expectations. A barrier to the research of specific KRAS inhibitors is that the mutant KRAS protein has lost its normal enzymatic function, and this loss of the mutant enzymatic function is more difficult to inhibit. The most effective method for KRAS-mutated NSCLC is a combination of targeted oncogenic KRAS and other therapeutics that are specific to the tumor molecular spectrum. However, realizing this prospect requires an understanding of these abnormalities and the compensatory mechanisms of tumor cells. In recent years, the synthetic lethal effects associated with KRAS-mutated NSCLC have been reported mainly including phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MEK, also known as MAPK)

pathways, exportin 1 (XPO1, also known as CRM1) pathways, Polo-like kinase 1 (PLK1), and RhoA/Rho kinase (ROCK) pathways.

Targeting the pathway downstream of KRAS is a potentially promising approach. Inhibitors of the PI3K/mTOR pathway are active in cancer with PI3K mutations and may be effective in treating KRAS-mutated lung cancers when combined with MEK inhibitors (Engelman et al. 2008). This elucidates the reason for the remarkable efficacy of receptor tyrosine kinase (RTK) targeted cancer therapy when RTK inhibition results in loss of PI3K and ERK signaling (She et al. 2005; Mellinghoff et al. 2005; Engelman 2007; Sharma et al. 2006). Engelman et al. (Engelman et al. 2008) treated mice with KRAS-mutated lung tumors with PI3K and MEK inhibitors simultaneously and found that this strategy resulted in significant combined tumor regression. In addition, serine threonine kinase 11 (STK11), which is also called liver kinase B1 (LKB1), is a multitask tumor suppressor kinase (Mahoney et al. 2009). LKB1 is inactivated by somatic cells in about 30% of NSCLC, and the homozygous loss of the gene combined with KRAS leads to a more aggressive tumor phenotype than that of KRAS alone (Ding et al. 2008; Makowski and Hayes 2008). NSCLC with both LKB1 inactivation and KRAS activation have been reported to be functionally different from other lung cancers, showing sensitivity to single dose therapy with the MEK inhibitor rapamycin or CI-1040 (Mahoney et al. 2009). In recent years, there have been reports that the combination of ataxia-telangiectasia mutation (ATM) dysfunction with MEK1/2 inhibitors has a synthetic lethal effect on KRAS-driven lung cancer, because ATM mediates the pro-survival interaction between MEK/ERK and AKT/mTOR pathways (Smida et al. 2016).

Recently, Kim J et al. reported that exportin 1 (XPO1, also known as CRM1) is a drug target for KRAS-mutated lung cancer. The authors demonstrate that KRAS-mutated NSCLC is dependent on nuclear output for KRAS-specific cellular autonomic addiction, and that chemical interference with XPO1 inhibitors produces a strong synthetic lethal interaction with KRAS. The primary mechanism by which XPO1 inhibitors are sensitive to KRAS-mutated NSCLC may be intolerance to the accumulation of nuclear factor IκBα (also known as NF-κBα), thereby inhibiting transcription factor activity of NF-κB. These findings suggest that clinically available XPO1 inhibitors combined with genome to guide patient selection are a promising treatment strategy for a significant number of patients with lung tumor (Kim et al. 2016).

In another research, Wang J et al. reported that combined inhibition of Polo-like kinase 1 (PLK1) and RhoA/Rho kinase (ROCK) leads to synthetic lethality in KRAS-mutated NSCLC. Research showed that the combined inhibition significantly increased the transcription and activity of p21, a cyclin-dependent kinase inhibitor, resulting in specific G2/M phase arrest in KRAS mutant cells. Overexpressed p21 can preferentially impair the growth of KRAS mutant cells through cDNA transfection or clinical drugs, suggesting that there is a synthetic lethality interaction between KRAS and p21 that can be used medicinally. Application of BI-2536, a selective inhibitor of PLK1, and fasudil, a ROCK inhibitor, inhibited tumor growth and significantly prolonged mouse survival in a KRAS

mouse model, suggesting a strong synergistic effect and potential for the therapy of KRAS-mutated cancers in vivo (Wang et al. 2016).

In addition, neurofibromatosis type 1 (NF1) pathway (Johannessen et al. 2008), Wilms tumor gene 1 (WT1) (Vicent et al. 2010), and cyclin CDK4 (Puyol et al. 2010) have also been reported to be involved in the synthetic lethality of KRAS-mutated NSCLC. However, much remains to be learned about the molecular details of KRAS proteins' function. We should summarize the tumor protein abnormalities that lead to the oncogene-specific synthetic lethal interactions, thus providing additional targeted therapy chances for KRAS-mutated NSCLC, and developing appropriate alternative markers to monitor medicine action, which is critical for the treatment of these patients.

5.6 Conclusion

Synthetic lethality as a concept does not seem to meet its promise of defining new clinical strategies to deal with tumors and their drug resistance due to the lack of some reproducibility between different researches and the difficulty in transforming any identified targets into clinical practice (Downward 2015). It is essential that practical steps be taken to deal with these difficulties and challenges. It is our view that for most of the identified synthetic lethal interactions, the underlying mechanisms how these genes contribute to lethality are mostly unknown. In order to exploit synthetic lethality fully, there is an urgent requirement to ascertain the effect of those genes on signaling networks. Furthermore, many identified synthetic lethal interactions are background dependent, which is referred to as a "soft" interaction (Ashworth et al. 2011; Lord and Ashworth 2013). The establishment of these background-dependent molecular bases enables the recognition and translation of these "soft" interactions into more powerful "hard" synthetic lethal effects. At the same time, understanding this background dependence can also provide messages for biomarker discovery to recognize the patients who will benefit from therapeutic strategy based on synthetic lethality. Our understanding of how synthetic lethality promotes tumor heterogeneity is also inadequate. Given that drug resistance is now confirmed to be driven by various resistance mechanisms in heterogeneous tumors (Hata et al. 2016; Ramirez et al. 2016; Bivona and Doebele 2016), it is imaginable that different subpopulations of tumor cells may need various synthetic lethality strategies to minimize tumor heterogeneity and avoid the growth of major components.

Therefore, synthetic lethality is a genetic notion that has had an important influence on cancer research. Bioinformatics analysis of synthetic lethal interaction data from experiments in vitro and in vivo will facilitate the screening of potential therapeutic targets for tumors. However, these data also highlight the mechanistic complexity of tumor phenotypes, which need to be untangled in order to successfully find specific targets that can be used to selectively kill tumor cells, thus realizing the full potential of individualized anticancer therapies.

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Chapter 6
Advanced Demand Forecasting and Inventory Management Methods in Hospital Pharmacy

Isabel Fernández, Pablo Velarde, M. Casas, and José M. Maestre

Abstract Inventory management is an essential task in a hospital that the pharmacy department has to carry out. It is a difficult problem that involves different and contradictory optimization criteria. Also, the problem becomes more challenging due to issues such as delays and constraints that naturally arise in this context. The chapter presents advanced demand estimation methods and control techniques for pharmacy management, which are then assessed using real data from a Spanish hospital.

Keywords Hospital pharmacy · Demand forecasting · Stock management · Optimization · Model predictive control

6.1 Introduction

Failures in stock management in a hospital pharmacy can be catastrophic because the lack of satisfaction of clinical needs can lead to the loss of human lives. On the other hand, the hospital budget must also be considered and imposes limits on the rise of average stock levels. As a matter of fact, about 35% of hospital expenses on services and goods are generated by the pharmacy department (Bermejo et al. 1999) and can reach tens of millions of euros per year in large hospitals. Thus, inventory control becomes a very relevant task that the pharmacy department has to carry out in a hospital. It is a complicated problem that requires dealing with conflicting goals to

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find a trade-off between service levels and budget and staff constraints. Likewise, there are other challenging issues to be considered, e.g., the restrictions for cold storage, delays in drug deliveries, and stochastic demands.

Typically, pharmacy managers apply straightforward control policies. In particular, an (*s, S*) policy is usually employed, which means that whenever inventory level drops below *s* units, an order is placed to raise it back to *S*. Alternatively, a fixed size *Q* can be assigned to orders, and then *s* is defined as the reorder point. Note that other periodic review inventory controls are described in the literature; see, for example, works as Tayur et al. (1999), Brewer et al. (2001). Nevertheless, these policies lack enough flexibility to consider all the factors involved in this decision-making problem in a systematic manner.

To begin with, hospital inventory managers seek to minimize stock costs while satisfying the drug demand, typically modeling the latter by means of a random variable; see, e.g., Parra (2005), Guerrero (2009), Toledano (2006), Ramos (2008). In particular, forecasting drug demand lies in the core of this decision-making problem, which must also account for transport delays and other complicating issues to avoid stock-outs. A simple and common method employed in practice is the ABC inventory classification, which sets different periods for reviewing the drug levels depending on each drug's economic impact. As a consequence, expensive drugs are frequently reordered and vice versa. One academic work dealing with this method is Ramanathan (2006), where weighted linear optimization is used to this end. Optimization via simulation has also been proposed in the literature from decades ago. For example, a simulation model was developed in Duclos (1993) to assess several standard inventory system variations and the hospital's ability to operate successfully under normal and emergency demand conditions. In Danas et al. (2002), the logistics activities of the hospital pharmacy are optimized as following the Just-In-Time (JIT) paradigm. To this end, an information system replaces the central hospital pharmacy. Finally, some works approach this challenge using a stochastic perspective, e.g., in Maestre et al. (2012), a method to determine the best value for the stock as a function of the risk level and the number of days without stock-outs is proposed.

The purpose of this chapter is twofold. On the one hand, we present different forecasting methods that can be used to exploit available historical data series in the hospital information systems. On the other hand, model predictive control (MPC) methods are proposed for the inventory management problem. MPC is a popular control strategy in the process industry due to its ability handle issues as multivariable interactions, constraints on system variables, and multiple optimization goals in a systematic manner (Camacho and Bordons 2004). To this end, it uses a model of the system to predict its future evolution along a given prediction horizon. Indeed, this method has already been implemented in very similar problems such as those of supply chain management. For example, Wang et al. (2004), Wenlin et al. (2005) applied MPC to supply chain management in semiconductor manufacturing. In Maestre et al. (2011), a popular supply chain benchmark, the MIT Beer Game, is used to test a distributed MPC algorithm with a low computational burden. Likewise, in Stoica et al. (2009), robust MPC is applied to the production-inventory system.

Also, in Rasku et al. (2004) a variation of MPC is used to reduce the number of tuning parameters when managing inventories and supply chains. Finally, the specific case of pharmacy inventory management is considered in Maestre et al. (2018), where results of the application of a simple MPC controller in a real hospital are given.

Another remarkable feature of MPC is that it can also be implemented in a stochastic manner. In the design of predictive controllers for dynamical systems subject to disturbances and uncertainty, it is well known that even if the controller finds a feasible solution, there is a certain probability that outputs violate the system constraints. A first way to overcome this issue is to follow a robust approach, but this requires increasing the pharmacy costs to guarantee the satisfaction of clinical needs. Hence, it may be preferable to adopt the stochastic viewpoint and reformulate constraints using probabilistic statements. In this way, the controller can work with a predefined risk level, thus improving performance at the expense of risk-controlled stock-out events. For example, in Maestre et al. (2013), a risk-aware MPC controller for pharmacy inventory management is proposed and tested via simulations. Another remarkable work is Fernandez et al. (2020), which reports the results of the application of a data-based MPC decision support system in a hospital during 3 months. In this way, the pharmacy manager becomes a human in the loop within the control system, selecting one of the different actuation possibilities suggested by the decision support system.

The contents of this work were developed in the framework of the project *Pharmacontrol*, where Spanish hospitals provided data to assess demand forecasting and stochastic MPC methods. The project's goal was to update inventory management methods to reduce average inventory levels while maintaining the same clinical guarantees, as can be seen in other related works such as Maestre et al. (2012, 2013, 2014, 2018), Fernandez et al. (2020), Velarde et al. (2014); Jurado et al. (2016). Also, in order to illustrate how complex the inventory management problem can become, it is enough to say that the largest hospital that participated in *Pharmacontrol* had a total capacity of 1200 beds. In addition, the pharmacy department of that hospital provides monthly more than 5000 drug dispensations for external patients. As a consequence, the hospital spends more than 50 million euros per year on drugs.

The remainder of the chapter is organized as follows. First, some demand forecasting methods are described in Sect. 6.2. A description of the inventory management problem is shown in Sect. 6.3. Section 6.4 presents the optimization problem and the robust techniques MPC for this problem. In Sect. 6.5, some simulations are shown. Finally, in Sect. 6.6, some conclusions are drawn.

6.2 Qualitative Demand Forecasting Methods

This section briefly summarizes some quantitative methods for estimating the demand, which can be classified as temporal series and causal methods (Pérez Navarro et al. 2007).

6.2.1 Temporal Series

These prediction models are based on historical data, which are analyzed to discover patterns like tendency, seasonality, and cycles. While these patterns are not useful for long prediction horizons, they can predict medium- and short-term demand periods (Ramírez et al. 2014). Let us explain next some alternatives.

6.2.1.1 Constant Approach

The simplest estimation assumes that the process changes very slowly so that the value of the variables does not change from one period to another:

$$\widehat{Y}_{n+1} = Y_n, \qquad n+1 > 2. \tag{6.1}$$

Here, Y_n is the demand in period n and $\widehat{Y}_{n+1}$ is its forecast for the period $n + 1$. It is straightforward to see that this method does not consider variations due to seasons, cycles, and uncertainty realizations. Nevertheless, it can be used as a starting point and to assess more sophisticated methods.

6.2.1.2 Simple Moving Average

This prediction method uses the last n periods to build the forecast:

$$\widehat{Y}_{n+1} = \sum_{i=t-n+1}^{t} \left(\frac{Y_i}{n}\right). \tag{6.2}$$

Here, the moving mean behavior depends on n. If the value of n is large, the average responds slowly to significant changes. Otherwise, i.e., if n is small, the response is quicker. One advantage of this procedure is that the calculations are straightforward, and, however, the system is flexible, so that the tendency is not forced to fit a particular math function.

6.2.1.3 Exponential Smoothing

This approach updates the prediction using the most recent demand information and a smoothness constant α. The demand forecasting for the period $n + 1$ is:

$$\widehat{Y}_{n+1} = \alpha Y_n + (1 - \alpha)\widehat{Y}_n, \quad n > 1. \tag{6.3}$$

with $\widehat{Y}_1 = Y_1$. Here, the smoothness constant $\alpha \in [0, 1]$ allows adjusting the influence of distant values. To do that, n weights α_i are obtained from according to the geometric progression with ratio $q = \alpha$, with $\alpha_i = \alpha$.

The prediction is built depending on the actual value of the demand and the previous forecasted value, although the n values of Y are considered implicitly. If large values are chosen for α, more weight is given to recent values, so that the model responds faster to changes in demand.

This method is recommended when the prediction horizon is short and no information about any independent factor that affects the demand is known. It does not require many resources nor efforts to make the prediction, and this forecast prediction can follow tendencies and seasonality.

6.2.1.4 ARIMA

ARIMA stands for an autoregressive integrated moving average model. In particular, the ARIMA model can be defined as a multiple linear regressive model based on possibly differentiated delayed values of the demand and the error. Its application requires identifying the possible prediction model, estimating its parameters, and determining its goodness (González Casimiro 2009; Arroyo et al. 2010).

The ARIMA models are built from ARMA models. The ARMA model typical expression (p, q) is the following:

$$Y_t = C + \underbrace{\phi_1 Y_{t-1} + \ldots + \phi_p Y_{t-p} + \theta_1 \epsilon_{t-1}}_{\text{Auto-regressive comp.}} + \ldots + \underbrace{\theta_1 \epsilon_{t-1} + \theta_q \epsilon_{t-q}}_{\text{Mobile mean comp.}} + \epsilon_t. \tag{6.4}$$

As can be seen, the temporal series Y_t depends on its past values (auto-regressive component AR), the error past values (mobile mean component MA), and a constant C. The number of samples in the model denotes the auto-regressive order and is denoted as p. The same holds for the number of past errors considered, which sets the mean average order of the model and is denoted by q.

An ARIMA model (p, d, q) is an ARMA model (p, q) of the d times differentiated series. The typical expression is given by:

$$Y_t^{(d)} = C + \underbrace{\phi_1 Y_{t-1}^{(d)} + \ldots + \phi_p Y_{t-p}^{(d)} + \theta_1 \epsilon_{t-1}^{(d)}}_{\text{Auto-regressive comp.}} + \ldots + \underbrace{\theta_1 \epsilon_{t-1}^{(d)} + \theta_q \epsilon_{t-q}^{(d)}}_{\text{Mobile mean comp.}} + \epsilon_t^{(d)}. \tag{6.5}$$

Here, $Y_t^{(d)}$ is the differences series of order d, and $\epsilon_t^{(d)}$ is the error series committed in the

last series.

These models provide optimal predictions in the short term, but finding the model that fits best the data series is not trivial, and wide knowledge is required about this methodology. It is typical that several alternative models have to be considered and assessed before one can be selected and applied. Once the model structure has been identified, the minimization of the quadratic error can be used to tune its parameters.

6.2.2 Causal Models

In general, causal prediction methods assume a cause-effect relation between a dependent variable (demand) and other independent variables. One of the most important characteristics of causal models is that they can predict changing points in the demand function.

Therefore, they are generally more accurate to formulate distant predictions. In contrast, the previously introduced temporal series models have a superior power to anticipate the pattern followed by the future demand.

6.2.2.1 Simple Linear Regression

A linear relation is assumed between the variables of interest, i.e.,

$$\widehat{Y} = a + bX. \tag{6.6}$$

with $\widehat{Y}$ and X respectively representing the demand forecast (dependent variable) and the time elapsed since the last visit of the patient (independent variable). Here, a and b can be adjusted using least squares.

6.2.2.2 Multiple Linear Regression

The previous method can be generalized using the model:

$$\widehat{Y} = a_1 X_1 + a_2 X_2 + \ldots + a_k X_k, \tag{6.7}$$

Here, $\widehat{Y}$ represents the expected demand (dependent variable), whereas X_1, X_2, ..., X_k refer to the time elapsed since last k visits of the patient (independent variables). Once more, least squares can be used to set the value of the coefficients a_1, a_2, ..., a_k.

6.3 Pharmacy Inventory Problem

A pharmacy with N_i different drugs is considered, with the stock level $s_i \in \mathbb{R}$ of each drug i evolving as:

$$s_i(t+1) = s_i(t) + \sum_{j=1}^{np_i} o_i^j\left(t - \tau_i^j\right) - d_i(t). \tag{6.8}$$

Here, the items ordered to the jth of the np_i providers are denoted by $o_i^j \in \mathbb{R}$; τ_i^j stands for the average transport delay of the corresponding provider; and $d_i(t)$ represents the overall demand of drug i. Depending on the problem formulation, it may be convenient to express the decision variable as $o_i^j = \delta_i^j(t) u_i^j(t)$ with $\delta_i^j(t)$ and $u_i^j \in \mathbb{R}$ respectively indicating whether an order to provider j is placed and how many items are ordered.

The following costs need to be considered for each drug i:

- Storage costs ($C_{s,i}$).
- Its price at provider j $\left(p_i^j\right)$, which is assumed independent of the number of units ordered.
- Shipping costs of ordering drug i to provider j $\left(C_{sh,i}^j\right)$.
- Pharmacy costs of ordering drug i ($C_{op,\,i}$).
- The cost associated with asking a loan to a nearby hospital whenever there is a shortage of drug i ($C_{os,i}$). This cost can be increased to penalize the superior risk of a stock-out event at this time.

The pharmacy manager uses this information to plan his or her orders according to the following goals, which appear listed in decreased order of priority:

1. Demand satisfaction, by minimizing the probability of stock-out despite the nondeterministic demand and transport delays, i.e.,

$$\min_{\delta_i^j, u_i^j \ \forall i,j} \sum_{k=0}^{N} \sum_{i=1}^{N_i} C_{os,i} Pr(s_i(t+k) < 0), \tag{6.9}$$

where $Pr(s_i(t + k) < 0)$ represents the probability of a stock-out of drug i and N determines length of the time window for which this goal must be fulfilled. Also, a safety stock can be imposed as a minimum limit or an optimization parameter to deal with the uncertainty of this problem.

2. Minimization of inventory costs and number of ordered items, i.e.,

$$\min_{\delta_i^j, u_i^j \ \forall i,j} \sum_{k=0}^{N} \sum_{i=1}^{N_i} \sum_{j=1}^{np_i} \delta_i^j(t+k) \left(p_i^j u_i^j(t+k) + C_{sh,i}^j \right) + \sum_{k=0}^{N} \sum_{i=1}^{N_i} C_{s,i} s_i(t+k). \tag{6.10}$$

3. Minimization of the number of orders by assigning a fixed cost to every order so as to decrease the burden of the limited human resources of the pharmacy department, i.e.,

$$\min_{\delta} \sum_{k=0}^{N} \sum_{i=1}^{N_i} \sum_{j=1}^{np_i} C_{op,i} \delta_i^j(t+k). \tag{6.11}$$

To illustrate this goal, consider that the largest hospital in the project *Pharmacontrol* generates more than 12,000 orders per year.

Furthermore, several constraints must be considered:

- Storage constraints, with the minimum limit set by the previously mentioned safety stock $\min_{s_i}$, and the upper bound $\max_{s_i}$ derived from space restrictions, which can be tight for cold storage, i.e.,

$$s_i \in [\min_{s_i}, \max_{s_i}]. \tag{6.12}$$

- Order constraints imposed by the provider, i.e.,

$$u_i^j \in \left[\min_{u_i^j}, \max_{u_i^j} \right]. \tag{6.13}$$

- Operational constraints, which stem from the maximum admissible work load that the pharmacy staff can handle regarding the placement of orders and the reception of deliveries, i.e.,

$$\sum_{k=0}^{N} \sum_{j=1}^{np_i} \delta_i^j(t+k) \leq \Delta_i, \tag{6.14}$$

Here, Δ_i stands for the limit on the number of orders of drug i that can be placed during the next N time periods.

- Budget constraints ($\max_{\$}$), i.e., a limit on the expenses during the considered time window of length N, i.e.,

$$\sum_{k=0}^{N} \sum_{i=1}^{N_i} \sum_{j=1}^{np_i} \delta_i^j(t+k) \left(p_i^j u_i^j(t+k) + C_{sh,i}^j + C_{op,i} \right) \leq \max_{\$} \tag{6.15}$$

6.4 Predictive Control of a Pharmacy Inventory

Figure 6.1 describes the essential elements of the optimization performed by the pharmacy manager, who must satisfy the demand, minimizing costs and work burden.

In this problem, the forecasted demand enters as an exogenous input, and decisions need to be made for each drug regarding the items to order subject to the previously introduced constraints. Stock levels and costs follow these decisions, which are optimized using a multi-criteria performance index that weights the satisfaction of the demand (*Dem*) based on historical data, the expenses (*Expenses*), and the number of orders (*Orders*) that will be placed, i.e.,

$$\min_u J = \beta_1 Dem(u,t) + \beta_2 Expenses(u,t) + \beta_3 Orders(u,t), \tag{6.16}$$

where β_1, β_2, and β_3 are tuning parameters that weight the relevance of each goal for the pharmacy manager.

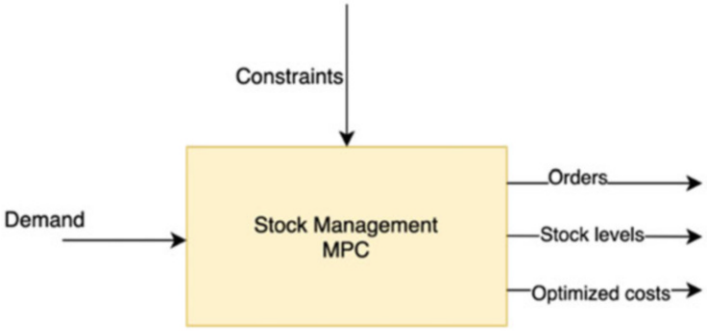

Fig. 6.1 Pharmacy inventory system

6.4.1 Model Predictive Control

MPC is a continuous re-planning method that generates predictions of the future of the system based on a model that relates its state with the sequence of inputs provided during a time horizon of length N (Camacho and Bordons 2004). This allows optimizing the sequence of orders based on the performance index (6.16) while considering the constraints on the problem variables, although only the first element of the calculated sequence is actually applied to the system, for the problem is solved again at the next time instant using the most recent information available.

In the following subsections, we offer a glimpse to some of the possible implementations of MPC in the context of pharmacy inventory management problems.

6.4.2 Model Predictive Control with Deterministic Demand

We consider first the case of a deterministic demand for the sake of simplicity. To this end, let us transform the model of Eq. (6.8) into:

$$s(t+1) = s(t) + o(t-\tau) - d(t), \tag{6.17}$$

which represents the evolution of the overall pharmacy stock, with $s(t) = [s_1(t), s_2(t), \ldots, s_{npi}(t)]$ and $d(t) = [d_1(t), d_2(t), \ldots, d_{Ni}(t)]$ being respectively the aggregated stock and demand vectors, and $o(t-\tau)$ representing the orders placed. Based on this model, it is possible to build the following optimization problem:

$$\min_{o} J \tag{6.18}$$

subject to the constraints of Eqs. (6.12)–(6.15). Since the domain of the aggregate decision variable o is non-convex, it may be preferable to replace o by the set of Boolean $\delta_i^j(t)$, which determine whether an order is placed, and the corresponding set of $u_i^j(t)$, which provide the amount to order. In this way, Eq. (6.18) becomes a mixed-integer optimization problem, which can be solved using exhaustive search or branch-and-bound algorithms.

6.4.3 Chance Constraints MPC

The aggregate demand $d(t)$ has a stochastic disturbance associated, due to the uncertain nature of $d(t)$. As the state is influenced by additive uncertainties $d(t)$, the constraints cannot be represented in a deterministic way. Therefore, they are rewritten in a probabilistic manner, i.e.,

$$P(s(t+k) \geq s_{\min}) \geq 1 - \delta_s, \quad \forall k \in \{1, .., N\},$$

where δ_s is the probability of failure, so it is the risk bound of stock-out.

The optimization problem can be written as:

$$\min {}_u \mathbf{E}[J], \tag{6.19}$$

subject to:

$$s(t+1) = s(t) + o(t-\tau) - d(t), \tag{6.20}$$

$$P(s_i \in [\min {}_{s_i}, \max {}_{s_i}]) \geq 1 - \delta_s, \tag{6.21}$$

$$u_i^j \in \left[\min {}_{u_i^j}, \max {}_{u_i^j}\right]. \tag{6.22}$$

and constraints of Eqs. (6.14) and (6.15).

Note that it is possible to consider the constraint given in Eq. (6.22) along the prediction horizon. In particular, if the disturbances follow a given probability distribution, it is possible to calculate the mean and standard deviation of the state variables as it was done in Velarde et al. (2017). This allows us to solve the problem in a stochastic manner, so that the variables of interest satisfy the constraints according to the desired probability of failure.

6.4.4 Multi-scenario Approach MPC

This technique does not require the probabilistic model of the demand; it is enough to know several scenarios containing possible evolutions of the demand. The calculation of the controller will result in a robust control action to satisfy all the potential disturbances of the extended system:

$$s_j(t+1) = s_j(t) + o(t-\tau) - d_j(t+k), \quad \forall j \in [1, K]. \tag{6.23}$$

where K is the number of scenarios considered.

In this way, the objective function to be considered is given by Eq. (6.16), subject to the system model (Eq. 6.17) and the constraints (Eqs. 6.12–6.15), replicated for all states of the *extended system*.

6.4.5 Tree-Based MPC

$$s_j(t+1) = s_j(t) + o_j(t-\tau) - d_j(t+k), \quad \forall j \in [1, R]. \tag{6.24}$$

where R is the number of reduced scenarios from the initial K scenarios considered.

The objective function is given by Eq. (6.16), subject to the system model (6.17) and the constraints introduced in Eqs. (6.12)–(6.15) for each of the possible scenarios contained in the tree.

6.5 Case Study and Results

In this section, the reviewed demand forecast and stochastic model predictive control methods are applied using historical data from a Spanish hospital. In particular, the results presented correspond to a summary of the results provided in previous works (Velarde et al. 2014; Ramírez et al. 2014), so the reader is encouraged to read the corresponding references. Likewise, reports from the practical application of these methods can be found in works as Maestre et al. (2018), Fernandez et al. (2020).

6.5.1 Demand Forecast

Prediction methods are compared with the procedure that the hospital uses, which is the mean daily consumption in the last 12 months as drug demand forecast. Our assessment will start with a sample drug to illustrate the process. In this regard, note that the parameters for each strategy are tailored for each drug, i.e., they are chosen by applying an iterative tuning method and the historical data employed is equal to 28 weeks.

To show the behavior of the different techniques, the results for drug considered are summarized in Table 6.1. Two error measurements are available: the mean absolute error and the standard deviation. Taking into account those values, a comparison is carried out among these prediction methods.

As can be seen, the lowest mean absolute value is that of the simple linear regression methods, although the rest of the methods considered are not far in terms of performance. Surprisingly, the best result regarding standard deviation is obtained by the hospital procedure. In particular, this method uses 52 weeks of historical data. This result is followed very closely by the simple linear regression method.

A quick assessment to determine the optimal method to predict the drug demand in a graphic manner is to provide the information contained in Table 6.1 for the drug considered, just as it is done in Fig. 6.2. In this way, the mean absolute error is

Table 6.1 Comparison of the different demand estimation techniques applied

Prediction method	Mean absolute error	Standard deviation
Hospital procedure	20.04	23.37
Simple approach	23.57	31.96
Simple moving mean	20.82	23.83
Exponential smoothing	20.46	23.54
ARIMA	22.50	26.09
Simple linear regression	18.21	24.98
Multiple linear regression	24.93	27.33

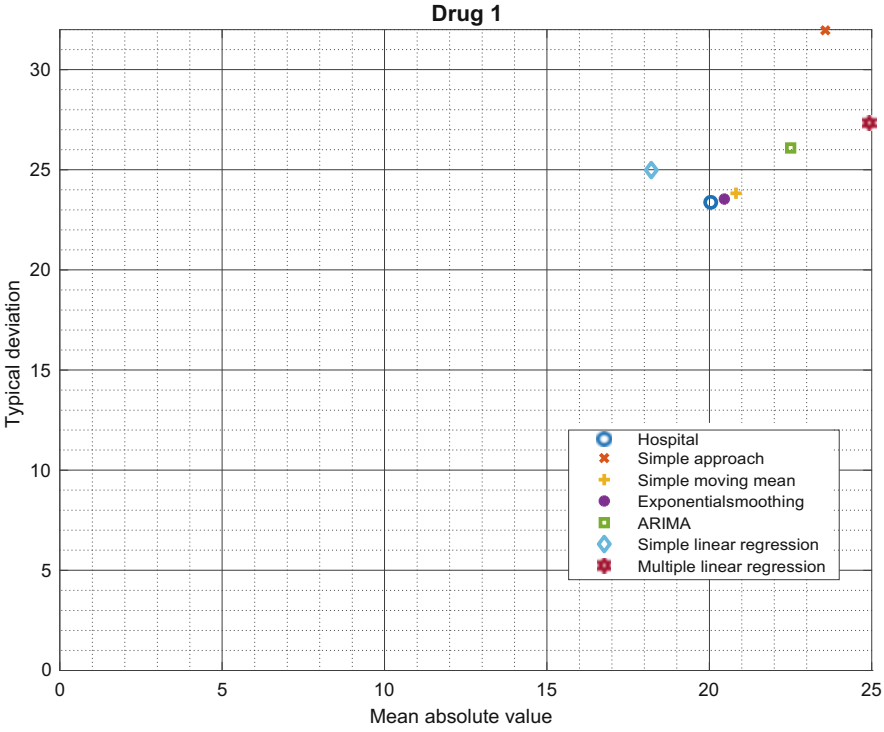

Fig. 6.2 Mean absolute value versus standard deviation for drug 1 by using prediction methods

represented in the x axis, while the standard deviation appears in the y axis for each method. The closer a method is to the point (0, 0), the better. From the figure, it can be concluded that the best procedure for this example is the one used by the hospital.

Since the previous analysis is too restricted, we extend it for ten drugs from the hospital inventory. From the results, no method outperforms the rest for all cases. For the ten drugs under study, the simple moving average, the exponential smoothing, and the ARIMA methods provide the best performance for one drug. The simple linear regression causal model is optimal for two drugs. And finally, the method used

by the hospital provides the best estimation for five drugs. This result could be attributed to the forecast being done using more historical data than the other ones, but it clearly shows there is room for improvement in this regard.

6.5.2 *Stochastic Model Predictive Control*

In this subsection, the presented MPC methods are employed to decide the orders of an expensive drug that requires cold storage, i.e., its storage limits are very strict. The actual name and price of the drug cannot be disclosed due to a confidentiality agreement.

The controllers are programmed based on a time window of 8 days and the evolution of the stock follows the model of Eq. (6.17). The provider requires a minimum of 4 units and imposes a maximum of 1000 for every order, and needs 2 days to serve the items requested. Likewise, we consider here a safety stock of 2 units, and a price of 250 euros per unit, with an additional cost of 2 euros for every order placed. Finally, a year of historical data from the hospital information system is used to characterize the stochasticity of the demand.

Figures 6.3, 6.4, and 6.5 illustrate the simulated evolution of the stock with the previously introduced methods (blue line), whereas the actual hospital policy is

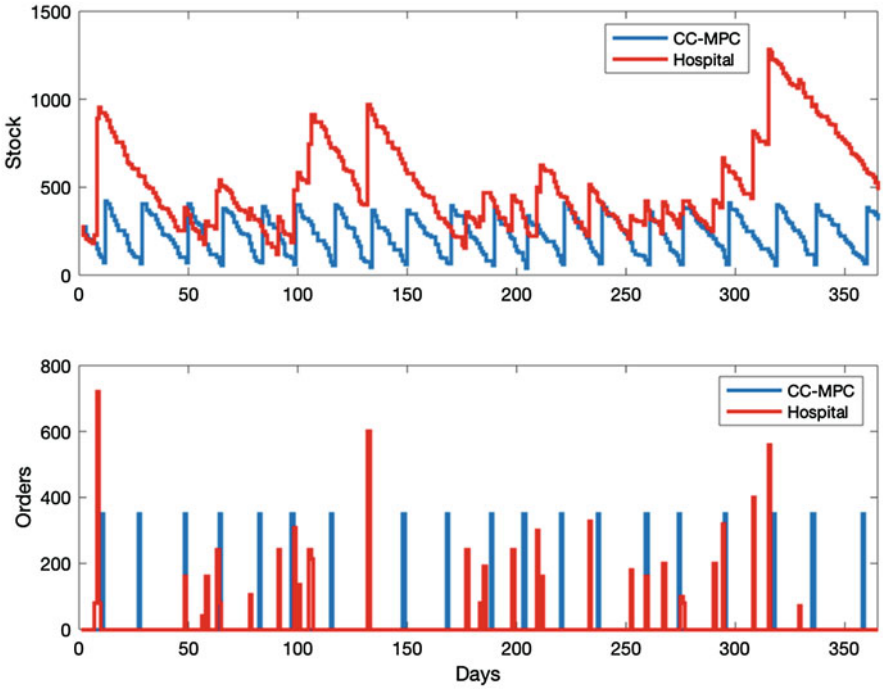

Fig. 6.3 Real and simulated stock evolution and placed orders applying chance constraints MPC

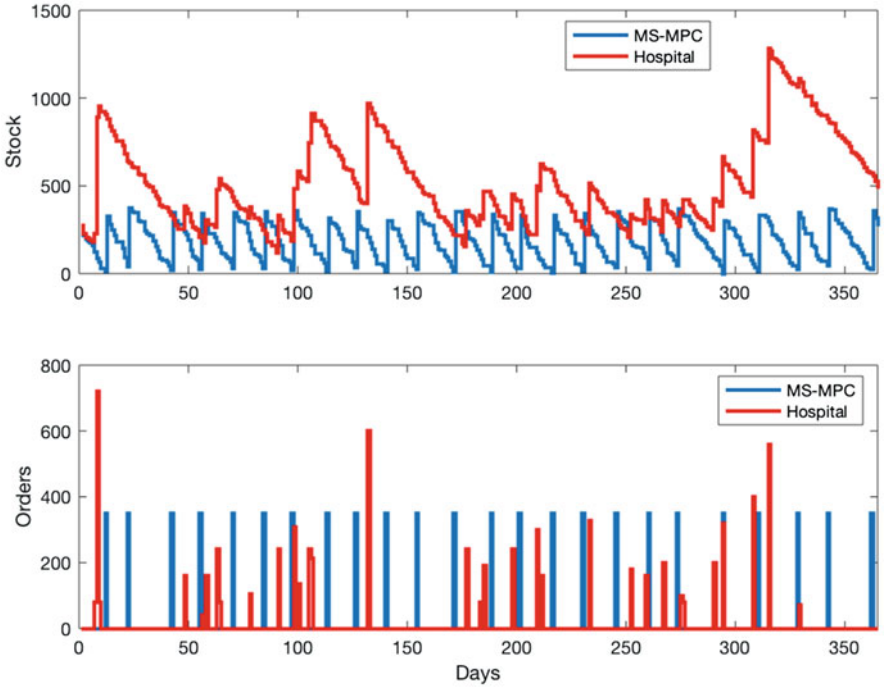

Fig. 6.4 Real and simulated stock evolution and placed orders applying multi-scenarios MPC

depicted using a red line. No stock-outs were registered during the assessment period. Table 6.2 summarizes the main statistical parameters of the different evolutions of the stock. For the price considered, the differences in stocked items can be greater than 30,000 euros. Likewise, it is remarkable that the proposed methods reduce the number of orders by a 30% in comparison with the hospital policy, thus relieving the work burden of the pharmacy staff.

Finally, we conclude this section with a final remark about the simulation results due to the uncertainty associated with the data provided by the hospital. In particular, it happens every now and then that drug dispensations and the deliveries are registered with delay. Also, there are some significant peaks, possibly derived from the large or ders before holidays. Nevertheless, the MPC methods significantly outperform that of the hospital, and therefore there are powerful reasons to support their application in this context.

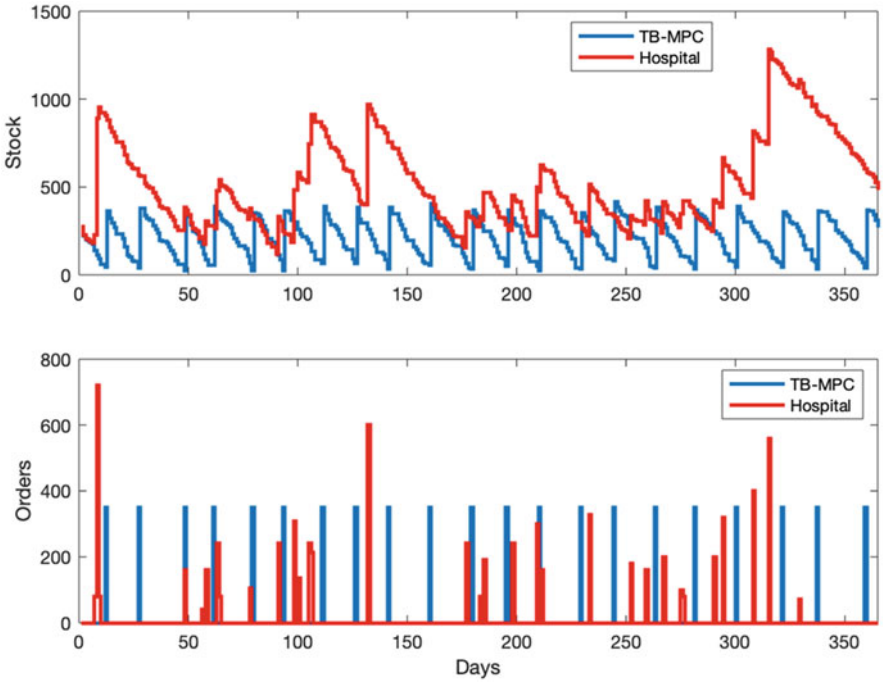

Fig. 6.5 Real and simulated stock evolution and placed orders applying tree-based MPC

Table 6.2 Comparison of the different MPC techniques applied

	Orders	Stock-out	Mean	Deviation
Chance constraints	20	0	230	102
Multi-scenario	24	0	148	180
Tree-based	21	0	208	103
Hospital	32	0	514	102

6.6 Conclusions

Inventory management is an essential task that the hospital pharmacies need to deal with. The problem is difficult due to the conflicting goals of satisfying the demand and minimizing the stock and the work burden for the pharmacy staff. To ease this task, this chapter described six demand estimation schemes and three advanced techniques for enhancing the inventory management toolbox.

The proposed methodologies allow us to forecast the demand and optimize the stock management providing important economical savings while guaranteeing with a very high probability that the drugs will be available for the patients. In this sense, the MPC framework is particularly useful because of its favorable properties, such as the ease of constraint-handling.

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Chapter 7
DNA Methylation in Pulmonary Inflammatory Diseases

Li Tang, Madhav Bhatia, and Xiangdong Wang

Abstract Epigenetics is genetic inheritance that is not based on DNA differences, that is, phenotypic inheritance determined by regulation of gene expression throughout the genome, without changing the DNA sequence during cell division. This altered genetic information can be passed on to the offspring and is reversible. Epigenetics can be said to be a bridge connecting environmental factors and genetic susceptibility factors. DNA methylation is one of the three major epigenetic markers in epigenetics. More and more studies have found that DNA methylation plays an important role in the development of pulmonary inflammatory diseases. Therefore, we briefly outline the recent advances in DNA methylation in epigenetics associated with asthma, chronic obstructive pulmonary disease (COPD), and lung cancer.

Keywords Epigenetics · DNA methylation · Asthma · COPD · Cancer · Biomarker

7.1 Introduction

Epigenetics is the study of heritable changes associated with gene expression caused by molecules that bind to DNA, rather than changes in the DNA base sequence. The three major epigenetic markers include DNA methylation, histone tail modifications, and noncoding RNA. In humans, most DNA methylation is the addition of a methyl group a cytosine base in the cytosine-phosphate-guanine (CpG) DNA sequence, and DNA methylation contributes to silencing gene expression by adding a methyl group to cytosine to form 5-methylcytosine (5mC), which is also the simplest form of

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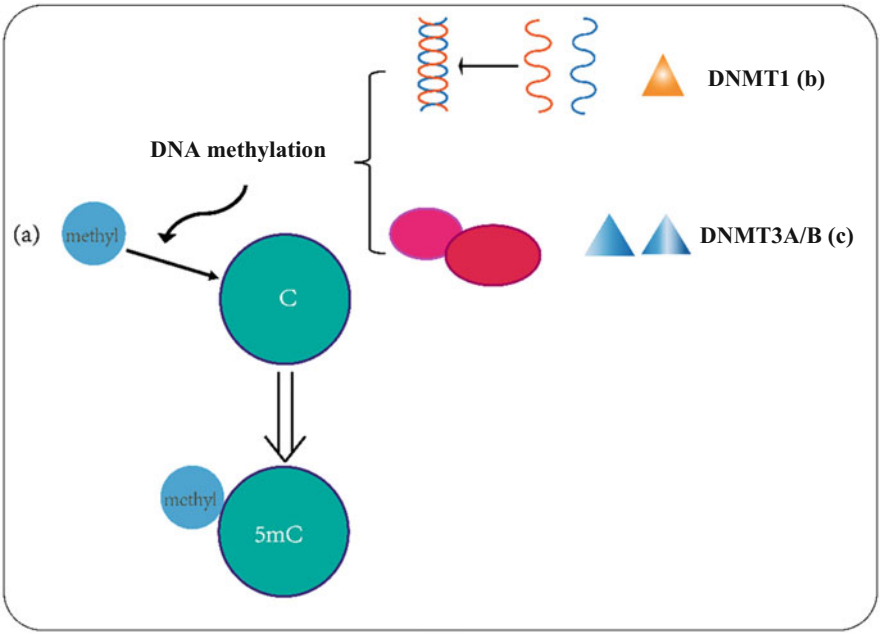

Fig. 7.1 (**a**) DNA methylation helps silence gene expression by adding methyl groups to cytosine (C) to form 5-methylcytosine (5mC). (**b**) DNMT1 is responsible for copying the methylation pattern from the parent chain to the daughter strand during DNA replication to maintain the level of DNA methylation. (**c**) DNMT3A/B initiates methylation during cell transformation

epigenetic regulation in eukaryotes (Jeltsch and Jurkowska 2014; Jones 2012). Methyl transfer is catalyzed by DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B (Fig. 7.1). DNMT1 is responsible for replicating the methylation pattern from the parent strand to the daughter strand during DNA replication, maintaining DNA methylation levels, while DNMT3A/B plays a role in initial methylation during cell transformation (Chhabra 2015). It is becoming increasingly apparent that basic genetic variation and epigenetic markers work together (Brikun et al. 2018). For example, allele-specific gene expression, in which allelic-specific differences in gene expression may occur due to sequence variation, can be marked by differences in DNA methylation, histone modifications, or chromatin structure (Dong et al. 2018). Unlike individual genetic makeup, epigenetic markers can be more easily affected by exposure, diet, and aging (Hagood 2014; Thomson et al. 2014; Coughlin 2014; Stel and Legler 2015). Epigenetic changes are now widely accepted to adapt static genomes to dynamic environments, and recent evidence suggests that epigenomes are dynamically changing, and can change with changes in environment, diet, and age (Mehta et al. 2015). In addition to a set of hereditary epigenetic markers, some nongenetic epigenetic markers are more dynamic and vary with environmental stimuli (da Silva et al. 2017). Epigenetic mechanisms affect the transcriptional activity of a particular gene at different time

points of different cell types (Mayran et al. 2015; Maree and Patterton 2014; Wang et al. 2018).

DNA methylation is primarily established in the womb or in early life, but it has also been shown to respond to environmental stressors in the later stages (Harb et al. 2016). Hypermethylation of CpG islands in gene promoters results in gene silencing, leading to transcriptional activity. Recent studies have shown that methylation in the tissue-specific genes and genes associated with carcinogenesis and lineage mechanism for controlling gene transcription (Dong et al. 2018; Cole et al. 2017). In addition, recent evidence suggests that DNA methylation is more prevalent in the genome than in promoters (de Antonellis et al. 2018; Heller et al. 2018; Vera et al. 2017).

Today, studies on epigenetic changes in human tissue focus on epigenetic and transcriptomic analysis of genome-wide integration (Lissa and Robles 2017; Machin et al. 2017). Studies have collected whole-genome bisulfite sequencing (WGBS) from frozen human lung tissue for whole-genome bisulfite sequencing (WGBS) and compared it with blood T lymphocytes for CpG methylation and transcriptome integration analysis. The difference between alveolar or bronchial epithelial cells and circulating T cells is even more pronounced, reinforcing the view that cellular embryonic origin and differentiation may be partially regulated by DNA methylation, confirming the relatively low methylation of CGI and 5'UTR (Dong et al. 2018). The study compared alveolar and bronchial cells, noting that DMRs (differentially methylated regions) of the TF target region are enriched in their target regions (this is a known cell type-specific regulatory site). DMRs and DEGs (differentially expressed genes) reflect the immune function of various types of epithelial cell. This suggests that methylation variation of chromatin may be of general regulatory importance. In addition, to some extent, DMRs preferably occur in the TF binding region, the open chromatin region, and the promoter, indicating important regulatory differences in the DNA methylation group.

There is also evidence that significant differences in the degree of methylation in the median of each of the 22 autosomes are associated with smoking, and 187 differentially methylated CpG sites were identified by array-based DNA methylation analysis. The findings confirm the widespread effects of smoking on human tissue and indicate that quitting smoking may regain the state of DNA methylation as never smokers (Zeilinger et al. 2013). Other studies have shown that perinatal environmental tobacco smoke (ETS) exposure induces sustained epigenetic changes in global DNA and IFN-γ and Thy-1 promoter methylation prior to adult onset of fibrotic lung pathology. These epigenetic findings may replace biomarkers of potential respiratory disease risk (Cole et al. 2017). The use of multi-walled carbon nanotubes (MWCNTs) is growing, which increases occupational exposure to these materials. Researchers have used pyrosequencing to measure promoter methylation of inflammatory genes (IFN-γ and TNF-α) after MWCNT exposure and found that they are associated with initial cytokine production. Using luminometric methylation analysis (LUMA) and 5-methylcytosine (5mC) quantitative analysis, it was found that MWCNTs cause DNA hypomethylation in the lungs and blood, which is consistent with disease progression. The initial data provided by this study show

that changes in gene-specific methylation correspond to inflammatory responses to MWCNT exposure. Furthermore, global DNA methylation in the lungs and blood is consistent with MWCNT-induced disease progression, suggesting its potential as a biomarker for exposure and disease progression. DNA methylation may be a potential pathogenic mechanism of MWCNT-induced lung injury progression in mice. This study demonstrates that MWCNTs cause global DNA hypomethylation in lung tissue 7 days after exposure. Blood DNA methylation is a promising biomarker for MWCNT-induced disease progression (Brown et al. 2015). IgE-mediated sensitization can be epigenetic editing in the uterus, but the early childhood environment may further alter complex traits and disease phenotypes through epigenetic plasticity. Epigenetic initiation during fetal development and early childhood may play an important role in IgE-mediated type I hypersensitivity.

In summary, using epigenetic plasticity from prenatal to childhood, their work identified differential methylation patterns in cord blood and the methylation levels of cord blood to childhood metaphase DNA and childhood intermediate IgE. Several cord blood methylation markers associated with IgE are not associated with postnatal changes in methylation levels. In addition, changes in methylation patterns of DNA from cord blood to childhood are associated with IgE alone or in combination with cord blood methylation markers (Peng et al. 2018).

7.2 DNA Methylation and Asthma

Despite the increasingly in-depth study of the pathology, genetics, and treatment of asthma at home and abroad, the prevalence, morbidity, and severity of the disease are still rising. A growing body of research suggests that DNA methylation may be a potential mechanism for asthma-associated inflammation (Yang and Schwartz 2012). Epigenetic studies of human asthma use nasal cell DNA. Airway inflammation is a key feature of childhood asthma pathogenesis and is characterized by the presence of inflammatory cells and the release of inflammatory mediators in the airways (Gunawardhana et al. 2014). There is increasing evidence that the expression and reactivity of several inflammatory mediators are programmed by epigenetic mechanisms, such as methylation (Baccarelli et al. 2012; Zhang et al. 2014a; Arathimos et al. 2017). One study has identified 27 methylated CpG (cytosine-phosphate-guanine) sites. Fourteen of the 27 were genome-widely significant in the meta-analysis. The methylation levels of all relevant loci in 4–16-year-old children with asthma were kept at a low level, and no methylation level was observed in cord blood at birth. Using a whole blood DNA copy study, 14 CpG sites were significantly associated with asthma and strongly associated with asthma with purified eosinophils. Whole blood transcription associated with the CpG site indicates increased activity of eosinophils, effector CD8T cells, memory CD8 T cells, and natural killer cells, and a decrease in the number of naïve T cells. Five of the 14 were associated with asthmatic airway epithelial cells, indicating a cross-tissue epigenetic effect. Decreased DNA methylation levels in 14 CpG sites after birth are closely

related to childhood asthma. These sites and their transcriptional profiles indicate eosinophil and cytotoxic T cell activation in childhood asthma (Xu et al. 2018a; Miller et al. 2017; DeVries and Vercelli 2015).

Although allergens are often associated with asthma, many other exposures, including smoking behavior, workplace medications, indoor and outdoor air pollution, viruses, family and occupational exposure to endotoxins, and immunization against certain infectious diseases, are associated with the development of the disease (Yang and Schwartz 2012; Comer et al. 2015; Yang et al. 2017a; Prunicki et al. 2018). Some population studies have shown that asthma-related exposure and changes in epigenetic markers, especially air pollution and tobacco smoke, are associated with asthma phenotypes (Jung et al. 2017). Studies have found hypermethylation of 82 gene-associated CpG islands throughout the genome, including extensive hypermethylation of prompters and decreased expression. DNA methylation at the CpG site at the genetic locus is associated with an increased risk of asthma in children exposed to ambient air pollutants (AAPs). Further identification of specific CpG sites and contaminants associated with methylation of these CpG sites in immune cells may influence our understanding of the pathophysiology of asthma (Biagini Myers et al. 2014). In one study, the researchers sought to identify some CpG sites (Foxp3 and IL10) in specific genes that may be involved in asthma regulation. In the short-term and long-term exposure to high levels of CO, NO_2, and PM2.5, Foxp3 and IL10 will undergo differential changes in methylation. These changes tend to last for a given period of time for any given individual. Asthma is associated with a higher change in methylation regions with higher Foxp3 and IL10 (Prunicki et al. 2018). Epigenetic mechanisms may partly explain the genetic and immunobiological characteristics of asthma. Several known genes show a parental effect on allergic diseases, including the FcεRI-β locus and Spink5 gene (Biagini Myers et al. 2014; Froidure et al. 2016). Interleukin-1 receptor-like 1(IL1RL1) is an important asthma gene. The IL1RL1 methylated CpG site and serum IL1RL1-a levels were not associated with asthma.

The heritability of asthma is approximately 60%, and large-scale genome-wide association studies (GWAS) have identified multiple susceptible sites. IL1RL1 encodes a member of the Toll-like/IL-1 receptor superfamily expressed on inflammatory and resident cells in the lung. Single nucleotide polymorphisms (SNPs) in IL1RL1 are associated with the onset of asthma and atopic traits. Analysis showed that IL1RL1 methylation was not important for protein expression, and the identification of methylation and IL1RL1-a levels by asthma-associated SNPs was not associated with asthma (Dijk et al. 2018). Asthma is an immune-mediated disease, and macrophage polarization has a profound effect on the pathogenesis of asthma. The interaction process between various cytokines, chemokines, and transcriptional regulation of macrophage polarization regulates complex factors and immunoregulatory cells.

There is growing interest in epigenetic changes such as DNA methylation by regulating cell signaling for hard cell functional responses and M1/M2 polarization (Song et al. 2017a; DeVries and Vercelli 2016). DNA methylation is closely related to the differential expression of the M1/M2 gene. DNMT1, 3A and B, are

differentially expressed in M1 and M2 macrophages and play a very critical role in gene silencing. DNMT3B gene knockout promotes macrophage polarization to M2 phenotype, and can inhibit macrophage inflammation, while overexpression of DNMT3B gene plays an opposite role (Collison et al. 2013). DNMT3B regulates macrophage polarization by modulating an important transcription factor PPARγ1 that regulates macrophage polarization. DNMT3B may be one of the major genes regulating macrophage polarization and lung inflammation in asthma (Saradna et al. 2018; Zhang et al. 2014b; Yu et al. 2012).

Functional changes in the airway epithelial cells and immune cell tilt in asthmatic patients are markers of asthma and are characterized by a predominantly Th2 phenotype. Epigenetic mechanisms regulate the expression of transcription factors involved in T cell differentiation (Th1, Th2, and Tregs) (Seumois et al. 2014). Some key questions about future research in asthma epigenetics revolve around understanding how epigenomes promote asthma inheritance; epigenetic genomic developmental vulnerability; environmental, dietary, and aging effects; and asthma (and other diseases) on the epigenome (Yang and Schwartz 2012). Epigenetic markers in airway epithelial cells are associated with allergic asthma (Singh et al. 2014). There is a causal relationship between DNA methylation and Th2 immunity and allergic airway disease. DNA methylation markers in peripheral blood mononuclear cells (PBMC) are associated with allergic asthma and account for 13.5% of serum IgE concentration variations (Gunawardhana et al. 2014). Gene expression in nasal epithelial cells is a proxy for gene expression in lower airway epithelial cells (Yang et al. 2017a). Methylation markers of nasal epithelial cells in children with allergic asthma are associated with changes in gene expression (Stefanowicz et al. 2017; Kohanski et al. 2018; Steelant et al. 2018). Genes differentially expressed in the airway epithelium of patients with allergic asthma may be regulated by epigenetic mechanisms (Yang et al. 2017b; Tumes et al. 2017).

Studies have shown that by constituting a mouse model of maternal allergic asthma (MAA), activation of the immune system can epigenetically alter fetal microglia, the resident immune cells of the brain (Thorburn et al. 2015; Gatford et al. 2017).

Genes involved in controlling microglia environmental sensitivity and shaping neuronal connections in developing brain were identified by differential expression analysis. Differentially expressed genes overlap significantly with genes that have altered expression in the human autism spectrum disorder (ASD), to illustrate the role of microglia in the pathogenesis of ASD (Vogel Ciernia et al. 2018). DNA methylation has changed in asthmatic blood cells, which may be atopic biomarkers. Studies have reported that different DNA methylation patterns are associated with asthma itself and the severity of the disease (Fig. 7.2). These methylation changes, in turn, are associated with changes in gene expression and miRNA expression, which may affect the function of ASMC in airway smooth muscle cells (Perry et al. 2018).

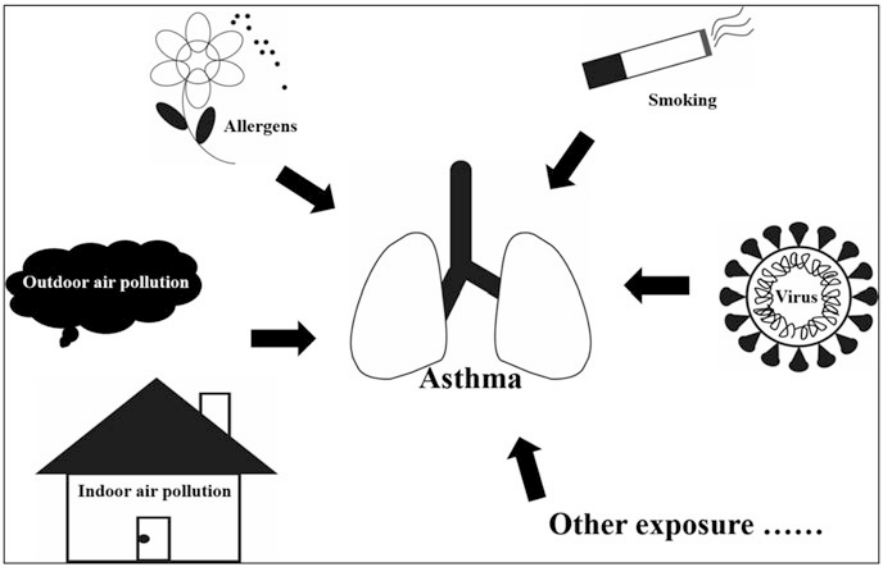

Fig. 7.2 Exposure factors related to the development of asthma

7.3 DNA Methylation and COPD

Changes in DNA methylation are involved in the molecular mechanisms of the pathogenesis of COPD and may represent new therapeutic targets (Clifford et al. 2018). Colocalization of methylated QTLs and GWAS loci provides a visible characterization of subthreshold GWAS findings, supporting the genetic control of methylation in the pathogenesis of COPD (Morrow et al. 2018). In patients with COPD, there is new evidence of abnormal expression of epigenetic markers, such as DNA methylation in blood, sputum, and lung tissue (Morrow et al. 2018; Zinellu et al. 2017; Sundar et al. 2017; Wan et al. 2015; Sarker et al. 2015; Meek et al. 2015). Future research focuses on functional studies of specific gene DNA methylation (Wu et al. 2018; Chan et al. 2017). The chromosome 19q13.2 region is associated with smoking and COPD, but its function is unclear. Studies have conducted DNA methylation of blood samples at different stages of human life, and the results show differential DNA at cg11298343 at five time points during pregnancy, birth, childhood, puberty, and middle age. Methylation was associated with rs7937 at all five time points, and lifetime changes in DNA methylation were associated with the onset of senile COPD (Nedeljkovic et al. 2018a). The association between chromosome 15q25.1 locus and genetic variation in COPD is independent of smoking (Nedeljkovic et al. 2018b; Al Tuwaijri et al. 2016).

In smokers, DNA from lymphoblasts and DNA from alveolar macrophages show changes in methylation, but the effects of smoking on methylation are generally

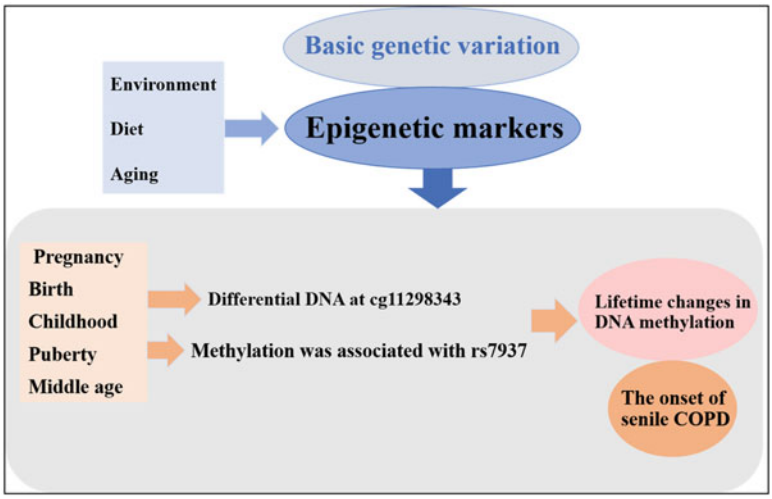

Fig. 7.3 Abnormal expression of epigenetic markers in COPD patients

more pronounced in alveolar macrophages (Barnawi et al. 2017; Busch et al. 2016; Hamvas et al. 2014). Other factors such as epigenetics are also important for understanding the genetic-environmental aspects of smokers' susceptibility to COPD. Chromatin immunoprecipitation studies indicate that enhanced DEEB1 expression is associated with H3K4 methylation. The published aGWAM on COPD tested 27,000 CpG methylations in COPD to establish the COPD family group. CpG hypomethylation near the SEROINA1 gene encoding α1-antitrypsin in COPD patients may be associated with this (Kabesch and Adcock 2012). Therefore, the difference in genetic analysis of blood cells can be used, and epigenetic spectrum analysis in airway diseases must be performed in a sample obtained from the airway of a subject having the disease (Song et al. 2017b; Puig-Vilanova et al. 2014a; Sato et al. 2014). It is now timely to draw and understand the genome-wide epigenetic changes in cell and tissue samples from asthma (Fig. 7.2) and COPD patients (Fig. 7.3). Similar studies are needed to determine the effects of environmental stimuli such as diesel particulates and cigarette smoke on these epigenetic profiles in order to discern the effects of the genetic environment on airway inflammation and disease. It is worth noting that for monozygotic twins who are more susceptible to chronic disease, the degree of epigenetic changes may exceed the environmental stress factor of 50 years (Hagood 2014; Puig-Vilanova et al. 2014b). Little is known about the role of DNA methylation in disease changes, but this area of research may lead to the development of new anti-inflammatory therapies aimed at regulating epigenetic processes in the future (Barnes 2013; Wagner et al. 2013; Elie et al. 2011; Xu et al. 2018b).

7.4 DNA Methylation and Lung Cancer

Research on cancer epigenetics over the past decade has revolutionized our perception of cancer pathogenesis and provides new insights into biomarker development. DNA methylation has rapidly become a potential biomarker in body fluids (Liu et al. 2015; Cree et al. 2017). Gene methylation patterns affect long sequences of DNA rather than single nucleotides, enabling more efficient and robust assay designs. Promoter hypermethylation often occurs in human cancers and is an early event in the development of cancer, making it an ideal candidate for early diagnosis, including premalignant dysplastic lesions and carcinoma in situ, especially for high-risk groups such as smokers (Mehta et al. 2015; Vera et al. 2017; Lissa and Robles 2017; Um et al. 2017; Jangani et al. 2014). The main limitations of DNA methylation as a biomarker are small population size, lack of proper population control, changes in sample collection, processing and storage techniques, lack of appropriate follow-up in control patients, and methodological methods for DNA methylation detection (Choux et al. 2018; Olkhov-Mitsel and Bapat 2012). There are many studies showing measurable differences between methylation levels in tumors and adjacent normal tissues (Liu et al. 2018; Farzanehfar et al. 2013; Shen et al. 2018). Some studies have shown that many promoters are abnormally hypermethylated, such as p16, RAS-associated domain protein 1(RASSF1), H-cadherin, RARB, and APC (Sarkar et al. 2015; Uekita et al. 2014). Hypomethylation of L1RE1 is common in tumors and has a higher level of correlation compared to benign controls, while tumors and higher levels of independent markers are increased when methylation of RARB is increased.

Hypermethylation of RASSF1 is common in tumors and is most prominent in neuroendocrine tumors (NET), making it an adjunct marker for distinguishing between non-small cell lung cancer (NSCLC) and NET. L1RE1 in combination with RARB or RASSF1 can serve as a biomarker for the isolation of lung and non-cancerous tissues and can be used for samples of limited size, such as biopsies. RARB and RASSF1 are important tumor suppressors, and expression loss is associated with tumor cell growth and immortalization. RARB is associated with the prognosis of adenocarcinoma (Jiang et al. 2014; Wu et al. 2016). Hypermethylation of RASSF1 is another common event in lung cancer affecting approximately 60% of adenocarcinomas (ADCs) and up to 100% of small cell lung cancers (SCLCs). The hypomethylation status of EFEMP1 is used as an independent prognostic marker for NSCLC. L1RE1 is another potential methylation biomarker that is an autonomous transposable element in mammals and is hypomethylated in several cancers. L1RE1 accounts for approximately 17% of the human genome, making it a global methylation marker (Walter et al. 2018).

Blood specimens represent the most readily available clinical specimens as it is routinely collected in clinical practice (Yao and Rahman 2009). Recent studies have highlighted the potential use of DNA methylation biomarkers to assess lung cancer prognosis and predict treatment response (Ooki et al. 2018; Koch et al. 2018), as exampled in (Fig. 7.4). DNA methylation abnormalities in lung cancer patients in

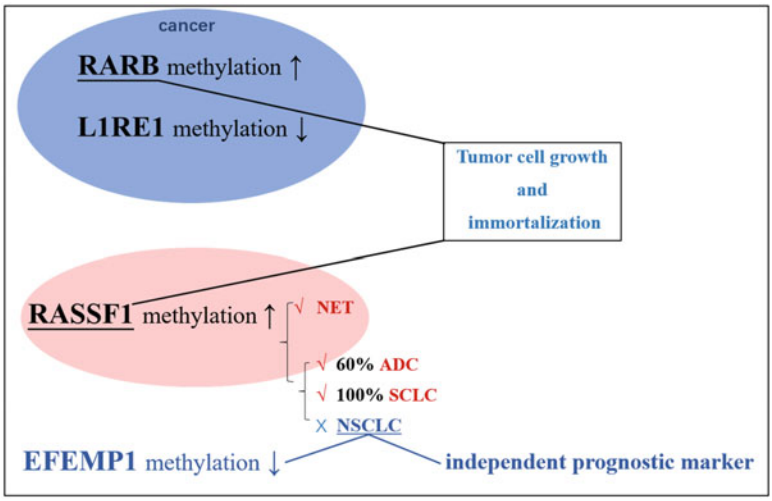

Fig. 7.4 Some typical methylation biomarkers in cancer

plasma and serum have been examined, suggesting many potential diagnostic targets. A panel of genes (APC, RASSF1A, CDH13, KLK10, and DLEC1) tested in plasma from NSCLC patients showed 84% sensitivity and 74% specificity. The SHOX2 gene methylation was detected in the plasma of lung cancer patients, with a sensitivity of 60% (Liloglou et al. 2012). Methylation analysis of bronchial washes may contribute to the detection of NSCLC. Smoking cessation in patients with benign lung disease may reduce DNA methylation in a gene-specific manner (Um et al. 2018). Low-dose CT (LDCT) used to screen for lung cancer, but future research directions are expected to allow for a simpler, less invasive screening tool (Lerner et al. 2018). The methylation of the promoter of $P16^{INK4a}$ gene is very common in lung cancer. The detection of promoter methylation of $P16^{INK4a}$ gene in serum or bronchoalveolar fluid/sputum may be a potential biomarker for the diagnosis of NSCLC; however, the sensitivity is relatively low, not suitable for NSCLC screening (Tuo et al. 2018). DNA methyltransferase inhibitors have been approved for the treatment of myelodysplastic syndromes and are being used in clinical trials for the treatment of solid tumors, and although currently available DNA methyltransferase inhibitors lack specificity for the gene of interest, gene-specific therapies are currently being developed (Yang et al. 2017a; Medina-Franco et al. 2015; Lu et al. 2013; Medina-Franco and Yoo 2013).

7.5 Conclusion

DNA methylation plays a pivotal role in lung inflammatory related diseases such as asthma, COPD, and lung cancer. The effects of various exposures on the lungs of the body are reflected by DNA methylation. The relationship between environmental exposure, inflammation, immunity, and DNA methylation is common in humans from birth to death. These epigenetic results may represent potential biomarkers of respiratory inflammatory related diseases. The challenge is to understand how genetic variation, transcriptome, epigenetic markers, the environment, and the immune system are interrelated. We need to explore more genetic loci that may be involved in methylation; it is possible to conduct early screening and targeted treatment of pulmonary inflammatory diseases in a more convenient and accurate way in the future.

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Chapter 8
Symptom and Life Quality Management in Oncology Patients

Melike Demir Doğan

Abstract Quality of life is a multidimensional concept. Therefore, its assessment includes many parameters ranging from happiness and well-being of individuals to environmental quality and ecological structures. A good symptom management is associated with less symptom formation and thus with a better quality of life. Non-pharmacological interventions typically include various psychosocial, behavioral and environmental strategies that can complete traditional treatment to increase the quality of life for cancer patients.

Keywords Quality of life · Cancer patients · Symptom management

8.1 Symptom and Life Quality Management in Oncology Patients

Quality of life is a multidimensional concept. Therefore, its assessment includes many parameters ranging from happiness and well-being of individuals to environmental quality and ecological structures (Pınar 2012; Mandzuk and Mc Millan 2005). The World Health Organization defined quality of life as the perception of individuals on their goals, expectations, criteria, and social relationships within the cultural structure and values system they live in (Health Organization Quality of Life Assessment (WHO-QOL) 1995). The quality of life related to health signifies how an individual or group perceives their physical and mental health (Eser 2006).

The quality of life in the field of health plays an active role in the evaluation of many cases in healthcare systems. It is used for the purposes like distribution of limited health resources, facilitating clinical decision-making, and helping patients about independent decision-making. In addition, studies on quality of life have begun to be conducted in various disease conditions, in comparing the efficiency of different treatment approaches, and in making suitable treatment decisions for the

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patient (Guyatt et al. 1993). Quality-of-life studies in oncology patients are used in areas such as estimating the survival time, determining the treatment type according to the patient's preferences, comparing the standard treatments with a new medicine, determining cost-effective treatments, and detecting the areas where patients need support.

Chemotherapy, radiotherapy, surgical treatment, or hormone therapies used in oncology patients all affect the functional states of the individual for a short or long term negatively. Quality of life is an important subject for the oncology patients, and it has effects on the quality of survival (Clark et al. 2013). It is known that cancer and cancer treatment negatively affect the physical health, psychological health, and quality of life of the individual.

When the symptoms constituting the side effects of oncological treatments are not managed well, they affect the quality of life, functional status, health perception, healthcare costs, and survival (Brant et al. 2016). A good symptom management is associated with less symptom formation and thus with a better quality of life (White et al. 2019).

Non-pharmacological interventions typically include various psychosocial, behavioral, and environmental strategies that can complete traditional treatment to increase the quality of life for cancer patients (Tong et al. 2014). For example, acupuncture reduces negative symptoms such as pain, fatigue, sleep disorders, and some gastrointestinal disturbances. Therefore, it is stated that the quality of life increases (Tao et al. 2016). In this section, measures and things that can be done to increase the quality of life and decrease the symptoms in symptom management will be focused.

8.2 Pain

Pain is one of the most fearful symptoms by the oncology patients and their relatives (Mercadante 2013; Paice 2004). The International Association for the Study of Pain defined pain as an unpleasant sensory and emotional sensation or behavior related to the past experiences of a person and associated with a strong or potential tissue damage originating from a certain part of the body (International Association for the Study of Pain 1979).

Cancer pain is recognized as a serious global problem affecting billions of people worldwide (European Society for Medical Oncology 2013). Pain is seen in 64% of patients with advanced or terminal disease and in 59% of patients receiving cancer treatment (van den Beuken-van Everdingen et al. 2016). WHO and international pain communities define cancer pain as a global pain problem. It is estimated that especially pain prevalence is higher in developing countries due to late diagnosis and major obstacles in accessing opioids and more than 80% of the world's population is not treated sufficiently for moderate or severe pain (Heidrich 2007). Cancer pain affects many aspects of the quality of life of patients including activities of daily

living, social functions, and sleep quality (Grotmol et al. 2018; Ganesh et al. 2018; Nishiura et al. 2015).

It is a fact that the use of pharmacological and non-pharmacological methods in pain control is effective in relieving pain (McMeramine 2011; Yıldırım 2006a, b). Non-pharmacological methods reduce the emotional response of the patient to pain rather than affecting the underlying pathology, pain perception, and pain feeling (Heidrich 2007). Non-pharmacological treatments decrease the stimulation of the sympathetic nervous system and ensure the release of endogenous pain-relieving agents (e.g., endorphins). It increases the individual sense of control and decreases fatigue/weakness feeling. It increases the activity level and functional capacity, decreases stress and anxiety, and decreases hopelessness and helplessness. Therefore, it reduces pain behavior and focused pain level (Heidrich 2007; Yıldırım 2006a, b).

Possible therapeutic benefits of massage, one of the non-pharmacological treatments, are reported to be relaxing the mind and body, reducing fatigue, facilitating falling asleep, reducing heart rate, and reducing pain by stimulating endorphins (Yıldırım 2006a; Corbin 2005). Massage is increasingly used in symptom control of cancer patients. Its use is becoming widespread especially in hospice and palliative care areas (Deng and Cassileth 2005). Massage is an intervention allowing relaxation and reduction of perceived pain severity and anxiety perceived in cancer patients (Cassileth and Vickers 2004; Wilkie et al. 2000). In a randomized controlled trial, it was determined that massage had beneficial effects on pain and mental state in advanced cancer patients but these effects were not long-lasting (Kutner et al. 2008). Therefore, it can be thought that massage can be effective in enhancing the quality of life.

It is stated in literature that acupuncture is a popular complementary therapy preferred by oncology patients, its use by cancer patients with chronic pain can be beneficial, and it reduces the pain level (Alimi et al. 2000, 2003; Cohen et al. 2005). As a result of the meta-analysis, it was found to enhance the quality of life (Tao et al. 2016).

In the National Institute of Health's Technology Diagnostic Panel, use of hypnosis in reducing chronic pain conditions such as cancer-related pain was recommended (Monti and Yang 2005). A randomized controlled study showed that hypnotherapy was effective in relieving mucositis pain associated with cancer (Syrjala et al. 1992). It is stated that hypnotherapy can be beneficial in palliative cancer patients. In a systematic review, encouraging evidences were found indicating that hypnotherapy can alleviate cancer pain (Rajasekaran et al. 2005). However, the number and quality of studies that can provide definitive evidence on the subject are still insufficient.

8.3 Fatigue

Fatigue related to cancer is one of the important and complex clinical problems commonly reported by oncology patients. Although the rate of patients experiencing cancer-related fatigue varies in the literature, 40% and 100% of all cancer patients generally report that this symptom affects them. The fatigue rate reported especially for patients receiving chemotherapy and radiotherapy treatment is 80% and 90%. It has been found that 22% of cancer patients experience constant and severe fatigue in the years following anticancer treatment (Mitchell 2011; Nail 2004; Koornstra et al. 2014).

Fatigue seen in each individual occurs as a result of many different factors. For this reason, the treatment plan should be multidimensional and individualized. In addition, treatment should be started early to prevent cancer-related fatigue from turning into a chronic problem. Many treatment approaches can be used together by considering the physical, mental, and cognitive state of the patients, the prevalence of functional disorder, and the patient's expression of the problem (Mitchell 2011; Nail 2004; Horneber et al. 2012).

In the meta-analysis and randomized controlled studies, it is stated that exercise is beneficial in fatigue management during cancer treatment or in the follow-up periods of the patients who have breast cancer, solid tumors, and hematopoietic stem cell transplantation (Mitchell 2011; Koornstra et al. 2014; NCCN Guidelines 2014; ONS PEP Guidelines 2014; Mock 2004; Mitchell et al. 2007).

In the randomized controlled studies, it was reported that training interventions helped patients to cope positively with fatigue. It was determined that fatigue states of the patients improved statistically after the care interventions for fatigue such as physical exercise, relaxation techniques, art therapy, being with peer groups, and providing information about cancer and psycho-social effects of cancer and coping strategies but this improvement did not continue in 3–6-month follow-ups (NCCN Guidelines 2014; ONS PEP Guidelines 2014; Mock 2004; Mitchell et al. 2007).

Approaches such as structured rehabilitation, reiki, art, music, animal therapy, therapeutic touch, psychotherapy, distraction, hypnosis, yoga, relaxation techniques, and stress-reducing interventions are evaluated as pilot studies in small sample groups and prior evidences about the effects of these methods on reliving the fatigue of cancer patients have been obtained. Since these studies include small sample group and have not been planned as control group studies, it is hard to accept their results about their competencies as reliable. Despite these limitations, studies support that these complementary therapies can be potentially used in the fatigue treatment of cancer patients (NCCN Guidelines 2014; ONS PEP Guidelines 2014; Mitchell et al. 2007). Therefore, it is believed that the complementary treatments stated above that will be applied along with pharmacological methods for the underlying cause in coping with fatigue will be beneficial in enhancing the quality of life.

8.4 Change in Taste and Smell

The sense of taste and smell has an important place in maintaining human life. The sense of taste and smell affects the individual's appetite by affecting his/her food preferences. In addition, these senses function in protecting the individual against harmful food and environmental toxins (Hong et al. 2009; Peregrin 2006; Jonathan and Elisa 2014).

The treatment process starting with the cancer diagnosis negatively affects the sense of taste and smell in many patients as well as their nutrition and food preferences and causes inadequate and unbalanced nutrition and weight loss. This may lead to the development of malnutrition which is a cause of morbidity in some oncology patients. Changes in taste and smell, which develop as complications related to the disease and treatment, reduce the quality of life of patients and their compliance to the treatment and cause a decrease in their response to treatment (Hong et al. 2009; Steinbach et al. 2009; Comeau et al. 2001; Halyard 2009).

In order to reduce/eliminate the severity of taste and smell changes developing due to cancer and its treatments, some suggestions can be made to patients and their families about the preparation and consumption of foods. Eating small amounts and, often, preferring popular foods and eating with family and friends can be recommended. When the patient feels good, he/she should prefer new foods. For those who have a metallic taste, the use of plastic forks, spoons, and glasses can be recommended. The use of sugar-free/flavored gum or mint sugar and consumption of fresh vegetables and fruits can be recommended. It can be recommended to consume foods with lemon, vinegar, or pickles if there is no wound in the mouth or throat. The use of spices for flavoring foods, the use of onion/garlic to add flavor, and consumption of meat with sauce can also be recommended. Consuming protein-rich foods such as eggs, fish, chicken, and cheese can be recommended if there is a difficulty in eating red meat. It may be recommended to consume food at room temperature or cold, as it may reduce the taste and odor of the food. Adding fresh fruits in ice cream or yogurt, drinking beverages thought to be smelling with a straw, and consuming the food uncooked if the smell is disturbed can be recommended. It may be recommended to consume cool/cold fruits such as melon, grape, orange, and watermelon. Preparing meals by others and not eating in very hot or airless environments may be recommended (Algorıthm Dysgeusia in Adults with Cancer 2014; American Cancer Society 2014; National Cancer Institute 2014).

8.5 Mucositis

Mucositis is defined as inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal system. High-dose chemotherapy and radiotherapy applied in cancer treatment are the main causes of mucositis. The World Health Organization (WHO) reports that three or five mucositis are seen in 85% of patients receiving radiotherapy

(60–70 Gy) due to head and neck cancer (Peterson et al. 2015). Mucositis comes to the fore as an inevitable problem to manage by affecting the social relations of the individual seriously, and as the severity of mucositis increases, it prevents the patients from being fed orally and may cause the development of opportunistic infections in the mouth. Therefore, it is a problem affecting the quality of life of patients.

MASCC (Multinational Association of Supportive Care in Cancer) and ISOO (International Society of Oral Oncology) published a guideline on the treatment of oral mucositis (Peterson et al. 2015; Jensen and Peterson 2013; Mucositis Study Group Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2013). According to this guideline, while mouthwashes containing benzydamine (radiotherapy over 50 Gy) are recommended to prevent oral mucositis in patient receiving head-neck cancer treatment, mouthwashes containing sucralfate are not recommended in preventing or treating mucositis (Peterson et al. 2015; Jensen and Peterson 2013; Mucositis Study Group Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2013). Similarly, ESMO guidelines recommend the use of benzydamine mouthwash to prevent oral mucositis in patients receiving medium-dose radiation treatment up to 50 Gy (Peterson et al. 2015). In both guidelines, oral protocols are recommended for all age groups to prevent mucositis. Low-level laser therapy (wavelength approx. 632.8 nm) is recommended in order to prevent mucositis (Peterson et al. 2015; Jensen and Peterson 2013; Mucositis Study Group Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2013). In MASCC and ISOO guidelines, zinc sulfate is also recommended for preventing mucositis (Peterson et al. 2015; Jensen and Peterson 2013; Mucositis Study Group Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2013). In ESMO guidelines, it was reported that systemic zinc supplements applied orally can be beneficial in preventing oral mucositis in oral cancer patients receiving radiation treatment or chemotherapy (Peterson et al. 2015).

According to the systematic review conducted with patients receiving head-neck chemoradiotherapy, the effectiveness of amifostine in preventing mucositis is controversial (Nicolatou-Galitis et al. 2013). Glutamine is a natural protein, and it was reported in the studies that it reduces the incidence of grade 2, 3, and 4 mucositis as well as delays the formation of mucositis. However, there is no information about the evidence level in the guidelines yet (Sayles et al. 2016). The effectiveness of black mulberry molasses on mucositis has been investigated in different laboratory studies, and it has been shown that it has antifungal activity especially on *C. albicans* from *Candida* species (Sohn et al. 2004; Khalid et al. 2011). In another randomized controlled study conducted on patients receiving head-neck radiotherapy, it was expressed that black mulberry molasses prevented the mucositis development by 38% (Demir Doğan et al. 2017). Since there are no enough evidences, black mulberry molasses is not included in the guidelines.

8.6 Nausea and Vomiting

One of the symptoms that is hard to control and seen frequently in advanced cancer patients is the nausea and vomiting. Although different treatment strategies have been developed in the management of this problem that affects quality of life and daily life activities of patients negatively, it is still hard to control it in some patients (Ang et al. 2010; Hamling 2011; Gordon et al. 2014).

The management of nausea and vomiting is planned based on the patient's level of being affected and the cause of the nausea-vomiting. While the use of distracting approaches such as music therapy, relaxing exercise, massage, yoga, and meditation along with food regulation is sufficient in mild nausea and vomiting, pharmacological treatment may need to be started in the management of more severe nausea and vomiting. In addition, acupressure, hypnosis, and acupuncture application can be made. Informing the patient and his/her family about the nausea-vomiting development process and coping strategies can be an effective coping approach especially in the management of chemotherapy-related nausea and vomiting (Reville et al. 2009; Rhodes and McDaniel 2001; Gu and Lil 2016).

In a study, self-care methods used for coping with nausea-vomiting were investigated. In the study, consuming fat-free and light foods; eating small amounts and, frequently, consuming plenty of fruit; consuming liquid foods such as soup and fruit juice; getting fresh air; not being in the environment where the food is prepared and staying away from the smelly foods; smelling lemon or orange when suffering from nausea; deep breathing; relaxation and mediation; acupuncture and acupressure; distraction methods such as watching television and listening to music; sucking mint and ginger sugar; consuming ginger; and finding something to be busy (housework, gardening, etc.) were reported as the other applied methods. It has been also reported that these approaches have a low level of reducing nausea and vomiting (Lou et al. 2014).

The studies have shown that ginger is a safe medication and has no severe side effects (Lou et al. 2014). The effectiveness of ginger in the management of nausea and vomiting has been investigated in many studies, but it is not possible to decide its use for antiemetic purposes since the obtained results are controversial and do not cover the advanced cancer patients (Ansari et al. 2016; Sanaati et al. 2016; Arslan and Özdemir 2015; Pillai et al. 2011; Panahi et al. 2012; Lee and Oh 2013).

In different studies, the effect of music therapy and guided imagery (Karagozoglu et al. 2012), relaxation (Sahler et al. 2003), and a special music program called as Nevasic (Moradian et al. 2015) has been examined. It was determined in these studies that the approaches providing relaxation for the patient significantly reduced the nausea-vomiting and the use of antiemetic.

8.7 Diarrhea and Constipation

In oncology patients, diarrhea may be a side effect of the agent used in chemotherapy, and it may be developed depending on pelvic and abdominal radiotherapy (Teo et al. 2015), enteral feeding, overdose laxative use, infection, and other medication treatments (Teo et al. 2015; Stein et al. 2010; Oncology Nursing Society 2018).

If this problem, which negatively affects the quality of life of patients, cannot be managed effectively, it may lead to dehydration, electrolyte imbalance, and malnutrition and increase the hospitalization frequency of patients and even death (Colleen and Loryn 2012). It was seen in the studies that glutamine is an effective approach in the management of radiotherapy-related diarrhea. Since the number of patients included in the study is low, more studies are needed in order to recommend the use of glutamines in the management of diarrhea associated with radiotherapy (Kucuktulu et al. 2013).

It is stated that the prevalence of constipation in oncology patients is between 2 and 10% (Economou 2010). Although it is not a life-threatening condition, constipation is one of the main problems negatively affecting the quality of life of both the patient and his/her family by negatively affecting the advanced cancer patients physically, psychologically, and economically (Larkin et al. 2008).

Since there are various risk factors causing constipation, the treatment type and the patient's response to the treatment are individual. Therefore, there is no rule set for the effective way of constipation management (Economou 2010). In the literature, it was reported that it is important to conduct patient trainings to acquire correct bowel habits (Itano et al. 2016) as well as pharmacological approaches in the management of constipation (Candy et al. 2015). It was reported that the training was effective when it was done by considering the individual characteristics of the patients, health history, medications used, and medical treatment, following a certain training program and possibly one-to-one (average 20–30 min), and focusing on the problem (Smith 2001; Hanai et al. 2016; Mollaoğlu and Erdoğan 2014; Ayaz and Hisar 2014). The number of studies conducted with the participation of oncology patients is very limited. The results of the studies conducted with the participation of general population have showed that increasing the intake of foods with fiber, water, and magnesium is an effective approach in reducing the incidence of constipation (Murakami et al. 2007) and constipation symptoms (Dukas et al. 2003). In the literature, the recommended daily water consumption is between 1500 and 3000 ml (Larkin et al. 2008; Itano et al. 2016; Ayaz and Hisar 2014; Fox et al. 2017; Holroyd 2015), and the recommended daily fiber amount is between 15 and 35 g (Larkin et al. 2008; Ayaz and Hisar 2014; Franklin et al. 2012; Christodoulides et al. 2016; Thomson et al. 2016; Yang et al. 2012). It has been reported in the studies that daily moderate-intensity exercise reduces chronic constipation by 44% (Dukas et al. 2003). Women who are physically active daily and get about 20 g fiber per day have three times lower constipation prevalence compared to women who rarely exercise and get about 7 g fiber per day (Dukas et al. 2003). Therefore, including physical activity and exercise programs into the treatment plan of the

individuals with constipation has been reported to be effective in preventing constipation (Orhan et al. 2015).

8.8 Hand-Foot Syndrome and Nail Change

Hand-foot syndrome also called as acral erythema, palmar plantar erythema, Burgdorf reaction, and toxic erythema on hands and feet is a condition where there are tingling, burning, redness, and pain in the palms and soles. Although its etiology is not fully known, it is one of the cutaneous toxicities seen in patients using chemotherapy drugs and target drugs (Goodman 2004; Gandy-Webster et al. 2007). Incidence of hand-foot syndrome depends on the medication given, its dosage, and the mode of administration. For example, it is most frequently seen in 5-fluorouracil infusion therapy (Goodman 2004). Treatments applied for hand-foot syndrome have no 100% effect. However, the use of results of evidence-based studies conducted on symptom management can be effective in preventing this problem (Gandy-Webster et al. 2007; Lacouture et al. 2008).

The incidence rates of nail changes are reported as 25–30% in patients using weekly paclitaxel and 19–23% in those who use doxorubicin and cyclophosphamide due to breast cancer (Miller et al. 2014). Nail changes associated with chemotherapy cause cosmetic problems, pain, and infection and affect the quality of life of patients. Nail changes can be seen in a few nails or in all 20 nails. Some nail changes are asymptomatic and may only result in cosmetic problems. In addition, other changes can cause pain and discomfort and impairment in daily life activities. Nail changes induced by drugs occur as a result of acute toxicity in the nail epithelium (Gilbar et al. 2009; Gupta et al. 2008).

Protective measures should be taken to prevent hand-foot syndrome and nail changes. While washing dishes or bathing, contacting hands and feet with hot water should be avoided, and if possible, cold shower should be recommended (Lacouture et al. 2008; Conway 2010; BC Cancer Agency 2013; Mangili et al. 2008). Dealing with intense chemicals in activities such as house cleaning and laundry should be avoided. While cleaning with hot water, rubber gloves should be avoided as rubber conduct heat easily to the skin (Conway 2010; BC Cancer Agency 2013). Individuals should not stay in front of a window in the sauna, sunbathing or sunny weather (Minisini et al. 2003) and should use sunscreen creams (BC Cancer Agency 2013). Long walks, aerobic exercise, friction to the feet and hands, or activities requiring excessive forces should also be avoided (Lacouture et al. 2008; BC Cancer Agency 2013). Works that could damage the hand skin (such as gardening, typewriting, screwing, etc.) should be avoided (BC Cancer Agency 2013; Moos et al. 2008). Existing calluses should be checked regularly, and if possible, hyperkeratotic areas and calluses should be treated prophylactically with the help of manicure or pedicure before and during treatment (Lacouture et al. 2008; Zhang et al. 2011; Wood et al. 2010). Pressure points in the hands and feet and areas sensitive to pressure should be protected, and shoes that do not squeeze and have soft soles should be preferred

(Lacouture et al. 2008; Zhang et al. 2011; Wood et al. 2010). Overweight patients should be consulted with an orthopedist/physical therapist about using an assistive device (Lacouture et al. 2008). Hands, feet, and all skin surface should be washed with warm water and dried thoroughly. The skin should not be left sweaty and moist (BC Cancer Agency 2013). Nails should be cut short. Chemicals and detergents that may damage the nails and the areas around the nails should not be used. Patients with delicate nails should be advised to soak their hands in water with vitamin B every day. The patients should be informed about not using nail polish, and if they use, they should be informed about being careful when using acetone if the nail bed is open (Miller et al. 2014; Gilbar et al. 2009; Gupta et al. 2008).

8.9 Lymphedema

Surgery, radiotherapy, and chemotherapy used in the treatment of breast cancer can prolong the patient's life expectancy and cause problems that can negatively affect the quality of life (such as infection, nausea, vomiting, pain, skin burns, lymphedema, and depression). Lymphedema, one of these problems, is the accumulation of protein-rich liquid in the interstitial area due to insufficiency in lymphatic system. It is one of the most common complications encountered after breast cancer treatment. The incidence of lymphedema after axillary dissection varies between 15 and 47% (Biffaud 2013; Demir 2008; Kebudi et al. 2005). Lymphedema causes insufficiency for the individual for fulfilling his/her daily activities and his/her caregiving roles in the family, weakness, functional insufficiency in the arm, deterioration in body image, and decreased self-esteem and quality of life (Sakorafas et al. 2006; Rodrick et al. 2013).

The development risk of lymphedema continues throughout life, and there is no definitive treatment approach when it develops; the best treatment is to prevent its development. In the literature, the use of different approaches such as patient training (Fleysher 2010; Thomas-MacLean et al. 2005; Ridner et al. 2011), starting arm exercises after surgery (McNeely et al. 2010; Kilbreath 2011), weight control, and using a pressure arm-band during flight (Kilbreath et al. 2010) has been recommended, and the effectiveness of these approaches has been evaluated in different studies. However, there is no definitive evidence yet so that we can say that any application is effective.

8.10 Radiotherapy Skin Reactions

Radiation treatment has many long- and short-term side effects. One of these side effects is radiotherapy-related skin reactions. Skin reactions, which can be seen in different severity in 85% of patients, develop depending on the changes formed in the normal cell division and regeneration of the skin with the effect of radiotherapy

(Salvo et al. 2010). These losses, which show themselves with the skin reactions, usually begin 2–3 weeks after the initiation of radiotherapy and reach a peak with the end of treatment (Bruner et al. 2005). Development of skin reactions caused problems in the planned treatment and negatively affects the daily life activities and quality of life of the individual. Individuals have difficulties in choosing clothes, self-care, and self-efficacy in relation to the affected area (McQuestion 2011; D'haese et al. 2010).

There are many factors in radiotherapy affecting the development of skin reactions. It is possible to investigate these factors under two groups associated with the patient and treatment. Surgical interventions made during and before radiotherapy, other treatments such as applied chemotherapy and biotherapy, drugs used, chronic and acute diseases affecting the healing process, systemic infections, and exposed environmental factors are also the causes affecting severity of skin reactions.

Although the interventions for skin reactions are limited, they are mostly for its prevention or management. The preventive strategies include avoiding skin irritation, keeping the treatment area clean, minimizing friction, reducing the frequency of washing, avoiding to use soap, avoiding to use creams and deodorants with irritating features, and avoiding from sun exposure (Salvo et al. 2010; McQuestion 2011; D'haese et al. 2010; Chan et al. 2014).

In the published meta-analysis, systematic review, and clinical guidelines, it has been stated that washing skin or hair during radiotherapy is generally beneficial for the patient and their restrictions do not reduce the severity of skin reactions (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014; Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010). In the guidelines of the Oncology Nursing Society and MASCC (Multinational Association of Supportive Care in Cancer), routine skin care and the use of deodorant are among the recommended practices. There is no data on the frequency of use, but the generally accepted approach is "maintaining routine practice" (Wong et al. 2013; Deborah Feight et al. 2011).

Although the studies investigating the topical steroids do not provide very strong evidences, they are believed to be effective particularly in reducing the discomfort experienced by patients (Wong et al. 2013; Deborah Feight et al. 2011). In clinical guidelines and other systematic reviews, the use of topical steroid creams against symptoms such as itching and burning sensation is recommended (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014; Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010).

In clinical guidelines and other systematic reviews, it was expressed that creams containing hyaluronic acid and its combinations may be useful but more studies are needed (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014; Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010). Although there are some studies showing that trolamine may be beneficial, the general evaluations mention that trolamine is not useful (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014;

Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010).

Although there are some studies stating that aloe vera may be beneficial, the general impression is that it is not effective in radiotherapy skin reactions (Wong et al. 2013; Deborah Feight et al. 2011). The general evaluation made in clinical guidelines and other systematic reviews is that aloe vera is not beneficial (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014; Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010). The general evaluation in the clinical guidelines and other systematic reviews is that there is no enough evidence to express that sucralfate is useful (Salvo et al. 2010; McQuestion 2011; Chan et al. 2014; Wong et al. 2013; Deborah Feight et al. 2011; Glover and Harmer 2014; Kumar et al. 2010; Zhang et al. 2013; Andrade et al. 2012; Chan et al. 2010).

8.11 Peripheral Neuropathy

"Peripheral neuropathy" is the dose-limiting toxicity caused by many chemotherapy and biotherapy drugs. Peripheral neuropathy developing due to cancer treatment can cause the change or termination of the treatment. In addition, it causes the deterioration of the patient's functions, prevention of daily life activities, and impairment of the quality of life and negatively affects the treatment process of the patient and increases health expenses (Tofthagen 2010; Hershman et al. 2014; Argyriou et al. 2014; Kolak et al. 2013).

Different non-pharmacological approaches have been used in the management of peripheral neuropathy: reflexology (Nicholas et al. 2007; Ihn 2006), massage (Nicholas et al. 2007; Ho and Roblew 2011), and acupuncture (Nicholas et al. 2007; Ho and Roblew 2011). However, the effectiveness of these approaches has been shown in the management of peripheral neuropathy due to diabetes and HIV in particular (Nicholas et al. 2007; Ihn 2006; Ho and Roblew 2011), but the number of randomized studies investigating the effectiveness of these approaches is few. In a limited number of studies conducted with cancer patients, the effectiveness of acupuncture (Donald et al. 2011; Schroeder et al. 2012), exercise (Wampler et al. 2005), and massage (Cunningham 2011) was evaluated or presented as case reports. Although these results are not sufficient for conclusive evidence, it is believed that these approaches can be effective in reducing peripheral neuropathy.

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Chapter 9
The Regionalization of Medical Management: The Practice and Exploration of Established Fudan-Minhang Medical Alliance

Meirong Ling, Manar M. Atyah, and Ning Ren

Abstract The Fudan-Minhang medical alliance focuses on developing a healthcare system that considers the medical, educational, and research aspects of healthcare services. Through strengthening regional medical management and enhancing service quality and ability, the alliance will provide a vital contribution that can reform and strengthen the medical and health system.

Keywords Regionalization · Medical management · Medical alliance

9.1 Introduction

Medical alliances are important methods in regionalizing medical management and implementing hierarchical diagnosis and treatment strategies. They play a vital role not only in deepening the medical and health system reformation but also in reaching the strategic goal of establishing healthy China. Shanghai Minhang District, in cooperation with Fudan University, has built a new medical alliance of medical services, medical education, and scientific research. It enhances the medical service system, improves the high-quality medical resources, strengthens the ability to provide basic medical care, and advances the orderly hierarchical model of medical treatment. The formation of Fudan-Minhang medical alliance provides a unique

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example and a developmental model that can be a valuable reference in enhanced regionalization of medical management both nationally and globally.

9.2 Background and Basis

9.2.1 Basic Conditions of Minhang District's Medical Services

Minhang district covers an area of 371 square kilometers. The total resident population is about 2,549,300. It has 4 grade-3 first-class medical hospitals, 3 general medical hospitals, and 4 specialized medical hospitals, in addition to 13 community health centers.

9.2.2 The Basis of Fudan-Minhang Medical Alliance Establishment

9.2.2.1 Theoretical Basis

Before the establishment of Fudan-Minhang medical alliance, Minhang district lacked any rational distribution of medical and health resources. Only one grade-3 first-class hospital was available (The Southern Division of Renji Hospital, Shanghai Jiao Tong University School of Medicine). At the time, large- and medium-size hospitals were overcrowded with patients, while primary healthcare hospitals were deserted. This situation led to an irrational use of medical and health resources and seriously impacted the public medical experience. That created an urgent need to develop medical alliances. By guiding and assisting medical institutions of different levels and categories, Fudan-Minhang medical alliance established a clear objective in division and cooperation, responsibilities and rights. It also improved the quality of medical resources and gradually solved the problem of irrational layout of medical services. The alliance provided a solution for the lack of available resources by aiming and promoting for a hierarchical medical system in which patients with minor illness or rehabilitation needs are directed to community medical centers, while hospitals attend to patients with serious illnesses and urgent medical needs.

9.2.2.2 Practical Basis

In 2010, the Bureau of Health of Shanghai Municipal issued "Guiding Opinions about Shanghai Regional Medical Alliance Setup," launching a nationwide reformation of medical alliances in China (Bureau of Health of Shanghai Municipal 2010). In 2011, two medical alliances (Ruijin-Luwan and Xinhua-Chongming

regional medical alliances) were launched. By establishing a unified, saving, efficient operating mechanism, the alliances planned the functional layout of affiliated medical institutions, promoted the flexible flow of staff, and improved the quality of resources, which provided the district residents with first-class hospitals' medical resources and care (Wang et al. 2014).

9.3 Exploration and Implementation of Fudan-Minhang Medical Alliance

9.3.1 Basic Framework of Fudan-Minhang Alliance Establishment

In 2014, Minhang and Fudan University signed a strategic cooperation agreement which included Fudan's affiliated grade-3 first-class hospitals, regional medical centers, and community health centers. The agreement aimed to establish a novel medical alliance that integrates medical services, medical education, and scientific research.

9.3.2 Basic Principles of Fudan-Minhang Alliance Establishment

9.3.2.1 The Disciplines and Resources Integration

By leading Minhang affiliated medical departments, the advanced medical departments of Fudan University integrate the resource system and explore the brand new alliance model through the comprehensive integration of medical work, affiliated staff, and scientific research of the major departments.

9.3.2.2 Unified Management and Enhanced Efficiency

Through a unified business leadership and management, the alliance establishes an intra-department unified management system. It clearly defines the roles and responsibilities, actively explores the workflow reinvention, and therefore enhances the operational and management efficiency.

9.3.2.3 Information Providing and Mode Transformation

Through establishing a medical information system, an intra-alliance medical data exchange and connectivity can be achieved. Based on residents' health records and medical history, an informative system can be established to support medical service and transform the service mode of residents' health management.

9.3.2.4 Mutual Beneficial Cooperation in Medical, Educational, and Research Fields

The alliance focuses on the coordinative development of the trinity of medical work, medical education, and scientific research. It can strengthen the medical care system, enhance the utilization and quality of resources, improve the medical skills of affiliated staff, strengthen the utilization of regional health information data, enhance the level of scientific research, accelerate the transformation and application of achievements, and therefore achieve a mutual beneficial cooperation for all affiliated parties.

9.3.3 The Three Models of Fudan-Minhang Alliance Establishment (Zhang et al. 2020a)

9.3.3.1 Medical Groups

Medical groups are formed with the structure of one grade-3 hospital as a leading unit, associated with grade-2 hospitals and community healthcare centers. They form a management model that shares resources, defines duties, and achieves cooperation. Two medical groups were established in Minhang district: Zhongshan Hospital-Minhang Hospital-community health service centers and Huashan Hospital-Shanghai Fifth People's Hospital-community health service centers.

1. **Zhongshan Hospital-Minhang Hospital-Community Health Service Centers**

   This medical group was established in July, 2017. The leading unit is Zhongshan Hospital, Minhang Hospital is the backbone, and seven community healthcare centers are the base in the group. Zhongshan Hospital assigned outstanding personnel to Minhang Hospital, including the president, vice-president, consulting specialists, department directors, academic directors, and assigned professors. The group aims to establish and enhance Minhang Hospital's departments, clinical medical technology, and scientific research through branding, management, talents, and service assistance.

   The alliance launches homogenized medical activities that follow the standards of Zhongshan Hospital. Through regular outpatient consultation, ward rotations, surgery, and educational training, experts help to improve the medical

capability of associated hospitals and centers. They also strengthen their educational and research work.

In addition, the alliance actively initiated several multidisciplinary outpatient services such as pulmonary nodules, prenatal screening, spinal orthopedic, and pharmacological outpatient services. Such services provided patients with high-quality, precise, and efficient diagnosis and treatment care. Minhang Hospital also arranged professional and excellent medical experts to community health centers and neighboring centers. They often conduct medical lectures, popularize medical knowledge, have remote clinics, etc. They increase the awareness and popularity of the hospital in public.

Through a standardized process of appointment referral, a two-way referral workflow has been actively initiated. Based on the alliance's appointment information platform, Minhang Hospital devotes a certain proportion of outpatient consultation vacancy for patients of associated community healthcare centers, which includes outpatient consultation services of specialists in Minhang Hospital and special consultation services of specialist in Zhongshan Hospital. Patients with difficult and complicated cases can be referred to Zhongshan Hospital. Recovering patients and patients with definite diagnosis will be referred back to regional centers, including central hospitals, community health service centers, private clinics, and endowment institution where patients are provided with standardized rehabilitation programs to improve their quality of life.

The alliance also explored a new model of grading and treatment of chronic diseases, such as COPD, strokes, and chronic waist/leg pain. It unifies the standards of medical diagnosis and treatments and formulates the medical route of outpatient consultation and service. That formulates the standards of associated hierarchical medical centers and implements the active appointment referral process. Based on the severity and risk levels, patients would receive personalized gradient medical care.

Relying on the branding and resources of Fudan University and Zhongshan Hospital, Minhang Hospital has gradually improved its medical, educational, and scientific research abilities. The hospital successfully developed into a regional medical center known for its solid basic subject, characteristic specialty, precise management, and optimized medical care. The hospital was successfully promoted to grade-3 general hospital and affiliated with Fudan University (Zhang 2019).

2. **Huashan Hospital-Shanghai Fifth People's Hospital-Community Health Service Centers**

The alliance was established in April, 2016. Through the establishment of the referral platform of this alliance (H_5M) and the two-way referral office, the hierarchical diagnosis and treatment system was actively implemented. The alliance established several facilities that enriched the medical resources and enhanced the regional medical care system, including the diabetes administrative center, remote consultation center, medical association of clinical test center, medical association of dermatology, and Fudan University's community health research center. The alliance also opened the consultation services of specialists

of Huashan Hospital and Fifth People's Hospital to regional community healthcare centers. Family doctors in community healthcare centers have advantages in signing up patients for radiology, laboratory, and endoscopic examinations in Fifth People's Hospital (Zhang et al. 2020b). Patients can receive priority of appointment, priority of treatment, priority of examination, and priority of hospitalization. The alliance also unified the development of research management and establishment, which included the applications of scientific research projects of affiliated centers, clinical and pharmacological trials, and ethical standards of research work. On the other hand, Minhang district provided the rich data resources of residents' medical records to fully support the research work with sufficient relevant data. Community healthcare centers were provided with enough support and have achieved rapid developments. So far, orthopedics, nephrology, and other disciplines of the Fifth People's Hospital have participated in the establishment and implementation of the National Clinical Research Center for geriatric diseases of Huashan Hospital. The outstanding achievements of the alliance received the evaluation of "Action Plan for Further Improving Medical Treatment Serving Quality" which was held by the National Health Commission of the People's Republic of China.

9.3.3.2 Specialized Unions

Specialized unions are formed with advanced specific departments of a certain medical field and similar departments from other hospitals. In this way, regional multi-department professional centers are formed to improve the medical care quality and treatment ability in a specific field of medicine and form a complementary development model. Such a horizontal model of revitalizing resources magnifies the ability and characteristics of the specific field. So far, four Fudan-Minhang unions have been formed: Fudan Pediatrics Union (Minhang Cooperative Network), Medical Association of Fudan Obstetrics and Gynecology, Fudan University Shanghai Cancer Center-Minhang Union, and Eye and ENT Hospital of Fudan University-Minhang Union.

1. **Fudan Pediatrics Union (Minhang Cooperative Network)**

   This union is led by the Children's Hospital of Fudan University and includes 3 Minhang regional general hospitals and 13 community healthcare centers. Standardized pediatric consultation rooms were established in all associated community healthcare centers with unified signs of "Fudan University Pediatric Medical Union," unified layout and decoration, and unified equipping of pediatric medical examination tools. Such measures helped in standardizing the service and workflow while relatively separating the pediatric medical service area from other areas of the centers. Healthcare centers were required to assign two to three pediatric family doctors to each consultation room. Through the adoption of management, skills, and branding styles and the unification of medical quality, medical safety measures, service models, research development plans, and data sharing systems, Fudan Pediatrics Union successfully transferred medical

resources to basic medical facilities and achieved the goal of providing medical care to patients in their areas while offering referral to those in need. At the same time, the union would refer clear simple cases or patients with common diseases who require simple treatment plans to basic community health centers. By developing the "Pediatric Medical Union's diagnosis and treatment routine of community common disease" and "Pediatric Medical Union's community nursing routine," the union established a clinical management approach of community pediatric consultation services that homogenizes the medical care and helps patients and families to seek care in their areas. The union also initiated screening, referral, and follow-up programs for children with diseases like enuresis, anemia, congenital heart diseases, and autism. Forming the two-way referral channel allowed regional medical staff to offer the required care to their patients when a referral is needed and enhanced the medical care environment of community centers by providing the facilities with additional services and sections such as pediatric rehabilitation bases, community medical rehabilitation models, and programs for disabled children and their families. Such enhancements improved the healthcare offered to children and community in this specific field of medicine (Jie et al. 2017).

2. **Medical Association of Fudan Obstetrics and Gynecology**

   With the goals of integrating resources, enhancing medical care, improving branding styles, and achieving common developments, the Union of Fudan Obstetrics and Gynecology Departments established three different platforms to reach its aims (Zhu 2016): (1) the two-way referral cooperation platform to facilitate examination results exchange and remote consultations; (2) the talent training platform to facilitate resident staff training, surgery training, link clinical work and ward rotations to educational programs, and complete class training of specialized medical skills; and (3) the scientific research cooperation platform to combine research plans and programs and apply for projects of multi-center scientific research. To ensure the rapid and effective development of the union, Fudan University assigned qualified experts specialized in diagnosis and treatment of special and important obstetrics and gynecology diseases. The team work was led by one center of the union but included experts from different affiliated centers; it focused on improving the clinical ability and research capability. The union also offered financial support to all medical teams involved to help them improve their abilities of clinical work, medical researching, team building, condition controlling, and management skills. By focusing on the qualified teams as basis, the union improved the referral and consultation systems and gradually established the medical care cooperation platform. That translated into an obvious improvement of medical care provided for complicated and critical diseases of gynecology and obstetrics.

3. **Fudan University Shanghai Cancer Center-Minhang Union**

   The Minhang cancer medical union, led by "Fudan University Shanghai Cancer Center," was established to manifest the comprehensive reformation of community and improve the regional standardized prevention and medical care strategies for cancer patients. They established hierarchical diagnosis/treatment

system and integrated management model of chronic diseases and cancer prevention. The union implemented a specific management process (screening registration – risk evaluation – initial screening – diagnosis – treatment – high-risk management – integration of patients' data) to improve the mobility and application of screening registration and management programs and link them to regional and union data platforms. The union also established a management system of cancer patients' survival and transitioned from a general practitioner-centered cancer patient management to a patient-centered survival management model relying on medical association. At the same time, the union focused on improving the regional comprehensive care system for cancer patients, improving the mobility and application of patients' management (through periodic assessment and collection of diagnosis, treatment, lifestyle, and appointment data), and providing online solutions and plans for patients' management, in order to improve the quality of care provided to the public and enhance the cancer prevention measures in the district.

4. **Eye and ENT Hospital of Fudan University-Minhang Union**

   The union was established in 2017. Specialists were assigned to attend local affiliated centers on regular bases to offer mentoring and practical clinical work. At the same time, a two-way referral channel was established to allow affiliated centers to provide the best medical care available. Through direct management and standardized formulation of skills, the hospital helped the district's medical facilities in discipline establishment and clinical and scientific research work. A cross-regional union was established through vital approaches, such as personnel training, critical case consultations, and counterpart support, to strengthen the regional resources of specialized departments. Recently, the union also helped to solve the problem of high myopia rates that had been affecting young population. In order to tackle the problem, the Eye and ENT Hospital of Fudan University actively viewed preventive measures adopted by district's hospitals, schools, and families. The hospital then created a cooperation and framework agreement with the educational and healthcare system of Minhang district regarding "myopia prevention and control in children and adolescents." Thus, the hospital helped in integrating the community resources, clarified the roles of different involved parties, and implanted an effective prevention system. The Minhang model of myopia prevention and control included 400 schools and 230,000 students. The model focuses on increasing the awareness of children's duty in maintaining eye heath. Healthcare teachers were asked to effectively track and examine the sight of students. At the same time, the model trained medical staff and healthcare givers to provide early detection, early treatment, and early prevention services in their clinical work. With the guidance of the union, all children and newborn babies in Minhang district now have an eye health record that not only includes their continuous results and record of eye health exams but also can predict the high-risk individuals based on the mass data analysis results (Zhang et al. 2020c).

9.3.3.3 Remote Medical Collaboration Network

Remote medical care models significantly improved the medical service quality in basic and regional centers. It not only extends the spatial and time limits of traditional medical care models but also strengthens the collaboration among medical institutions. The communication among specialists are enhanced. The successful application of remote medical collaboration network by Fudan-Minhang alliance helped in achieving an effective system in which advanced hospitals (grade-2, grade-3 hospitals) can provide the needed support to basic medical and health organizations. Such services include remote consultation services for critical and complicated cases, remote diagnosis assistance (pathological, radiological, and electrocardiographic diagnosis), remote educational training programs, and two-way referral services (Gao et al. 2019). Online hospitals have already created a new medical infrastructure that connects internet accessibility to medical health and services. In the special era of COVID-19 pandemic, Fudan-Minhang alliance has focused on continuously expanding its remote and online medical services, in order to meet the demands of prevention and control. The alliance provided a complete online medical care process and enhanced its online hospital service model. The online service platform also focused on chronic diseases management and services, providing a new level of assistance and convenience to both doctors and patients. The platform provided access to medical assistance and medical management expertise and gradually created a complete management system of care that included screening services, follow-up prescriptions, medication delivery, and insurance payment services. That increased the efficacy and precision of chronic diseases management and provided better specialized online services for patients.

9.4 Achievements and Considerations of Fudan-Minhang Medical Alliance

9.4.1 Achievements of Fudan-Minhang Medical Alliance

9.4.1.1 Implementing Oriental Functioning of Medical Institutions

Through the mechanisms developed by Fudan-Minhang medical alliance, regional medical institutions gradually developed the ability of oriental functioning and enhanced the ability to separate between chronic and urgent medical care requirements. That reduced the exhaustion of leading hospitals' resources by reducing the number of patients with common, stable, and chronic diseases. Patients already recovering from critic diseases or surgical treatments and in stable status would be referred to seek care and continue treatment in secondary health centers that provide them with treatment, rehabilitation, and long-term nursing services. Such work enhanced the healthcare management system and improved the disease control and prevention efficacy.

9.4.1.2 Enhancing the Sharing and Integration of the Alliance's Resources

The alliance implemented the leading role of major grade-3 hospitals that are required to provide basic medical institutions with professional, technical, and management support. It focused on providing standardized and unified services and optimizing the sharing and distribution of enhanced medical resources. They often strengthen the medical quality control, establish medical radiology and laboratory examination centers, and achieve an effective exchange and sharing of prescriptions and medication resources.

9.4.1.3 Standardizing the Two-Way Referral Service Process

The alliance created a communication channel for medical data exchange that depends on established platforms and two-way referral system. Doctors can share health records. By setting standards for the complete referral process, the alliance successfully provided patients with smooth referral services and continuous healthcare.

9.4.1.4 Optimizing the Ability to Provide Basic Medical Services

The special structure of the alliance implements the public welfares of hospitals. It also creates regional backbones for the medical care system by assigning medical directors and management teams to local centers. They provide regular clinical rotations, ward managements, and educational and surgical training programs for local staff. By allowing medical staff of local basic institutions to participate in training and rotation programs of advanced hospitals, the alliance homogenizes the medical teams' technical and service capabilities. It improves the level of care in local institutions, which brings the first-class care level of major hospitals to local patients (Chengyan et al. 2020).

9.4.1.5 Promoting the Role and Signing of Family Doctors

The alliance focuses on linking the role of family doctors and other specialists when providing healthcare to patients. By achieving the connection and cooperation between local family doctors and doctors in leading hospitals, the alliance creates special functioning medical units that include local family doctors and major hospital specialists, harmonize their work, and provide the team services to locals through signing up and communicating with their local family doctors (Chengyan et al. 2020).

9.4.1.6 Establishing a Healthcare Service System that Integrates Clinical and Preventive Medicine Approaches

The alliance focuses on forming expert teams from associated members that work on enhancing the ability of medical early intervention and prevention through several approaches, such as providing knowledge and lectures about chronic diseases, promoting for healthy lifestyles, providing physical examination programs for district's residents, and screening programs for high-risk groups of residents. By providing regular consultation, medication management, condition monitoring, and complication prevention services to patients with chronic diseases, the alliance succeeded in optimizing and integrating the prevention, treatment, and management strategies of chronic diseases, shifting the focus from "treatment" to "health," and gradually repositioning the concepts of the public and periodic health services (Han et al. 2019).

9.4.2 Considerations of Fudan-Minhang Medical Alliance

9.4.2.1 Enabling the Governmental Leading Role

In accordance with the strategic cooperation agreement signed by Fudan University and the regional government of Minhang district, the Fudan-Minhang medical alliance took into consideration the regional population status, the layout of available medical resources, and the regional burden of diseases. They set up a goal to maximize the efficacy of work, according to the requirements of work relevance, advantages complementation, persist development, and double-sided selection. Through the establishment of the "Education and Research Collaborative Health Service System Management Committee," the alliance continuously enhanced the adopted management mechanisms, the human resources system, the financial allocation, and insurance policies, in order to guarantee the financial equality, the quality, the continuity, and the convenience of provided medical services. According to standard polices, the district's government appropriately guided qualified private hospitals to participate in the establishment of Fudan-Minhang medical alliance, giving such hospitals the allowed flexibility and maximizing the public welfares for involved medical institutions. Therefore, the public gets better medical services, while the development of medical resources is improved.

9.4.2.2 Expanding the Social Support and Sense of Identity

The publicity and influential support the government provided to the alliance ensured its continuous development. Firstly, the social media publicity of Fudan-Minhang medical alliance (through WeChat application and online and printed newspaper advertisement) led to an increased public awareness of the alliance and

its affiliated teams and members. That helped in guiding patients to choose the appropriate medical centers of different levels to seek care according to severity of the cases and changed the old habits of medical care seeking. Secondly, the publicity of affiliated doctors has been strengthened through developing various training activities and enhancing doctors' awareness and support of the hierarchical medical system, ensuring that affiliated doctors can accurately implement the standard procedures of referral system and provide patients with suitable effective care. Thirdly, the alliance held large-scale free clinic activities to guide patients' participation in the establishment and promotion of the alliance's work and help the public in realizing the value and benefits of the alliance to the community and its residents and realizing how the alliance practically tackled the well-known challenges of far-distant, expensive, and inconvenient medical care seeking, in order to strengthen the acceptance and rapport between the alliance and the public.

9.5 Challenges and Countermeasures

9.5.1 Challenges

9.5.1.1 The Existing Barriers Facing the Unification of Alliance's Resources Management

So far, the medical alliance has yet to overcome the personal, financial, and material management barriers in its operating mechanisms, which prevent its unified adjustments and operational management of internal resources (Zhang et al. 2020d). Several restrictions are still encountered when unification attempts of management and operations are practically carried out, since hospital management group is an unincorporated association. For example, since human resources management is part of the main hospital management, it is hard for specialists to adjust and share hospital resources with other assisting basic units and centers. In addition, the differences in insurance policies and protocols create differences between the services. Such differences are highly affected by the ranking of affiliated units, which translates into different medical insurance treatment within the alliance.

9.5.1.2 The Unfulfilled Intelligence in Combining the Internet with Medical Care

Establishing an informative network is the most effective method to achieve the alliance's goal of sharing. However, since major differences exist among the different information systems in the alliance, it is challenging to connect and integrate data of alliance's health service institutions, affecting the alliance's ability to share and exchange data and forming what can be called as "information islands" within the alliance. So far, the complicated information system patterns are still considered as a

huge obstacle against the communication of information (Chen et al. 2020). Regardless of the generous governmental funding, medical staff devotion, and investment, the public health information systems and electronic health records of patients are still left unconnected or shared due to the incomplete implementation. The available electronic medical data are not linked to electronic records which prevents the ability of online inquiry or standardization when needed.

9.5.1.3 The Lack of Enhanced Assessment System

The imperfect assessment mechanism of the alliance made it impossible to measure the efficacy of affiliated institutions. It cannot focus and compact the alliance's responsibilities (Yin 2019).

9.5.2 Active Countermeasures

9.5.2.1 The Further Enhancement of Medical Alliance's Internal Supporting Policies

Firstly, the alliance vigorously promotes the reformation of human resources management system, aiming to change the original model of unit-based management and establish a new model of district level of management. Such a model considers the district health community as a whole, by setting appropriate employment procedures and unifying training programs. That helps affiliated specialists to adopt to the multi-center work environment and the two-way procedures to enhance the flexibility and quality of community health services. Secondly, the alliance addresses the funding management of its affiliated centers by unifying and integrating the governmental funding and treating it as a funding for the alliance as a whole, rather than the original style of management where centers are funded separately (Lv et al. 2019). At the same time, the alliance may establish a performance-based support mechanism to distribute the governmental funding based on the ability and location of centers and help in controlling the challenge of major hospitals wasting resources on common diseases' treatment and consultation, by encouraging the referral of such cases to basic health centers. Thirdly, the alliance fully implements the financial supporting role of medical insurance, by enhancing the payment system and changing the payment style form "item-based" to "disease-based," which guarantees the quality of medical insurance and standardizes insurance styles of different affiliated centers. The unification of medical insurance and prices of medical service for similar diseases in different centers leads to the gradual decrease of healthcare cost in major hospitals and simultaneously promotes the referral of common diseases to basic centers, which gradually form a better order in medical care providing. At the same time, such changes will accelerate the promotion of the reformed "package-payment" style of insurance, which implements the style of "total

prepayment and balance retention," basing the package payment on the number of persons covered by the service contract, to strengthen the internal management of the alliance, control the cost, improve the operational efficacy, activate appropriate use of resources, and reduce morbidity (Gong et al. 2020).

9.5.2.2 The Thorough Development of the "interconnection + healthcare" Combination

The alliance emphasizes the importance of developing its information support system. Firstly, by using modern technologies, the alliance can establish its online medical care system, nursing service system, and remote healthcare service system. Such systems allow the alliance to remotely provide appropriate health services to the public even when local experts are unavailable. These basic approaches allow major hospitals to provide its services and help with the shortage of local qualified experts in basic regional centers. Secondly, the alliance focuses on establishing a functioning platform to assign family doctors and help them promote their services, improve their quality of service, and effectively use available referral channels, to form a stable service system that ensures the public welfare. Thirdly, the alliance improves its inquiry and standardization methods of electronic public health records, links public health databases to relevant records, and forms a comprehensive recording system and an effective management of public health data (Tang and Gong 2020).

9.5.2.3 The Deepening of Performance Assessment

The medical alliance mainly assesses the operation mechanisms of its centers, the conditions of cooperation and duty assignments, the regional implementation and sharing of resources, the role of technology radiation, the development sustaining ability, and the enhancement of public health conditions. The specialized unions and remote medical cooperation networks focus on assessing the performance of the lead unit's technology and the improvement of residents' health. The alliance assigns qualified specialists to customize the assessment mechanism. After the assessment is completed, the alliance provides the support needed to improve the efficacy of affiliated centers and staff, based on data of the different aspects of assessment, such as ward rotations, consultations, surgeries, and offered lectures (Cheng and Jiang 2019).

9.6 Future Development

9.6.1 Establishing a "Closer Medical Alliance"

Establishing strong medical alliances is a vital method to fulfill the goal of "healthy China." It broadens the road to develop enhanced medical services that effectively cover the country. Through strengthening the leading role of public hospitals, the Fudan-Minhang alliance will aim to improve the regional healthcare system, strengthen the management of chronic diseases, and tighten the bonds within the alliance and community. We aim to establish "one network, one platform, and five mega-centers" unified unit. The content of establishment is shown in Fig. 9.1. The alliance will actively advance the establishment and management of medical care, pharmacological services, information, insurance, human resources, financial funding, and performance of its centers to gradually achieve a hierarchical linked system, databases, and platforms that bring affiliated centers closer and form a unified unit with unified management mechanisms. Through planning the development of the alliance and improving its resource sharing ability, the alliance aims to form a tight strong unit that creates a novel model of cooperation and brings a new reform to regional medical communities.

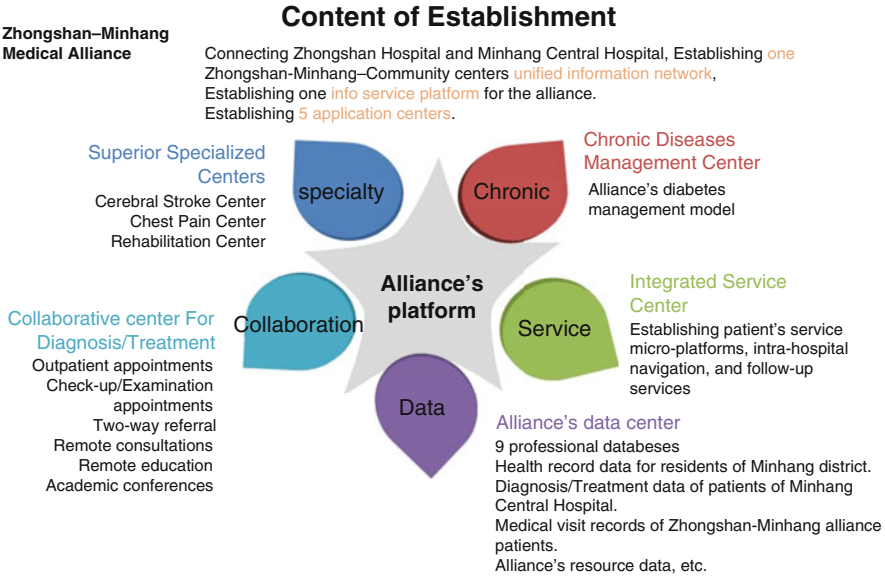

Fig. 9.1 The future construction contents in Zhongshan-Minhang medical alliance

9.6.2 Deepening the Establishment of Health Alliance

In 2018, the health committee of Minhang district and Fudan University's school of public health signed on the establishment of Fudan-Minhang health alliance, which focuses with its services on preventing major diseases, controlling chronic diseases, and promoting public health. By considering basic medical centers and health management centers as the main body, and depending on regional core medical institutions, the alliance will provide appropriate health management, information, and insurance technologies. It is going to create a brand new service model that combines treatment and prevention strategies, strengthens medical bases, and advances medical services efficacy. As a result, patients with chronic diseases will receive the needed medical care and monitoring services of professional experts without leaving their neighborhood. That will directly enhance the quality of patients' lives and medical seeking experiences. Figure 9.2 shows the establishment framework of health alliance. The alliance can also provide the district with regular health activities and lectures, to spread advanced health concepts and create an atmosphere where everyone in the community understands and focuses on health. That will gradually strengthen the public concept of how individuals are responsible for their own health and encourage the residents to adopt new behavioral and lifestyle based on healthy choices and knowledge. In other words, the alliance is going to establish a health management model that focuses on the individuals' role, social communication, social support, and governmental guidance. In addition, the alliance has established "Minhang branch of Fudan University's school of public health" to create a collaborative platform where the advanced expertise of Fudan University's school of public health can be used to offer specialists and members of Minhang public health community the required assistance and training programs in fields like epidemiology, health statistics, and health management. This active cooperation will advance the district's research and management ability of chronic non-communicable diseases, improve the establishment of district's healthcare system, and provide sufficient data to promote the research and practice of health service management. Such huge efforts are dedicated to create a national leading role of Minhang district in prevention and disease control and establish an innovation base of health management and emergency response.

9.6.3 Exploring the Establishment of Intelligent Health Alliance

Considering the new circumstances, the reformation of public health focuses on the importance of basic structures and the leading role of innovative reformation, prevention, integration of western and Chinese medicine, public sharing, and unification of health policies. Therefore, we actively explore the possibility of establishing an intelligent health alliance in the northern area of Minhang district,

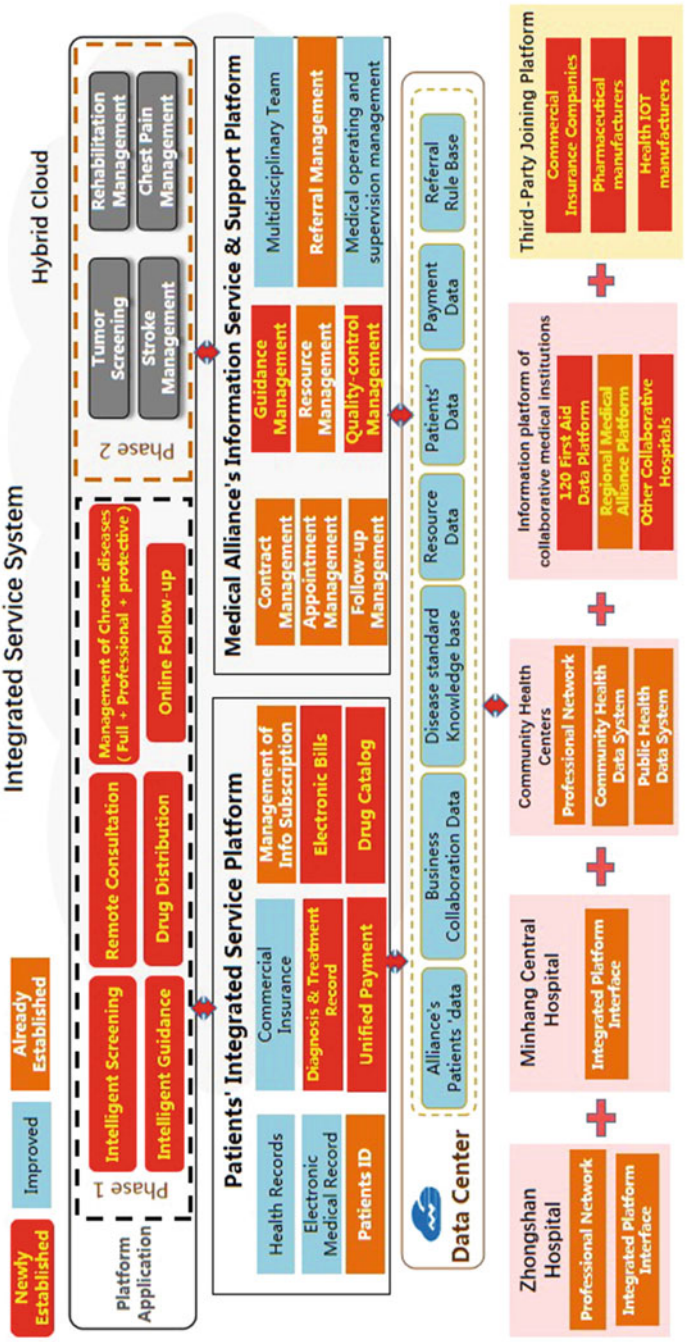

Fig. 9.2 The establishment framework of health alliance integrated service system

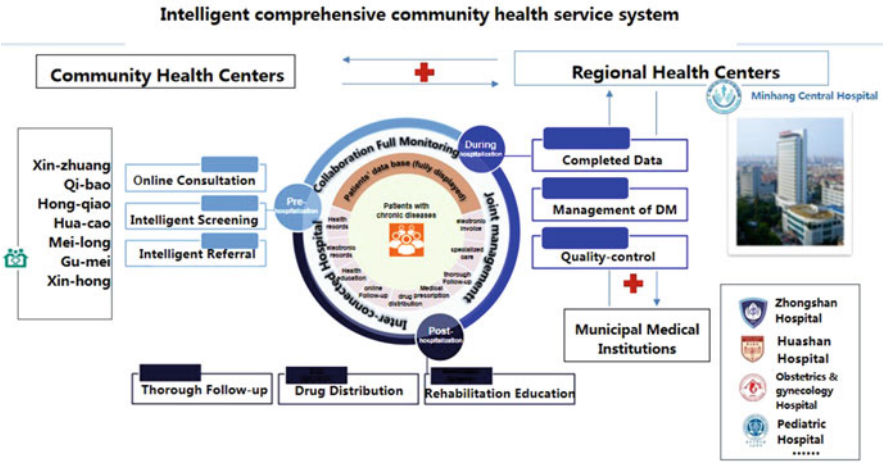

Fig. 9.3 Intelligent comprehensive community health service system

which is based on the basic medical structure and institutions. The service system is represented in Fig. 9.3. Under the guidance of district's government, an intelligent alliance will be formed with the central hospital of Minhang district serving as the backbone and seven other community health centers being affiliated. The alliance is going to create a reformed model of integrated medical and preventive services that focuses on the trinity of disease prevention, precise treatment, and health promotion. The alliance focuses on preserving each center's legal personal status, legal position, public welfare, organization function, property right relationship, and staff identity. At the same time, central hospital of Minhang district will be endowed with the power of business decision-making, staff allocation, right of assets, and financial management of the alliance. The alliance also tries to reform the systems of medical insurance payment and staff salary payment, to integrate the central management of community healthcare services. In order to strengthen the use of talents and resources, and improve the basic service ability and public satisfaction, the alliance will focus on resource sharing and forming a community of services, responsibilities, interests, and management. The implementation of 5G technology also will help in establishing an enhanced health information platform and a digital intelligent health alliance that can improve the efficacy and quality of services and resources. The alliance always expands the scope of intelligent convenient medical services and further explores the ability to form a complete, convenient, efficient, and intelligent medical system with a practical interactive management model. The alliance's aim is to achieve "strong system and strong service." It will also increase the level of public health and satisfaction through the continuous improvement of medical resources distribution in the district and the enhancement of staff flow and basic institutions' ability. That will implement an appropriate standardized order in medical care system. It is going to improve the regional management and focus on important

concepts such as first treatment in community, dual referral, treatment classification, and effective coordination at different levels.

In the future, the Fudan-Minhang medical alliance will focus on developing a healthcare system that considers the medical, educational, and research aspects of healthcare services. Through strengthening regional medical management and enhancing service quality and ability, the alliance will provide a vital contribution that can reform and strengthen the medical and health system.

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Chapter 10
Bed-Occupancy Management and Hospital Planning: A Handbook

Smaranda Belciug

Abstract When dealing with bed-occupancy management and hospital planning, one must take into account many factors, whether we are discussing diseases, patients' characteristics, cultural background, budget, local and national political considerations, etc. Daily, hospital managers are faced with decision-making processes, having to find the correct balance between all of the abovementioned aspects. The aim of this chapter is to provide scientifically valid models of healthcare planning that can be applied cross-national.

Keywords Bed-occupancy management · Length of stay · Indifference curves · Genetic algorithms · Artificial immune systems

10.1 Introduction

Decisions in the healthcare planning system must not be left to chance. Efficient and effective services can be developed using intelligent decision systems that take into account different socio-cultural-political factors as well as scientific facts. Intelligent patient management started ever since "the Lady with the Lamp" or "Angel of Crimea," Florence Nightingale, used statistics and common sense to manage the disaster that was happening during the Crimean war at the Selimiye Barracks. After Nightingale's ideas were put into practice, the death rate dropped from 60% to 42%, reaching in the end a rate of 2.2%. Ever since, data regarding common statistics started being collected in hospitals (White 1977).

With the healthcare costs on the rise, executives are faced with all sorts of decisions in order to reduce these expenditures and improve the system. Having to deal with massive amount of data makes this task overwhelming. One step in resolving these issues is forecasting the patients' length of stay (LOS) in the hospital. Even if all the patients that present themselves in the emergency room (E.R.) have

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their own personal medical background, social, cultural, and financial status, they all have one thing in common: if they need to be admitted, they will occupy a bed in a hospital department. Once this happens, a multitude of mechanisms are put in motion from the physician who examines the patient to the nurses that start prepping her/him for the stay; from the social workers that collect data regarding financial and/or social support to the bed managers that verify the available beds; etc. (Millard 1996).

Two possible, yet undesirable, situations may appear: an under-provision of hospital beds or an over-provision of hospital beds. In the first case, an executive can choose one from the following alternatives: (a) postpone the service until beds are available and the service can be postponed, situation in which waiting lists are definitely needed; (b) refer patients to another hospital; or (c) spill the patients into other departments, if and only if that is possible. No matter the decision, the hospital will get a bad reputation, which will lead to money loss. The latter case leads again to a waste of money. The over-provision refers to all the hospital resources such as beds, linen, different machines that are not used, and medical staff. The cost of maintenance is high, even if they are not used.

LOS does not mean only the time spent to diagnose and treat a patient. LOS means rehabilitation also. One may never know how a certain patient's rehabilitation might progress: the process might be smooth, implying a fast recovery, it can be slow and steady, or it can be a fast recovery followed by a fallback. The rehabilitation process consists in many milestones such as breathing on her/his own, eating by themselves, walking, moving a limb, etc. These milestones are taken into consideration when we are trying to forecast the LOS of a patient (Belciug and Gorunescu 2020).

When a patient is discharged, many other aspects should be considered. Rushing into discharging a patient, so that more beds are available, can lead to other unpredicted costs. Before discharging a person, the hospital should take into account the existent support system of that person: Does she/he have a support network? Does she/he have a caregiver? Does that area have available nursing homes, residential homes, home help, meals on wheels, etc.? If not, what are the odds of that person returning to the hospital in a worse condition? Are the costs higher if we discharge fast and they return or if we play it safe and let the patients stay longer in the hospital?

To resolve these issues, data scientists develop new modeling techniques and simulate different situations so that they can predict and somehow control the real system without actually experimenting on it (McClean 1994).

The goal of this chapter is to show how classical queuing models can be used to optimize bed allocation and improve patient care, as well as how they can be transformed by cross-fertilizing them using to different artificial intelligence (AI) techniques.

10.2 Queuing Theory

Queuing theory is mostly used in industry: banks, customs, supermarkets, pharmacies, fast foods, etc. Obviously, if one is not satisfied with the service time, she/he simply goes elsewhere. One question arises: can classical queuing models be applied when it comes to healthcare? If hospital beds are fully occupied, the patient has no other option but to wait: wait at home, wait in the E.R., etc.

A way to plan healthcare using queuing theory is to use *compartmental models*. For example, such a model can be divided into three "compartments": short or acute, medium or rehabilitation, or long stay. In literature, we find different compartmental models. For instance, a two-compartment discrete-time deterministic model that described the geriatric patients flow was developed in Harrison and Millard (1991) and applied in Millard (1988). Irvine et al. (1994) proposed a continuous-time stochastic analogue extension of the above model, whereas (Taylor et al. 1998) developed a four-compartment discrete-time deterministic model, and (Taylor et al. 2000) proposed a five- and six-compartment model. Cochran et al. (2009) developed a queuing approach based on non-homogeneous arrival patterns, multiple patient types with spreadsheet implementations, and non-exponential service time distribution, whereas (Bruin et al. 2010) presented a decision support system that was based on the Erlang loss model and evaluated the nursing units' size.

In what follows, we shall discuss a M/PH/c queuing model that was introduced by Gorunescu et al. (2002) and was used for optimizing hospital resources both in a loss model and also in an extended model which provided an extra waiting room. The model was applied for a geriatric ward. The M/PH/c queue denotes a system in which the arrivals (M) are Poisson (Markov), the service distribution is phase type (PH), and the number of servers, in our case beds, is c (Cooper 1972; Tijms 1986). In this type of model, no queue is allowed, implying the fact that if a patient arrives and finds out that all the beds c are occupied, then she/he is lost to the system. In real life, the patient is sent home, or she/he waits in the E.R. until a bed becomes available. Recall that the arrivals are Poisson, with rate λ, whereas the service time is phase type. Then the probability density function is given by:

$$f(t) = \sum_{i=1}^{k} \alpha_i \rho_i e^{-\alpha_i t}$$

where $\sum_{i=1}^{k} \rho_i = 1$ and the corresponding mean is $\tau = \sum_{i=1}^{k} \frac{\rho_i}{\alpha_i}$. Using likelihood ratio tests, we can determine the number of compartments (phases), the mixing proportions α_is, and the transition rates ρ_is (Faddy 1994; Cox 1962). During a time interval t, we have an average number of arrivals, λt. The offered load, the average number a of arrivals during an average length of stay τ, is $a = \lambda\tau$. Hence, if we have j beds in our ward, the probability of them being occupied is:

$$p_j = \frac{a^j/j!}{\sum_{k=0}^{c} a^k/k!}.$$

Thus, the probability that all the c beds from a certain ward are occupied is computed using the *Erlang loss* formula:

$$B(c,a) = \frac{a^c/c!}{\sum_{k=0}^{c} a^k/k!}.$$

One way of approximating $B(c,a)$ is if we use the normal approximation of the Poisson distribution. Let us denote the normal probability function by $\Phi(x)$. Thus, if we presume that the offered load, $\lambda\tau$, is not too small, then we have:

$$\sum_{j=c}^{\infty} \frac{(\lambda\tau)^j}{j!} e^{-\lambda\tau} \approx 1 - \Phi\left(\frac{c - \lambda\tau - 0.5}{\sqrt{\lambda\tau}}\right).$$

Another parameter that we are interested in is the *carried load*, the mean number of occupied beds, which is computed using the following formula:

$$a' = a[1 - B(c,a)].$$

If we multiply the average length of stay of a patient in the geriatric ward by the probability of her/him being admitted, we obtain the average time spent in the facility by a patient:

$$W = \tau[1 - B(c,a)].$$

The bed occupancy is defined by:

$$\rho = \frac{a'}{c},$$

having $\rho \leq 1$, so that the system is in steady state.

10.3 Optimization of the Number of Beds

10.3.1 Indifference Curves

In the process of optimizing the number of beds, we are faced with the following dilemma: how can we minimize the number of beds and also keep to the minimum

the delay probability? Hence, we need to find the inverse function that takes as parameter the delay probability $B(c, a)$ and returns the c value. Let us suppose that we predefine the value of the delay probability to v, which is the highest proportion of refused patients that the system can tolerate. Our goal is to determine c_0, the smallest value of c, that verifies:

$$B(c, a) = \frac{a^c/c!}{\sum_{k=0}^{c} (a^k/k!)} \geq 1 - \quad v.$$

To determine this trade-off, Gorunescu et al. adapted the base-stock policy, which is basically used in inventory theory (Harrison and Millard 1991; Stevenson 1996). The authors assumed that the total number of beds in the geriatric compartment is c, that is, the sum of occupied plus idle beds. Making a parallel to the base-stock policy, we can say that the idle beds are on-hand inventory, whereas the occupied beds are unfilled orders. Continuing with the parallel, we consider the arrival of a patient a demand, the length of stay the waiting time for replenishment, and the turned away patients the unsatisfied demands.

The related costs are as follows: the *holding cost* per day per empty bed, $h > 0$; the fixed *penalty cost* for each patient that has been turned away, $\pi > 0$; and the profit per patient per day, $p > 0$. The total cost is computed as the sum of the treatment, holding costs, profit, and penalty costs. In Gorunescu et al. (2002), the authors studied the situation where the treatment is paid directly by the health service purchaser, insurance company, or patient, while the penalty and holding costs are paid by the service provider. Hence, the number of beds c is given by a function of the λ, τ, h, π, and p parameters. Using all the above-presented formulas, we can compute the average service provider income per day with c number of beds using the formula:

$$r(c) = -\pi\lambda B(c, a) - h\{c - a[1 - B(c, a)]\} + pa[1 - B(c, a)].$$

The optimal trade-off between the number of empty beds and the number of delayed patients is obtained by maximizing $r(c)$ in order to find c. If we apply the model to a public health service, then we have $p = 0$, making the ratio $\frac{\pi}{h}$ the factor that determines the optimum. To minimize the cost, or maximize the revenue, we need to optimize the following function that gives the average cost per day:

$$g(c) = \pi\lambda B(c, a) + h\{c - a[1 - B(c, a)]\}.$$

The optimization process is sensitive to the changes in the arrival rate and also of the length of stay. The average cost per day $g(c)$ might not be influenced so much by the value of c; hence, determining the holding costs, penalty costs, and profit might be difficult. The authors used the *indifference curves* to solve these issues (Silver and Smith 1977). Mathematically speaking, using the indifference curves gives us the

possibility to determine in which conditions we care be indifferent between neighboring values of c, i.e., $g(c) = g\ (c + 1)$. Hence, we can say that the equation is the same as:

$$\lambda\tau\{B(c, \lambda\tau) - B(c + 1, \lambda\tau)\} = \left(1 + \frac{\pi}{h\tau}\right)^{-1}.$$

Technically, we can see that the optimization process depends strictly on the choice of the values of the parameters $\lambda\tau$ and $\pi/h\tau$. We can evaluate the indifference curves for a specific value of c, by plotting in a two-dimensional graph the parameters (Cox 1962). If by using different values of c we see that the difference curves are close together, we can state that we are indifferent to the choice of the value for π/h. Hence, if the penalty cost π is hard to be determined, this is not a concern since the optimal number of beds is not dependent on the ratio that includes it.

This model was applied successfully on bed occupancy data which had been collected from the Department of Geriatric Medicine of St. George's Hospital, London (Vinicchayakul 2000). The use of this methodology and this optimization method lets the hospital manager estimate the probability of lost demands and the bed occupancy. By using it, the optimal trade-off between optimal bed number and an acceptable level of patient rejection can be computed.

10.3.2 Evolutionary Computation Approach

In this section, we shall present another method for optimizing bed allocation and other resources that concern patient management. In conjunction with the queuing system, we shall describe a compartmental model that emphasizes a hospital department. The optimizing method used is the evolutionary paradigm (Belciug and Gorunescu 2015).

Recall that the theoretical queuing model is the M/PH/c. We are interested in three parameters for this model:

- $L = a \cdot [1 - B(c, a)]$ is the average number of patients in the hospital department (*Little's formula*).
- $W = \tau \cdot [1 - B(c, a)]$ is the average time spent by a patient in hospital.
- $\rho = \frac{L}{c}$ is the bed occupancy.

Different from the goal presented in the previous section, here the authors were interested in estimating three parameters c, λ, and τ, so that they can optimize the delay probability $B(c, a)$, the average time spent in hospital, as well as the average number of patients admitted in hospital. Besides them, the holding cost per empty bed per day, h, and the penalty cost for each turned away patient, π, are considered as input parameters for the cost function, g. In the study, there has been used the two-compartmental model depicted in Fig. 10.1.

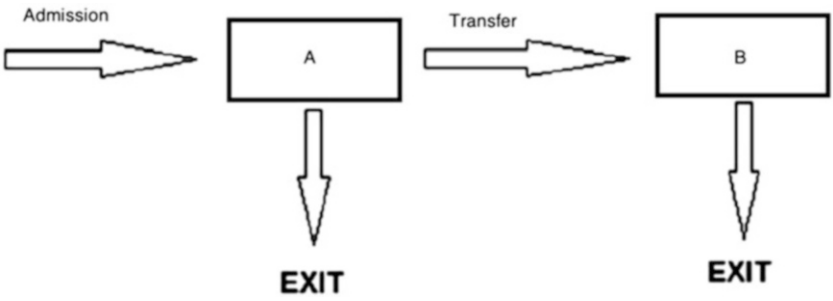

Fig. 10.1 Two-compartment model for patient flow

In the previous section, we have seen how indifference curves can be used to optimize the resource allocation. In this section, we are going to present another approach that uses evolutionary computation for the optimization process. The authors chose genetic algorithms (GAs) to estimate the cost function, $g(c)$, as well as the delay probability $B(c, a)$.

GA usage increased during the last two decades. GAs use different bio-inspired operators (e.g., selection, recombination, and mutation) to find optimal solutions to certain problems. Mimicking Darwin's natural selection process, GAs start with a *population*, which consists of randomly generated individuals, named *chromosomes*. Each chromosome is considered to be a candidate solution for our optimization problem. To create a chromosome, we use a certain number of genes that model the function that we need to maximize/minimize. The genes can be binary, integer, or real-coded.

The function that we need to optimize is called the *fitness function*, $f(x_i)$, $i = 1, 2, \ldots, n$, where n is the number of candidate solutions—number of chromosomes in the population. Technically, by using the fitness function, we simulate a competition between the chromosomes, to measure their adaptability to the environment. The best chromosomes are selected for reproduction in order to form the next generation of candidate solutions.

An important concept of GA is represented by the overall performance of a population, which is the sum of the fitness value of each chromosome:

$$F = \sum_{i=1}^{n} f(x_i).$$

In what follows, we shall discuss the three abovementioned GA operators. We start with the *selection*, which is used for parent selection in the recombination phase, as well as for the replenishing of the population. Depending on the problem at hand, we can use one of the following types of selection for the recombination phase:

1. The *fitness proportionate selection* or the *roulette wheel selection* computes the probability of a chromosome to be selected, taking into account the fact that this probability is proportionate to its fitness. The following equation is used:

$$P(i) = \frac{f(i)}{\sum_{j=1}^{n} f(j)}.$$

2. The *ranking selection* computes the rank of a chromosome and selects in hierarchical order, from the highest rank to the lowest, the ones that will be chosen. By computing the fitness score, we assign each chromosome a certain rank. The probability of a chromosome to be selected is computed using the following equation:

$$P(i) = \frac{rank(i)}{n \cdot (n-1)}.$$

3. The *exponential rank selection* can be thought of as a variant of the rank selection, the only difference being the fact that the chromosomes are weighted exponentially. In computing the probability of a chromosome to be selected, we use a parameter, c, for the base of the exponent, $0 < c < 1$.

$$P(i) = \frac{c^{N-i}}{\sum_{j=1}^{N} c^{N-j}}.$$

4. The most used type of selection is the *tournament selection*, which simulates a competition between k chromosomes. For each chromosome, we compute the fitness score, and afterward, we compare them. The chromosomes that obtain the best fitness score are chosen. The probability is computed as follows:

$$P(i) = \begin{cases} \frac{C_{n-1}^{k-1}}{C_n^k}, \text{if } i \in [1, n-k-1], \\ 0, \text{if } i \in [n-k, n]. \end{cases}$$

We refer the reader for more details to Blickle and Thiele (1995), Jebari and Madiafi (2013), Belciug (2020).

In what regards the selection for the replenishment of the population, either we can use the selection types presented above, which are fitness based, or we can use the *age-based selection*. In the latter, the chromosomes survive upon their age.

The *recombination* operator uses a *recombination probability*, $p_c \in [0, 1]$, to obtain new offspring. Technically, for each pair of parents, we generate a number between 0 and 1. Depending on the p_c's value, either the recombination can be asexual (random number $> p_c$), technically the parents being cloned, or the process

of recombination can actually start (random number $< p_c$). In general, the recombination scheme is applied for $p = q = 2$.

There are several types of recombination, all of them taking into account the chromosome's representation. For instance, if we are dealing with the binary or integer representation schemes, we can use the one-point recombination, *n*-point recombination, or the uniform one; as for the real-coded representation, besides the abovementioned processes, we can also use the simple arithmetic recombination, the single arithmetic recombination, the total arithmetic recombination, the blend crossover, the linear BGA crossover, or Wright's heuristic crossover (Eiben and Smith 2015; Eiben 2003).

Mutation is the last GA operator. Just like in the case of the recombination process, the mutation uses a parameter named the *mutation probability*. This parameter establishes whether the original chromosome will have all, a part, or none of its gene mutated. Taking into account the chromosome's representation, we may have the following mutation types: the binary representation implies a bitwise mutation, the integer representation implies either a random setting or a creep mutation, and the real-coded representation implies either a uniform mutation or a normally distributed mutation.

The GA algorithm has the following steps:

(*Step 1*)—encode the data in one-dimensional arrays and set the recombination and mutation probabilities.
(*Step 2*)—evaluate each chromosome using the appropriate fitness function.
(*Step 3*)—apply the selection, recombination, and mutation operators.
(*Step 4*)—replace the current population with the new one.
(*Step 5*)—use a certain termination criterion and end the GA algorithm.

In Belciug and Gorunescu (2015), the authors chose a population of 100 chromosomes, the total arithmetic recombination with parameter $\alpha = 0.3$ and recombination probability of 0.35, and the normally distributed mutation with a mutation probability of 0.4. This GA approach was successfully applied on data from different medical departments: geriatric (collected from the Department of Geriatric Medicine—St. George's Hospital, London) (Millard et al. 2009), surgical (collected from the American Hospital Association (AHA) Annual Survey of Hospitals—http://www.cdc.gov/nchs/data/hus/2010/104.pdf), neuro (collected from the United Kingdom's Hospital Episode Statistics (HES)) (Vasilakis and Marshal 2005; Vasilakis et al. 2008), and mental health (collected from the Center for Mental Health Policy and Services Research (CMHPSR), Department of Psychiatry, School of Medicine, University of Pennsylvania (Medicaid)) (Koizumi et al. 2005).

10.3.3 Artificial Immune System Approach

In this subsection, we shall discuss another bio-inspired algorithm—artificial immune systems (AIS) – that has been applied successfully in optimizing the bed

occupancy and resource management in pandemics. Again, the task at hand was to estimate $B(c, a)$ and to minimize the cost function $g(c)$ (Belciug et al. 2020).

AIS algorithms are split into three types: clonal selection, negative selection, and immune network algorithms. The abovementioned paper explored the clonal selection algorithm, which was first introduced by Burnet (1957, 1959). AIS are quite similar with GAs. AIS start by generating a population of antibodies that changes over time in response to a certain antigen. Just as in the GA case, where we consider chromosomes as potential solutions to a problem, in the AIS, we consider the antibodies as the potential candidates. In the selection process, we compute the affinity of each antibody toward an antigen, represented by the problem at hand.

Besides the population of antibodies, we also deal with a population of clones. The clone population is made out of the clones of the best antibodies, established based on their affinity. After the cloning process is done, a mutation process comes up, followed by a replenishing process, in order to get out of the local optima. The paper uses the following AIS algorithm:

(*Step 0*)—generate a random population of antibodies; repeat the following steps until termination criterion is reached.
(*Step 1*)—compute the affinity of each antibody toward the antigen, and select the best ones.
(*Step 2*)—clone the selected antibodies proportionally to their computed affinity.
(*Step 3*)—hypermutate the clones inverse proportional to their affinities.
(*Step 4*)—select population for next generation.
(*Step 5*)—replenish the population, replacing the low-affinity antibodies with new randomly generated ones.

This approach was successfully applied on data regarding the COVID-19 patients in Italy. The inventory policy used official data from the Italian Ministry of Health (https://pselab.chem.polimi.it/bollenttino-pandemia-covid-19/—accessed August, 27, 2020) and from the European Society of Anaesthesiology and Intensive Care (https://www.esahq.org/esa-news/dynamics-of-icu-patients-and-deaths-in-italy-and-lombardy-due-to-covid-19-analysis-updated-to-30-march-day-38-evening/—accessed August, 27, 2020). The compartment model had two parts: sub-ICU and ICU.

10.4 Conclusions and Future Outlook

In this chapter, we have explored three ways of optimizing bed occupancy and hospital resources, indifference curves, genetic algorithms, and artificial immune systems, all of which were combined with operations research. Our goal was to provide an overview for the healthcare professionals of different intelligent decision systems that can be used in choosing different policies in order to improve healthcare management. Future research's goal should be to explore new mergers between

artificial intelligence algorithms and operations research, in order to develop more efficient tools for hospital administrators.

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Chapter 11
Management of Next-Generation Sequencing in Precision Medicine

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Abstract Next-generation sequencing (NGS) has transformed DNA sequencing in terms of speed and data volume, rendering genomics affordable and achievable by individual laboratories rather than big science that was once managed by international consortiums. In parallel, it is propelling contemporary healthcare into the age of precision medicine, whereby genetic variability of an individual is incorporated into the formulation of a bespoke treatment plan. However, due to the complexity of NGS workflow and the large volume of both NGS and phenotypic data, management of the NGS "big data" in precision medicine has been challenging. This chapter mainly discusses these challenges and their solutions from several perspectives, including (i) sample logistics; (ii) electronic health records; (iii) sequencing procedures; (iv) bioinformatics analysis; (v) interpretation and delivery of results; (vi) the storage and reanalysis of NGS data; and (vii) the laboratory information management system (LIMS) as an overall management suite. Finally, we outline several current developments including artificial intelligence (AI), Internet of Things (IoT), wearable technologies, and 5G communication. Presumably, these technologies are capable of bringing impacts to precision medicine in terms of the range of phenotypic data, which can be acquired continuously and transferred with enhanced connectivity and speed and in real time.

Keywords Big data · Data management · LIMS · Personalized medicine

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11.1 Introduction

Precision medicine (PM) is an emerging paradigm in contemporary healthcare. In comparison to how medicine is currently practiced, PM takes into account the variability of an individual such as one's genetics, lifestyle, and environment prior to formulating and customizing a treatment plan so as to provide a precisely tailor-made therapy to each patient. Consequently, PM allows accurate predictions of disease susceptibility, diagnosis, and prognosis and has been touted as the only way forward for optimizing patient care (Roberts and Julius 2016). One major driving force behind PM is next-generation sequencing (NGS) which offers multiple advantages over the past generations of DNA sequencing technologies (Morash et al. 2018; Gonzalez-Garay 2014). For example, NGS (i) is highly sensitive; (ii) allows simultaneous sequencing of millions of genetic fragments at a high coverage and depth; (iii) requires only a low input of starting material; and (iv) is capable of detecting chromosomal aberrations, copy number variations, and novel low-frequency genetic variants.

Owing to the strength of NGS, several high-profile genomic initiatives have employed NGS for cataloging molecular variations in human diseases (Table 11.1). One example is The Cancer Genome Atlas (TCGA), which has profiled the molecular landscape of 33 tumor types derived from over 11,000 patients (Blum et al. 2018). TCGA data have contributed meaningfully to precision oncology. For instance, based on the molecular profiles, gliomas can now be classified into distinct subtypes, namely, those with IDH/t(1p;19q)/TERT alterations; IDH/TERT mutations; IDH mutations only; TERT mutations only; or triple-negative gliomas (Eckel-Passow et al. 2015). Similarly, gastric cancer can be categorized into four or five different subtypes (depending on the classification system used), including a microsatellite unstable subtype and an Epstein-Barr virus (EBV)-positive subtype (Bass et al. 2014; Setia et al. 2016). Besides tumor classification, NGS data generated from TCGA also revealed several actionable mutations and gene fusions in several subtypes of cancer, which may provide insights for targeted therapies (Gao et al. 2018; Grabiner et al. 2014; Wagle et al. 2014).

Another PM initiative enabled by NGS is the Human Microbiome Project (HMP). The first phase of the HMP established the baseline taxonomic and strain-specific compositions of the microbiome within and between body sites, whereas the second phase characterized the dynamic changes in microbiome and host profiles during pregnancy and preterm birth; the onset of inflammatory bowel diseases; and the onset of type 2 diabetes (Sinha et al. 2015; The Integrative Human Microbiome Project 2019; Proctor et al. 2019; The Integrative HMP (iHMP) Research Network Consortium 2014). HMP data improve our understanding of host-microbiome interactions and their underlying mechanisms. As the roles of host-microbiome interactions become more apparent, NGS data from the HMP can be tapped to facilitate the development of precision diagnostics and therapeutics (ElRakaiby et al. 2014; Doestzada et al. 2018).

Table 11.1 Examples of high-profile genomic initiatives which employed NGS for molecular profiling

Initiative	Launch year	Goal
The Cancer Genome Atlas (TCGA)	2005	To catalog and discover major cancer-causing genomic alterations through large-scale genome sequencing and integrated multi-dimensional analyses
Human Microbiome Project	2007	To characterize the human microbiome and analyze its role in human health and disease
Encyclopedia of DNA Elements Consortium (ENCODE)	2003	To identify all functional elements in the human and mouse genomes, including elements that act at the protein and RNA levels, and regulatory elements that control cells and circumstances in which a gene is active
1000 Genomes Project	2008	To identify genetic variants with frequencies of at least 1% in the populations studied
100,000 Genomes Project	2012	To sequence 100,000 genomes from around 85,000 UK National Health Service (NHS) patients affected by rare diseases, cancers, and infectious diseases
1+ Million Genomes Initiative	2018	To sequence at least one million genomes in the European Union for improving disease prevention, allowing for more personalized treatments, and providing a sufficient scale for new clinically impactful research
All of Us Research Program	2015 (enrollment started 2018)	To collect genetic and health data from one million volunteers to accelerate health research and medical breakthroughs, enabling individualized prevention, treatment, and care

Several other large-scale projects have also exploited NGS for decoding the genome, epigenome, transcriptome, regulome, and interactome of the study participants. These efforts include the Encyclopedia of DNA Elements Consortium (ENCODE) project (Dunham et al. 2012), the 1000 Genomes Project (Auton et al. 2015; Sudmant et al. 2015), and more recently the 100,000 Genomes Project of the United Kingdom (Peplow 2016; Turnbull et al. 2018), the 1+ Million Genomes Initiative of the Europe (Saunders et al. 2019), and the All of Us Research Program of the United States (US) (Sankar and Parker 2017). Many smaller-scale studies also utilized NGS for identifying molecular biomarkers that can improve precision diagnostics and prognostication (Alonso et al. 2019; Zacher et al. 2017; Acha et al. 2019; Na et al. 2019; Oberg et al. 2016; Volckmar et al. 2019; Dubbink et al. 2016). The widespread use of NGS in these projects highlights its potential in accelerating PM. Nevertheless, the large volume of data generated by NGS poses a challenge in its management. In this chapter, we first describe the general workflow of NGS and its challenges and further discuss the use of laboratory information management system (LIMS) in managing NGS.

11.2 Workflow of Next-Generation Sequencing Experiments

Genome-scale PM projects that incorporate NGS workflows are often complicated, consisting of multiple steps that require multidisciplinary expertise. Due to such complexity, the success of such projects relies heavily on excellent management and logistics of samples, NGS data, patients' records, and other ancillary data. In the following, we discuss the current practice of NGS data management, paying particular attention to the following aspects: (i) the management of sample logistics; (ii) archiving and retrieval of patients' electronic medical records; (iii) the sequencing procedures; (iv) bioinformatics analysis; (v) the interpretation and delivery of results; (vi) the storage and reanalysis of archived NGS data; and (vii) the laboratory information management system (LIMS) to enable seamless and overall connection and coordination for NGS samples, workflows, and data.

11.2.1 Sample Acquisition and Management

Managing sample logistics is the very first step of NGS-based projects. Once a patient has provided informed consent to a PM regimen, the next crucial step is to ensure acquisition of high-quality sample(s) from patients. To do this, there must be stringent quality control in the collection, temporary and long-term storage, as well as processing of samples (Moore et al. 2011). As such, prior to sample collection, patients should have undergone consultation and counseling by clinicians and genetic counselors; have agreed to various terms and conditions of the diagnosis/treatment workflow; and have been briefed about the sample collection process. While all patient- and sample-related information should be documented, personal identifiers should strictly be kept confidential. Depending on the nature of investigations, biospecimens, such as blood, saliva, buccal swabs, urine, and stool, will be acquired from the patients (Basik et al. 2013; Woo and Lu 2019; van Noord 2003; Malsagova et al. 2020). Drawing of blood requires the assistance of a qualified phlebotomist, while acquisition of buccal swabs, urine, and stool may be performed by the patients themselves. Some tissues, such as tumor tissues or endoscopic swabs, can only be obtained with the help of clinicians in hospitals. Care must be taken by all process operators to minimize the contamination of samples with other sources of nucleic acid.

Once obtained, biospecimens should be kept at temperatures optimal for nucleic acid extraction. A transport temperature of 4 °C is deemed optimal for delivery of samples for nucleic acid extraction; nevertheless, delivery at 25 °C or below for samples such as buccal swabs may be accepted, if cold chain is not available. Nucleic acids extracted from the biospecimens should be kept at −20 °C until NGS is performed. Indeed, best practices and standardization for quality control of biospecimens prior to analytical process have been developed by various

organizations, including the Clinical and Laboratory Standards Institute (CLSI) Standards, the National Cancer Institute (NCI) Best Practices (NCI Best Practices for Biospecimen Resources 2016), and the College of American Pathologists (CAP) Guidelines (Stumptner et al. 2019). In addition, laboratories involved in the NGS workflow should ideally be accredited with ISO 15189:2012 (Medical Laboratories – Requirements for Quality and Competence) (Gutowska-Ding et al. 2020).

Biobanking of samples plays an important role in PM research. Therefore, patients may choose to bank their samples or nucleic acids for follow-up/future investigation. It is also imperative that biobanks adopt clearly defined guidelines on the ownership, usage, and disposal or destruction of patient samples to ensure high quality of archived samples for future usage (Malsagova et al. 2020; Ollier et al. 2005; Nagai et al. 2017; Langhof et al. 2018).

11.2.2 Medical and Health Informatics

The Health Information System (HIS) is an indispensable component of contemporary healthcare management. Notably, many healthcare providers have implemented electronic health records (EHRs) for sharing and managing clinical data according to predetermined standards and classifications (Kho et al. 2013). Such data categories encompass billing information, time of visitation, clinical symptoms and interpretations, prescription, laboratory test results, and other patient-linked data (Jensen et al. 2012). Hence, EHRs customarily adopt a structured format, comprising unchanged administrative data such as demographic details and updatable particulars such as disease diagnoses and treatment procedures (Wu et al. 2017). EHRs may also contain unstructured data. For instance, patients' clinical conditions can be described in free-text clinical notes to supplement existing structured data; and therefore natural language processing (NLP) capability has been incorporated in newer EHR systems (Nadkarni et al. 2011). A non-exhaustive list of EHR software in the market and their features is shown in Table 11.2.

In 2015, the US Precision Medicine Initiative proposed to incorporate omics data into EHRs (Wu et al. 2017; Collins and Varmus 2015). Such a link extends the roles of EHRs to medical research, whereby clinical information and healthcare-related biological products can be used to supplement genetic investigation of diseases at both individual and population-wide levels and to drive large cohort studies (Kho et al. 2013; Kohane 2011). Vice versa, omics modalities, such as NGS data, together with EHRs can be exploited for the study of healthcare efficiency and safety across the population (Wu et al. 2017). Technically, EHR-driven genomic research (EDGR) is an emerging area that employs a combination of structured, codified, and narrative texts to describe phenotyping, sample selection, and acquisition. Alternatively, clinical characterization can be applied as an addition to fill in missing details of collected samples as a form of phenotypic augmentation (Kohane 2011). Indeed, NGS data has assisted the development of drugs targeting tumor-driving mutations (Morash et al. 2018). Besides, by linking biorepositories to clinical data,

Table 11.2 A list of electronic health records (EHR) software in the market and their features

No.	Vendor name	Product name	Features
1.	Varian Medical Systems	ARIA® Oncology Information System	• Cloud-based and on premise • Support clinical workflow and document management • No insurance and claim information • No lab integration • Demographics and portal of patients • Reporting and analytics
2.	Elation Health	Elation HER	• Cloud-based only • Support clinical workflow and document management • No insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
3.	Allscripts	TouchWorks HER	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
4.	Epic	Epic HER	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
5.	eClinicalWorks	eClinicalWorks 10e	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, portal, and referrals of patients • Reporting and analytics
6.	GE Healthcare	Centricity EMR	• Cloud-based only • Support clinical workflow and but not document management • No insurance and claim information • Lab integration • Demographics and history of

(continued)

Table 11.2 (continued)

No.	Vendor name	Product name	Features
			patients • Reporting and analytics
7.	Flatiron	OncologyCloud	• Cloud-based only • Support clinical workflow and document management • No insurance and claim information • No lab integration • Demographics, history, and portal of patients • Reporting and analytics
8.	ChartLogic	ChartLogic EHR	• Cloud-based and on premise • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
9.	Bizmatics	PrognoCIS	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
10.	AdvancedMD	AdvancedEHR	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
11.	CureMD	All in One EHR	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
12.	RXNT	RXNT EHR	• Cloud-based only • Support clinical workflow and document management

(continued)

Table 11.2 (continued)

No.	Vendor name	Product name	Features
			• Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
13.	MDVision	MDVision EMR	• Cloud-based and on premise • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics
14.	Kareo	Kareo Clinical	• Cloud-based only • Support clinical workflow and document management • Contains insurance and claim information • Lab integration • Demographics, history, portal, and referrals of patients • Reporting and analytics

more sophisticated and personalized disease management can be followed through by clinician-scientists. Furthermore, the information on family history and genetic testing can also help to support and educate clinicians in adopting evidence-based strategies in clinical care and decision support (Scheuner et al. 2009). By referring to sequencing results to identify a patient's cancer genome, for instance, both treatment options and management can be facilitated; and this has yielded benefits in providing assessment of new treatments, improvements in patient outcomes, or healthcare savings (Cowie et al. 2017).

While transparent health information systems facilitate data sharing and collaborative research, it is noteworthy that impending risks may arise in the form of infringements of privacy, social stratification and discrimination, or identity theft. This can lead to the erosion of public trust in healthcare providers and governments. Therefore, management of EHRs should preferably incorporate a legislative framework of privacy protection, besides issues in data security and cyber-security.

11.2.3 Next-Generation Sequencing Techniques

Selecting appropriate NGS technology platforms, the associating data structures and formats, as well as the bioinformatics pipelines are important determinants for downstream data management such as storage and retrieval. The first commercial NGS technology was initially launched in 2004 by the 454 Life Sciences based on the pyrosequencing method (Margulies et al. 2005). Subsequently, Illumina launched its "sequencing by synthesis" technology—the principle behind Illumina's fleet of sequencers such as Solexa, MiSeq, HiSeq, and NextSeq (Meyer and Kircher 2010). Life Technologies later launched the SOLiD platform (Valouev et al. 2008), which introduced "sequencing by ligation," and, later, the Ion Torrent and Ion Proton semiconductor sequencing platforms, which perform "sequencing by synthesis" (Pennisi 2010). Following this, Beijing Genome Institute (BGI) acquired Complete Genomics's "DNA nanoballs" sequencing by ligation technology with its BGISEQ-500 flagship sequencer (Porreca 2010). In 2013, the 454 pyrosequencing platform was discontinued by Roche, while Thermo Fisher Scientific, which acquired Life Technologies, discontinued SOLiD sequencing in 2016. This leaves Illumina, Ion, and BGI sequencing as the main players in NGS technologies. The timeline for major development milestones of both NGS and TGS platforms is illustrated in Fig. 11.1.

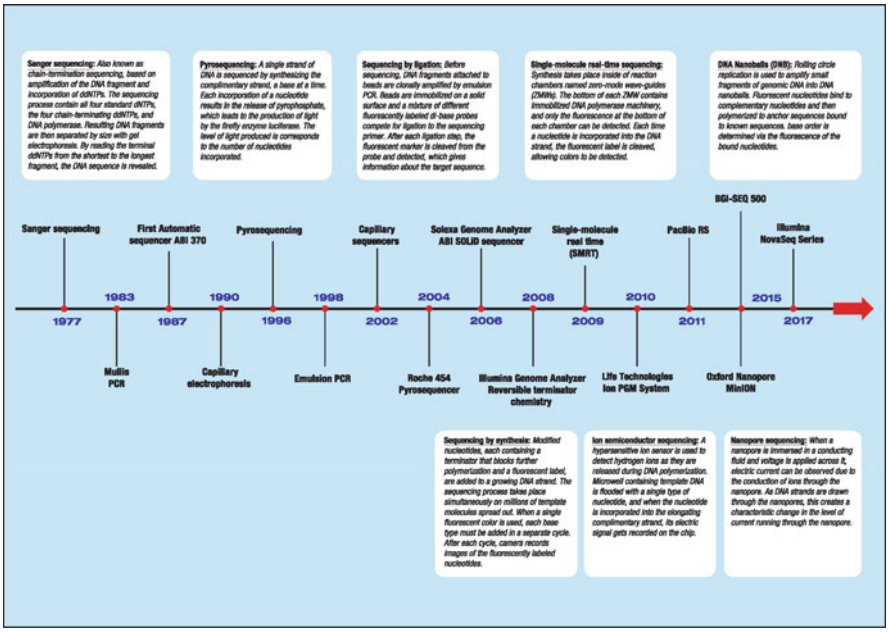

Fig. 11.1 Timeline for major development milestones of both NGS and TGS platforms

Almost all NGS platforms produce short sequencing reads of between 100 and 400 bases. Short sequences can sometimes be difficult to assemble (Margulies et al. 2005). In contrast, PacBio and Oxford Nanopore introduced long-read sequencing, where reads from these third-generation sequencing (TGS) platforms can span 10 kb or longer. TGS reads are easier to assemble, and they may reveal structural variation and allow easier determination of maternal and paternal chromosomes for neonatal PM (Rhoads and Au 2015; Tyson et al. 2017).

Regardless of NGS or TGS, the sequencing process can be divided into four phases, namely, library preparation, amplification, sequencing, and data analysis. Besides whole genome sequencing (WGS) in cases of unknown causes of disease, patients can opt for the smaller whole exome sequencing (WES) if suspected mutations or single-nucleotide polymorphism (SNPs) of genes of interest are confirmed to be located in the exons. Sequencing of targeted-gene panels will reveal mutations or SNPs which have been clinically proven to be related with specific diseases or treatment outcomes. In cases where diseases or traits are confirmed or suspected to be epigenetically related, patients may also opt for epigenome and transcriptome sequencing (RNA-Seq) (Maróti et al. 2018; Zhang et al. 2018). Besides, as the role of specific microbes in health and disease becomes more apparent, microbiome profiling may soon find its immediate applicability in PM (ElRakaiby et al. 2014; Doestzada et al. 2018).

11.2.4 Bioinformatics

NGS technology generates a plethora of data. These data need to be bioinformatically analyzed before they can be translated into clinically meaningful information. The general bioinformatics analysis workflow for NGS is shown in Fig. 11.2. The first-hand data that have not been modified since acquisition are termed raw data. The file types and structures of raw data vary according to the platforms used, but they are generally large in size. Raw data typically contains noises from upstream analyses. Removal of these noises results in processed data, which can be further analyzed to obtain clinically meaningful information. Nonetheless, processed raw data should preferably be stored to allow reanalysis with future versions of data processing algorithms which can achieve greater precision and accuracy (Hart et al. 2016). In addition to raw data, cryptographic hash such as SHA or MD5 should be generated and stored to prevent data corruption. Also, data stored on local computers or institutional servers should be backed up periodically to other locations to protect against data loss (Mangul et al. 2018).

NGS data are often flooded with sequencing artifacts, which include reads error, poor-quality reads, and primer or adaptor contamination (Endrullat et al. 2016). Hence, quality control (QC) of NGS data is vital to filter out low-quality data that would have imposed negative impacts on the downstream analyses and misleading conclusions (Patel et al. 2012). Several different software programs can be used for converting sequence data into nucleotide reads and their annotation. These programs

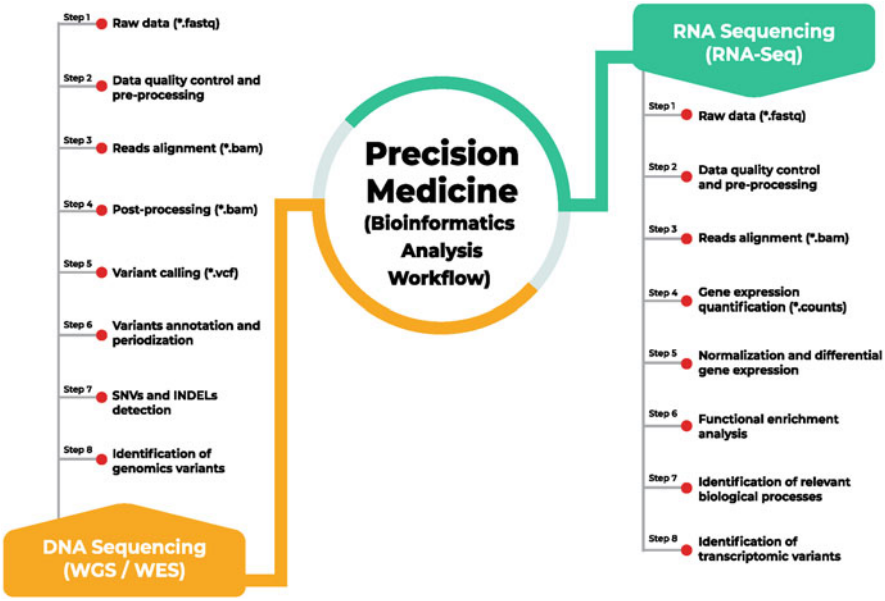

Fig. 11.2 A step-by-step bioinformatics analysis workflow for DNA-Seq and RNA-Seq acquired with NGS or TGS platforms

can be broadly classified into (i) open-source software and (ii) commercial software. While open-source programs are freely available and allow user preview of the logical flow and customization of the pipelines, programming skills are needed to execute and implement the program (Mangul et al. 2018). Commercial software, on the other hand, combines several analytical programs in a package and is usually equipped with a point-and-click interface. The downside of commercial software is that they are expensive in terms of licensing and upgrading costs (Smith 2014). Both open-source and commercial software receive version updates from their developers regularly. While the new updates are usually hassle-free for commercial software (since they are all contained in a suite package), open-source software requires additional checking for hardware and software compatibility issues and might need to recompile from codes again, which makes the time-stamping and management of the software versions more complicated (Gullapalli 2020).

11.2.5 Delivery of Results

To apply NGS data to the clinical setting, NGS data need to be translated into outputs that are informative to the healthcare providers as well as to the patients (Manrai and Kohane 2017; Mehandziska et al. 2020). To this end, bioinformaticians play an important role in identifying changes in the tested samples in comparison to controls.

Depending on the tests, bioinformaticians and geneticists/molecular biologists will need to work together to match these changes to available literature and databases on the investigated illness/traits and deliver the results to medical practitioners for patient disclosure. In cases where the cause of the investigated disease/trait is still unclear, a multidisciplinary team composed of bioinformaticians, scientists, and clinicians will be important for NGS results interpretation (Bylstra et al. 2019).

During results disclosure to individuals carrying high genetic risks, it is important to have medical professionals explaining the biological meaning of the results. It will also be ideal to have genetic counseling at the same time or at a subsequent session (Stoll et al. 2018). This is particularly important if the investigated condition is hereditary, so that the patients are made aware of not only their health condition but also the probable impact on their families and offsprings. Subsequently, the tested patient and/or probands can go through a confirmatory testing or be referred to specialist clinics for clinical management (Bylstra et al. 2019). On the other hand, if the patient is not found to carry any pathogenic mutation, they can be informed via an official letter from the clinic, with the option of a final meeting with the attending clinician, if required.

As NGS-based PM results contain sensitive information about the tested patient's genome, all folders containing these data should be encrypted with no personal identifiers to patients (Martinez-Martin and Magnus 2019). After consultation and counseling, it depends on the patient's prior discussion and agreement with the attending clinician on how their data will be managed after NGS results are delivered – whether this data should be destroyed or archived for future usage.

11.2.6 Data Storage

Storage of NGS data allows data reanalysis in the future. With the surge of NGS datasets, the demand in computing power and storage has increased exponentially. The processing of large-scale NGS data often requires high-performance computing (HPC) resources (Pérez-Wohlfeil et al. 2018). Despite enhancing productivity, HPC systems harbor security risks due to possible attacks by hackers, an inherited problem from conventional computer, and network security issues (Hou et al. 2020). Since HPC systems are essentially large-scale computing infrastructure, they can be remotely accessed by any registered users. Therefore, security mechanisms must be employed to prevent any suspicious activities or attempts from accessing sensitive information.

The increase in the volume and variety of NGS data has posed new challenges, where HPC is now dealing with big data garnering terabytes/petabytes of information. By tying together all aspects of computing power and storage, cluster computing helps to eliminate gridlocks that can interfere with performances (Ocaña and De Oliveira 2015). The greatest advantage of computer clusters is the scalability that they offer, in which, unlike mainframe computers that have a fixed processing

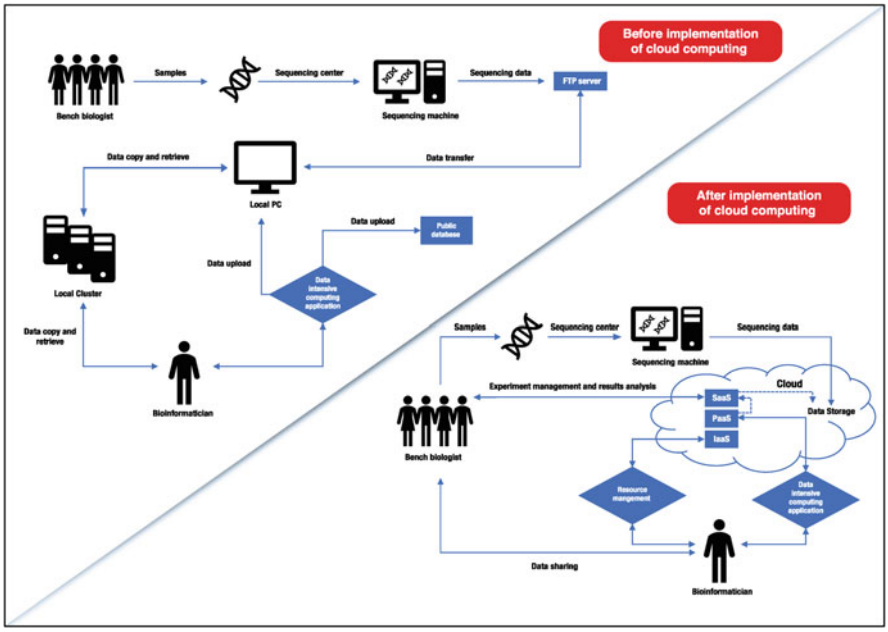

Fig. 11.3 Computational infrastructure, requirements, and logistics for NGS data analysis – before and after implementation of cloud computing

capacity, computer clusters can be easily expanded as requirements change and grow, simply by adding additional nodes and storages to the cluster.

Bioinformatics services have generally been provided via web servers, and are usually hosted at institutional computing infrastructures, and simultaneously serve multiple users via remote access. Due to the expanding number of users, data sizes, and new requirements in terms of speed and availability, this model has become outdated (El-Kalioby et al. 2012). In recent years, cloud computing and storage have emerged as a powerful, flexible, and scalable approach to tackle computational and data-intensive problems (Fig. 11.3). Examples of public clouds include Amazon Web Services (AWS), Google Cloud Platform (GCP), and Microsoft Azure. Several common cloud types include (i) software as a service (SaaS), which enables the user to use the cloud provider's applications that are running on the cloud infrastructure; (ii) platform as a service (PaaS), which enables the user to create or acquire applications and tools and deploy them on the cloud provider's infrastructure; and (iii) infrastructure as a service (IaaS), which enables the user to utilize processing, storage, networks, and other fundamental computing resources (Navale and Bourne 2018).

11.3 Challenges in Next-Generation Sequencing

Apart from data storage, there are several other technical challenges in applying NGS in precision medicine. First, there is a need for quality management and workflow standardization (Endrullat et al. 2016). This ensures the comparability of the sequencing data among different laboratories and reproducibility of the results, thus improving testing accuracy and reliability. Currently, there is a lack of consensus in the development of a standardized workflow among different laboratories. Even when standardization guidelines are developed, there might be difficulties implementing the standards due to incompatibility of the guidelines in different NGS applications (Cargill 2011). Moreover, a vast majority of standardization guidelines are from the United States; thus, it is unknown whether these guidelines are implementable in other countries (Endrullat et al. 2016). Apart from that, there is also an issue concerning the bandwidth limitations if sequencing and data analysis are performed at different centers, thus requiring data transfer from one place to another (Wandelt et al. 2012). In addition, as NGS involves multiple procedures over multiple days which may be performed by multiple technologists, it is often difficult to track the NGS workflow and trace the samples, the personnel who performed the experiment, reagent consumption, etc.

11.4 Laboratory Information Management System

Fortuitously, laboratory information management systems (LIMS) are available, which can be used to manage NGS data and workflow, and make the tracking and tracing above uncomplicated. LIMS is a type of software developed and used in many clinical laboratories since the 1980s to manage basic operations in the laboratory. Traditionally, the functions of LIMS focused on the management of samples, such as sample registration, barcode label generation, and location tracking (including assigning the samples to a particular freezer compartment) (Gibbon 1996). Over time, the functionalities have been enhanced by including management of personnel (such as assignment of job to laboratory staff and their work schedules); estimation and tracking of experiment completion time; assessment of instrument or test performance; reagent and inventory tracking; recording of experimental procedures (i.e., electronic laboratory notebook); and tax invoicing (Argento 2020; De Block 2019). Implementation of LIMS in clinical laboratories can reduce human errors during the entire experimental workflow and aid in the enhancement of work quality and productivity and is among the first steps toward laboratory automation and digitalization (Chen et al. 2016; Junaid and Jangda 2020).

Despite this, the unprecedented volume of NGS data, along with the complexity of the NGS workflow, poses new challenges to the conventional LIMS (Chen et al. 2016). For this reason, many conventional LIMS have been refined or even revamped, and many other new LIMS have been developed, to meet the demands

of modern genomic laboratories. For example, apart from tracking the identity of the samples and their location in the freezer, modern LIMS also records the status of the samples (e.g., whether they are successfully completed) at each stage of the complex NGS pipeline, as well as the batch number of the reagents used. Modern LIMS also allows protocol automation and customization for different NGS applications and platforms and contains quality control tools that identify samples of poor quality. Besides, many modern LIMS have raw data processing functionalities, which can ease the delivery of sequencing results, often in a systematic and organized manner, to the healthcare providers or the patients. Due to the enormous size of NGS data files, modern LIMS are also moving toward cloud computing and storage, as discussed in Sect. 11.2.6 (Paul et al. 2017; Guo et al. 2020). For this reason, most modern LIMS applications require connectivity with a high-speed internet and normally function through a server computer and several PC workstations.

11.5 How to Select a Laboratory Information Management System?

Dozens of LIMS offering different functionalities are currently available in the market, and each one has its own pros and cons. Several main aspects that need to be considered when selecting a LIMS for NGS management are discussed below.

11.5.1 Ability to Integrate with NGS Instrumentation

To improve the workflow efficiency in the laboratory, a LIMS needs to be able to directly provide instructions or data to, or retrieve data from, the existing NGS instruments. In other words, a LIMS should be integrated with NGS instrumentations rather than operating independently (Chen et al. 2016). This will allow automation of the process, instead of relying on laboratory staff to manually feed or retrieve the information between LIMS and the instruments. It should be noted that distinct NGS platforms use different reagents, protocols, and instruments to achieve their optimal performance. Ideally, a LIMS should be able to recognize and communicate with instrumentations from all major platforms, so that users can simply specify the type of NGS application to be performed and the LIMS automatically generates the correct instructions for the sequencers. In addition, the ability to integrate with NGS instrumentations can allow LIMS to continuously monitor metrics such as the Phred quality score to track the status and quality of the sequencing in real time.

11.5.2 Ease of Configuration and Customization

Every laboratory has its own demands for LIMS. In addition, NGS workflows, protocols, methodologies, and technologies are also continuously evolving (Durmaz et al. 2015; Cała et al. 2014). Thus, it is imperative that LIMS be flexible for configuration and customization (Chen et al. 2016; Tagger 2011). Configuration of LIMS refers to the use of built-in system tools, often in the user interface, to redesign the appearance or functionality of the software. Examples of configuration tasks include creating a new user profile, adding new sample preparation procedures or analytical methodologies, devising the sample nomenclature, and inserting additional fields in the report form. Customization, on the other hand, refers to extension of the system functionalities by modifying the programming codes associated with the software. This is necessary when, for example, the LIMS needs to be catered for new NGS technologies or instrumentations. Customization often requires the skills of expert programmers and involves rigorous testing and validation of the new codes to ensure that they do not clash with the system (Paul et al. 2017; Bianchi et al. 2016; Rafid Raeen 2018). Thus, it is clear that LIMS which allows easy configurations and customizations can allow laboratories to work efficiently to match their current and future informatics needs.

11.5.3 Accommodativeness to Different Users

Implementation of NGS in the clinical practice typically requires the involvement of several parties including laboratory managers, technicians, application specialists, bioinformaticians, authorized signatories, and clinicians/healthcare providers. Each of these parties has their own responsibilities and thus requires access to different information (Tagger 2011). For example, a technician does not need to know the medical history of a patient, whereas a healthcare provider does not need to know the rate of reagent consumption for an NGS assay. To improve work efficiency, a LIMS should provide targeted interfaces for different users, so that each of them can access only the information that is relevant to them, rather than spending time retrieving the necessary data from the system.

11.5.4 Comprehensiveness of Sample Tracking

The accuracy of an NGS assay is dependent on the quality of the sample in each step of the workflow ("garbage in, garbage out") (Robles-Espinoza and Adams 2014; Conrads and Abdelbary 2019). As such, it is important to keep close track of the samples throughout the entire workflow, from sample collection to final result delivery (Matthijs et al. 2016). To enable effective analysis of a large volume of

NGS data, LIMS needs to be able to track the samples and their associated metadata comprehensively. Examples of information that needs to be captured by a LIMS include the approach by which the samples were collected, the purity and concentration of the nucleic acids isolated, sample and nucleic acid storage conditions, the protocols and reagents (including batch numbers) used to create the sequencing library, quality control metrics of the sequencing library, etc. A comprehensive sample tracking can allow validation and/or troubleshooting work to be performed effectively.

11.5.5 Compliance Support

The use of NGS in precision medicine involves human samples and is thus governed by a number of regulations. In the United States, for example, healthcare providers need to adhere to the Health Insurance Portability and Accountability Act (HIPAA), Clinical Laboratory Improvement Amendments (CLIA), and General Data Protection Regulation (GDPR), in addition to other guidelines and requirements from international agencies and professional organizations (see Sect. 11.2.1) (Roy et al. 2018). Apart from that, an NGS laboratory should ideally comply with the ISO 15189:2012 accreditation standards (Gutowska-Ding et al. 2020). A good LIMS should have a set of controls that monitor compliance with these regulations, guidelines, and standards to ensure integrity and validity of the NGS data and to safeguard patients' privacy.

11.5.6 Cost

Both commercial and non-commercial (open-source) LIMS are widely available in the market. Commercial LIMS are usually easier to install and use, and have more advanced features, compared to the open-source ones. However, the costs needed to implement a commercial LIMS are often unaffordable for smaller laboratories which do not run NGS as the core business and rely on research grants as the main source of funding (Lemmon et al. 2011).

11.6 Examples of LIMS for NGS

The rise of NGS has also pushed the rapid development of LIMS. A number of LIMS are now available to manage NGS data (Table 11.3). Laboratories using the Illumina NGS platform are probably familiar with the Illumina BaseSpace Clarity (BaseSpace Clarity LIMS 2020), a web-based LIMS which can receive encrypted data directly from the sequencers and used for monitoring sequencing runs,

Table 11.3 A non-exhaustive list of commercial and open-source LIMS for NGS

LIMS	Licensing
Illumina BaseSpace Clarity	Commercial
Agilent SLIMS	Commercial
Exemplar	Commercial
GNomEx	Open-source[a]
openBIS	Open-source
Wasp	Open-source
MendeLIMS	Open-source
SLIMS	Open-source
SMITH	Open-source
Galaxy LIMS	Open-source
Parkour LIMS	Open-source
SeqBench	Open-source
MISO	Open-source
NG6	Open-source

[a]Free disk space allocation is 100 GB. A bill of $2.00 will be charged each month for every additional 100 GB ($240 per TB per year)

processing and storing the sequencing data on the BaseSpace Cloud, and easy sharing of the sequencing data with collaborators. Likewise, Agilent users may be familiar with SLIMS, which provides comprehensive tools for managing the entire NGS workflow. Another LIMS which can be used for NGS data management is openBIS (Barillari et al. 2016), which also features an electronic laboratory notebook function. GNomEx LIMS (GNomEx 2020), which is developed by the Huntsman Cancer Institute, can also be used for reporting of both NGS and microarray data. The Wasp system (McLellan et al. 2012) is another genomics LIMS that provides embedded pipelines for various massively parallel sequencing assays for use in the clinic. Similarly, MendeLIMS (Grimes and Ji 2014) also emphasizes on the management of clinical genome sequencing projects. The Sample-based Laboratory Information Management System (SLIMS, not to be confused with the Agilent SLIMS which shares the same name above) (Van Rossum et al. 2010), on the other hand, is a LIMS designed for laboratories focusing on genotyping and genome-wide association studies. In addition, SMITH (Venco et al. 2014) provides a fully automated system in managing sequencing data on high-performance computing clusters. Besides, the Galaxy LIMS (Scholtalbers et al. 2013) was developed as an extension to the existing Galaxy platform; thus, the sequencing data are directly available for processing using the analytical pipelines stored in the platform. The Parkour LIMS (Anatskiy et al. 2019) is designed to maximize the efficiency of NGS sample processing and quality management in academic core laboratories. SeqBench (Dander et al. 2014) is another LIMS that is developed to cater analysis of whole exome sequencing data, either locally, on a cluster, or in the cloud. Many other LIMS, such as Exemplar (Laboratory Information Management System Software (LIMS) | Sapio Sciences 2020), MISO (2020), and NG6 (Mariette et al. 2012), also provide a variety of tools for the management of NGS experiments.

11.7 Other Issues to Consider

Apart from scientific, technical, and logistic challenges, there are other ancillary aspects that one must consider in managing NGS data. First, the acquisition, storage, and usage of personalized omics data may lead to unintentional legal, social, and ethical breaches; hence, appropriate framework should be put in place (Minkoff and Ecker 2008). For instance, it remains controversial as to whether first-degree relatives and insurance companies are eligible to access and use personal genomic information, in addition to possible genetic discrimination (Federal Register 2015). Other considerations include the consent process and the communication results and counseling (Fossey et al. 2018). The European Union introduced the General Data Protection Regulation (GDPR), introduced in 2016, to set specific provisions for the processing of sensitive data, such as technical and organizational measures on adapting pseudonymization which intended to deliver adequate protection rights and freedoms of data subjects (Sanchini and Marelli 2020).

Translation of big data into PM requires healthcare providers to possess knowledge in molecular life sciences, so that they are able to understand and interpret these big data reports, as well as to incorporate these data into disease treatment and prevention, and to deliver the appropriate knowledge to patients (Reference GH 2020). However, the current generation of clinicians and nursing staff often lack the background for managing EHRs, omics data, and biobanks, besides differentiating actionable genes and providing options for participants to receive limited results or to withdraw from the study at a later stage. It is therefore imperative to incorporate these cross-disciplinary components in tertiary education and continuing professional development. To facilitate knowledge sharing, it is also highly beneficial to standardize terminologies and nomenclatures, besides NGS data structures and formats in this emergent field. Besides, pioneering endeavors are often greeted with skepticism and resistance by the public due to the lack of exposure. As such, public education and campaigns are equally important for creating public awareness and acceptance.

Another compelling factor for health institutions is the cost. Storing and managing NGS datasets, EHRs, and other lab tests require hefty initial investment in high-performance computing, maintenance, and periodic upgrade, not to mention hefty investment in human capital and infrastructure upon scaling up to nationwide public health efforts. This will inevitably involve politics whereby public debates on health economics, crafting of new budgets, and policies will take place.

11.8 Conclusion and Future Perspectives

The improved reliability and lowering cost have rendered NGS being increasingly adopted in the clinics; and these have also further expanded the NGS “big data” (Pennell et al. 2019; Hulsen et al. 2019). Such advancement should have been

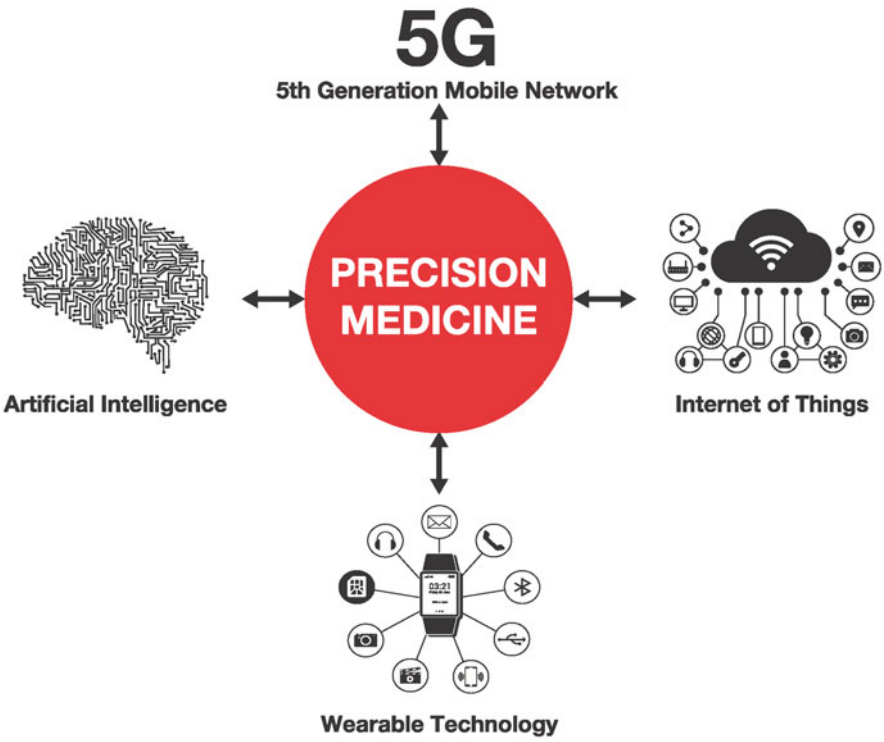

Fig. 11.4 Developments in the Fourth Industrial Revolution (4IR) that can improve the quality, quantity, variety, and connectivity of acquired NGS and phenotypic data for precision medicine

matched with an equivalent capacity in automated data analysis and interpretation, but NGS data are still mainly curated by bioinformaticians and subject matter experts manually. We envisage that a major revolution in precision medicine will be artificial intelligence (AI), an indispensable component of the Fourth Industrial Revolution (4IR) which will alleviate the bottleneck in NGS data analysis (Fig. 11.4). AI refers to a range of computational capabilities, i.e., rule-based computing, machine learning (ML), deep learning, natural language processing (NLP), and computer vision, that can facilitate and speed up tasks requiring human intelligence in reasoning, decision-making, as well as speech recognition, visual perception, or detection of data patterns.

Currently AI has begun to exhibit its prowess in NGS data analysis. Firstly, in the variant calling process whereby a sample nucleic acid sequence is compared to a reference sequence to detect any differences, manual annotations of variants often produce errors and biases (Hwang et al. 2015). AI algorithms such as DeepVariant can learn these biases from a single genome with a reference standard of variant calls and produce premium variant calls (Poplin et al. 2018). Meanwhile, in genome annotation and variant classification, prediction of both (i) the functional elements from primary DNA sequence and (ii) the effects of genetic variations on these

functional elements can also be facilitated by AI, as exemplified by algorithms such as combined annotation-dependent depletion (CADD) (Kircher et al. 2014), SpliceAI (Jaganathan et al. 2019), and DeepSEA (Bernstein et al. 2010). Thirdly, another process that can be expedited by AI is the mapping of phenotypes to genotypes. Every predicted pathogenic variant should preferably be matched to an expected disease phenotype to ease subsequent clinical diagnosis. Through an interdisciplinary area named computer vision, AI-based deep learning has been implemented on medical imaging data obtained from different diseases; and it has been reported to outperform expert pathologists and dermatologists (De Fauw et al. 2018; Bejnordi et al. 2017). A good example of such an AI-based facial image analysis algorithm is DeepGestalt (Gurovich et al. 2019). DeepGestalt can be incorporated into PEDIA, a genome interpretation system. PEDIA was able to analyze phenotypic features extracted from facial photographs to accurately prioritize candidate pathogenic variants for 105 different monogenic disorders across 679 individuals (Hsieh et al. 2019). Likewise, AI-based speech recognition has been applied to detect diseases such as chronic pharyngitis, which negatively affects speech ability (Li et al. 2019). Finally, NLP can be used to recognize and capture patterns in EHRs so that other patient-related data such as laboratory tests or family history can also be incorporated so as to predict diagnoses, to drive phenotype-informed genetic analysis, and to inform clinical decision-making (Clark et al. 2019).

Apart from AI, Internet of Things (IoT) is another upcoming trend in PM. At the moment, apart from mobile devices, various wearable smart devices such as smartwatches, fitness trackers, smart jewelry, smart clothing, and head-mounted displays are already in the consumer electronics market. These wearables are usually worn close to the skin surface so that the embedded sensors can continuously detect, analyze, and transmit signals of vital signs, ambient data, or physical activity to the users (Düking et al. 2018). Importantly, these constantly acquired data can be transmitted and uploaded to cloud storage in real time, so that they can provide phenotypic features that can be interpreted by AI. At the other end, this form of portable, real-time, on-site, and IoT-based analysis has also been realized in nanopore-based DNA/RNA sequencing, which has recently been commercialized (Liu et al. 2016). Together with the impending fifth-generation mobile network (5G) that is designed to connect virtually everyone and every device at an elevated speed and reliability, we therefore believe that healthcare will be completely transformed.

In short, current strategies for NGS data management in PM, as discussed in detail here, are still very much under development, and not many healthcare providers, even in the advanced countries, have even started to embrace NGS-based PM. Even then, the pace of technologies has moved so rapidly that NGS data strategies need to be redesigned from time to time in order to keep abreast of this age of 4IR. To remain future-compliant, new ideas such as AI, IoT, wearable technologies, and 5G communication will need to be assimilated into PM so that it can further benefit from the real-time phenotypic data that we have started to accumulate on a daily basis.

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Chapter 12
Management of Severe Childhood Pneumonia in Low-Resource Setting Countries

Yasmin Jahan

Abstract Pneumonia is the main cause of death in under-five children globally. There are more than 1400 cases of pneumonia per 100,000 children globally, where the highest prevalence appears in South Asia and Sub-Saharan Africa. There are various factors like low socioeconomic status, maternal lower education, incomplete immunization, poor child feeding and hand hygiene, overcrowding, indoor air pollution, and so on were associated with the incidence of pneumonia among under-five children. According to the World Health Organization, supportive treatment such as suctioning, oxygen therapy, fluid and nutritional management, close monitoring is needed; therefore, hospitalization is required. In a country like Bangladesh, there is a shortage of pediatric hospital beds for patients which is a major challenge. With regards, this book chapter aims to depict the case management processes of severe pneumonia in a low resource setting country perspective.

Keywords Severe childhood pneumonia · Management · Low resource setting countries

Abbreviations

CHWs	Community health workers
IM	Intramuscular
IV	Intravenous
LMICs	Low- and middle-income countries
PCP	*Pneumocystis jirovecii* pneumonia
RSV	*Respiratory Syncytial Virus*
WHO	World Health Organization

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12.1 Background

Pneumonia is defined as inflammation of the alveoli and terminal airspaces of the lungs in response to invasion by an infectious agent (e.g., bacteria, virus, etc.). It can be classified by where or how it was acquired, as community- or hospital-acquired pneumonia, aspiration- or ventilator-associated pneumonia, lobar pneumonia, bronchial pneumonia, or acute interstitial pneumonia, and based on its clinical severity can be defined as "pneumonia" or "severe pneumonia" (Mackenzie 2016; Revised 2014; Kalil et al. 2016).

Worldwide, pneumonia is the main cause of death in under 5 children. It is claiming that pneumonia kills over 800,000 under 5 children every year or around 2200 in each day including over 153,000 newborns which is more than any other infectious diseases. In 2018, 437,000 under 5 children died with diarrhea whereas 272,000 for malaria. There are more than 1400 cases of pneumonia per 100,000 children globally, with the highest prevalence appearing in South Asia (2500 cases per 100,000 children) and sub-Saharan Africa (1620 cases per 100,000 children) (UNICEF n.d.).

Studies found that various factors like low socioeconomic status, maternal lower education, incomplete immunization, poor child feeding and hand hygiene, overcrowding, indoor air pollution, and so on were associated with the incidence of pneumonia among under 5 children (Abuka 2017; Gritly et al. 2018; Gothankar et al. 2018; Jackson et al. 2013; Dherani et al. 2008; Dadi et al. 2014; Jiang et al. 2018; Norbäck et al. 2018). Nonetheless, since 2000, deaths due to pneumonia among children under 5 have considerably reduced to 54% (Gessner 2011). The reason behind that was decreasing the magnitude of its key risk factors, expanding socioeconomic development and preventive interventions, improved access to care, and quality of care in hospitals. In spite of this enhancement, pneumonia is still a major public health concern for under 5 children especially for developing countries.

For the management of severe childhood pneumonia, the World Health Organization (WHO) stated that supportive treatment such as suctioning, oxygen therapy, fluid and nutritional management, and close monitoring is needed; therefore, hospitalization is required (Gessner 2011; Graham et al. 2008; Chisti et al. 2009; Ayieko and English 2007). In a developing country like Bangladesh, the shortage of pediatric hospital beds for patients is a major challenge. Regarding this, a prospective observational study mentioned that daycare facility-based primary care treatment for severe pneumonia can be more successful and cost-effective alternative ways to hospitalization (Ashraf et al. 2008). Previous research also indicated positive outcomes (both efficacy and safety) with respect to daycare facility-based management at community clinic. In Bangladesh, the International Centre for Diarrhoeal Disease Research developed a groundbreaking model of daycare-based management approach as a safer and cost-effective alternative to hospital management for severe childhood pneumonia (Jahan and Rahman 2018). The main objective of that model was to introducing patient management in the community level particularly for those who cannot be hospitalized. In the long run, it is expected that the daycare-based

management model can become a validated approach for low- and middle-income countries (LMICs) where hospital beds are scarce (Ashraf et al. 2010). Regarding this, this book chapter aims to depict the case management processes of severe pneumonia in a low-resource setting country perspective.

12.2 Epidemiology of Pneumonia

Recently developed radiological pulmonary shadowing can be found in acute respiratory illness which may be segmental, lobar, or multi-lobar.

It is usually characterized by consolidation in which the air that usually fills the small airways in lungs is replaced with a mixture of exudates, bacteria, and leucocytes. Pneumonia can occur throughout the year, though it's more prevalent in colder months, the reason behind that could be that the direct transmission of infected droplets is enhanced by indoor crowding. The reasons are unknown because a different virus causes peaks of infection at different times, though peaks of infection follow no common pattern especially in tropical regions and can occur during any seasons (Arruda et al. 2006).

However, the recent WHO global report (2013) projected that approximately 120 million cases of pneumonia account for each year (Hotiana 2016) where 12% progress to severe pneumonia (Zar et al. 2013). In 2013, the WHO has revised the case definition of pneumonia with fast breathing and/or chest indrawing, which requires home care advice with oral antibiotic (amoxicillin), and severe pneumonia requires referral and hospital admission for injectable therapy if there is presence of cough or breathing difficulty and tachypnea, plus one or more of the general danger signs, but no lower chest indrawing (Revised 2014). General danger signs include the inability to drink; persistent vomiting; convulsions; lethargy; unconsciousness; stridor in a calm child; severe malnutrition; central cyanosis; or oxygen saturation <90% in room air. Many LMICs have adopted these abovementioned criteria (Rudan et al. 2008).

12.3 Clinical Manifestations

Fever.
Rigors.
Shivering.
Vomiting.
Pulmonary symptoms like pleuritic chest pain and retractions.
Cough (short, painful, dry, later accompanied with mucopurulent sputum).
Hemoptysis (in patients with *Streptococcus pneumoniae*).
Pleuritic chest pain (Rudan et al. 2008) (Table 12.1).

Table 12.1 Host and environmental risk factors responsible for the incidence of childhood pneumonia

Host-related factors.	Environment-related factors
Malnutrition (weight-for-age z-score < -2)	Indoor air pollution
Low birth weight (<2500 g)	Crowding
Non-exclusive breastfeeding (during the first 4 months of life)	Rainfall (humidity)
Lack of measles immunization (within the first 12 months of life)	High altitude (cold air)
Parental smoking	Outdoor air pollution
Zinc deficiency	–
Mother's experience as a caregiver	–
Concomitant diseases (e.g., diarrhea, heart disease, asthma)	–
Mother's education	–
Vitamin A deficiency	–
Birth order	–

Adapted from Rudan et al. (2008)

12.4 Causes

Childhood pneumonia is caused by a combination of exposure to risk factors related to the host, the environment, and infection.

12.4.1 Infectious Causes

Most causes of pneumonia are caused by organisms (infectious).

Community-acquired pneumonia usually is caused by infectious agents, and it's varying by age. The most common cause to develop pneumonia for infants is *Respiratory Syncytial Virus* (RSV). The other respiratory viruses such as parainfluenza virus, influenza virus, and adenovirus cause pneumonia in under 5 children. *M. pneumoniae* and *S. pneumoniae* cause pneumonia in children older than 5 years. The principal causes for developing atypical pneumonia are *M. pneumoniae* and *C. pneumoniae*. Few agents rarely cause hospital-acquired pneumonia, especially for immunocompromised patients.

12.4.2 Non-infectious Causes

Pneumonia can be caused by aspiration of food, foreign bodies, hydrocarbons, and lipid substances and by drug or be radiation induced.

12.5 Complications of Pneumonia

Even with proper treatment, some children may experience some complications like pleural effusion, empyema, lung abscess, pneumothorax, respiratory failure, and activation of latent tuberculosis (TB).

12.6 Management

The children who are at risk of death will have to be recognized promptly and should be referred to the nearest health facility if required. The WHO has already modified their referral guidelines for pneumonia and severe pneumonia (Bari et al. 2011). Though there is enormous improvement that occurs between community and referral facilities in developing countries, still there are numerous pneumonia and severe pneumonia children who never reach the health facility timely (Molyneux and Graham 2011). Daycare facility-based primary care treatment of pneumonia and severe pneumonia at the community level has shown to be effective in this regard and reduce pneumonia mortality (World Health Organization 2010). The WHO and the United Nations International Children's Emergency Fund recommend it where the access to care for illness is low (Chowdhury et al. 2008).

The reasons may perhaps be the remoteness, geographical barriers of access, climate, expenditure, cultural belief, and lack of adequate childcare to effective and appropriate treatment (Chowdhury et al. 2008; Peterson et al. 2004). Many developing countries have shortage of pediatric hospital beds to accommodate the need for admission, and/or referral is difficult or impossible for all children with severe pneumonia (Lambrechts et al. 1999). Moreover, when referral is not possible, there is only option for the patient to take treatment at the nearest community-level health facility. At that time, healthcare personnel of those facilities may have to take critical decision about referral or to manage the child locally.

Regarding this, WHO revised pneumonia guidelines will increase receiving child care at the community-level health facility to reduce the need for referrals and improve treatment outcomes as well especially in the countries with the high burden of pneumonia (World Health Organization 2010). Hence, many developing countries have started hiring and training the community health workers (CHWs) to diagnose and treat pneumonia (Schellenberg et al. 2004). Studies showed that an intensive basic training and routine supervision of CHWs could make them be able to identify the fast breathing for pneumonia as well as treatment in their communities (Revised 2014). If the CHWs train properly, then it would be possible to treat the pneumonia children at community level and thus reduce the childhood mortality.

12.6.1 Equipment and Supply Obtainability at Community-Level Health Facilities

In WHO guideline, they stated that for the management of severe childhood pneumonia, suctioning, oxygen therapy, antibiotic treatment, and close observation (Gessner 2011; Graham et al. 2008; Chisti et al. 2009; Ayieko and English 2007; Jahan and Rahman 2018) like supportive treatments will be required. If all these facilities are available at community health facility, then severe childhood pneumonia can be treated successfully.

A study conducted at 62 first-level health facilities of 3 countries found that most of the community-level health facilities had a refrigerator to store vaccines, weighing scales, thermometers, syringes and needles, and intramuscular injection (i.e., penicillin). Besides, three-quarters of those facilities had rectal and/or intravenous diazepam, whereas one-third of the facilities had nasogastric tubes for giving intravenous fluids; however, enormous differences were observed between countries. There was only one center where they found a nebulizer, two centers had a blood-giving set, and three had 50% glucose (dextrose), though 5% had a source of oxygen, but without nasal cannulas (Simoes et al. 2003). Therefore, it is necessary to confirm that all the treatment modalities such as suction machine, oxygen therapy, and fluid and nutritional management are available at community-level health facilities for the management of severe pneumonia. However, research agreed with the above statement that childhood severe pneumonia can be treated at community-level health facilities, which is effective as the hospital management according to WHO guidelines (Ashraf et al. 2008; Jahan and Rahman 2018) (Fig. 12.1).

Availability of new evidence	Revised classification and treatment for childhood pneumonia at health facility	
	Signs/Symptoms	**Management**
Child age 2–59 months with cough and/or difficult breathing	Cough and cold: no pneumonia	Homecare advice
	Fast breathing and/or chest indrawing: pneumonia	Oral amoxicillin and home care advice
	General danger signs: † severe pneumonia or very severe disease	First dose antibiotic and referral to facility for injectable antibiotic/supportive therapy

† Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

Fig. 12.1 Revised classification and treatment of childhood pneumonia at community health facility. Adapted from revised WHO classification

12.6.2 Operational Definition

Community-level health facility—this is the closest available healthcare facility for ill children commenced in developing countries which is usually run by medical staff who are not physicians. These facilities do not have beds for patient's admission and essential drugs and supplies also (Nolan et al. 2001).

WHO recommended guidelines for the management of pneumonia and severe pneumonia (World Health Organization 2014).

12.6.3 For Pneumonia

Children should be treated with oral amoxicillin at least 40 mg/kg/dose twice daily (80 mg/kg/day) for 5 days who have fast breathing pneumonia with no chest indrawing or general danger sign. In the low HIV prevalence areas, oral amoxicillin can be given for 3 days.

Children with fast breathing who fail on the first-line treatment with amoxicillin should be referred to a facility and started with appropriate second-line treatment.

Children aged 2–59 months with chest indrawing should be treated with oral amoxicillin: at least 40 mg/kg/dose twice daily for 5 days.

12.6.4 For Severe Pneumonia

Children aged 2–59 months should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

Inj. ampicillin: 50 mg/kg (IM)/intravenous (IV) every 6 h for at least 5 days and Inj. gentamicin: 7.5 mg/kg IM/IV once a day for at least 5 days.

Inj. ceftriaxone can be used as a second-line treatment for those who failed the first-line treatment.

For HIV-infected and HIV-exposed infants and for under 5 children with chest indrawing, pneumonia, or severe pneumonia, Inj. ampicillin plus gentamicin or Inj. ceftriaxone are recommended as a first-line treatment, but for those who do not respond with these treatments, Inj. ceftriaxone alone is recommended as a second-line treatment.

12.7 Conclusion

In developing countries, severe pneumonia management at community-level health facility may be an attainable strategy of applying limited hospital beds, more competently by choosing daycare-based treatment. The arrangement can be applied in those community-level health facilities where hospitalization is required. This realistic approach would be helpful for both developing and underdeveloped countries where similar health resources and infrastructures are available. Besides, the healthcare providers would be aware about clinical indicators so that they could understand the presence of danger signs of pneumonia like hypoxemia. Furthermore, incorporating daycare-based management at community-level health facilities will create a novel healthcare policy in a cost-effective manner.

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Chapter 13
Clinical Application of Molecular Bioinformatics

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Abstract With the rapid development of bioinformatics, this subject is more and more closely combined with clinical practice. Clinical bioinformatics not only is used more and more in disease diagnosis and prognosis prediction but also plays an important role in the study of pathogenesis, the search of disease markers, the prediction of drug targets, and other aspects. Here, we highlight some of the techniques of clinical bioinformatics and add examples of using bioinformatics methods to solve clinical problems. It focuses on how molecular networks or protein-protein interaction networks influence diseases and how gene co-expression networks relate to clinical phenotypes. The possibility of assigning chronic obstructive pulmonary disease subtypes based on gene expression was also explored.

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The application of molecular bioinformatics to re-understand diseases is very important and will provide a broader prospect for the diagnosis and treatment of diseases.

Keywords Clinical bioinformatics · Molecular networks · Subtype · Genomics · Regional medical

13.1 Introduction

Bioinformatics plays an important role in clinical diagnosis and research. At present, clinical bioinformatics has been widely used in the discovery of disease-related genes, determination of new drug molecular targets, disease diagnosis, and prognosis prediction (Wooller et al. 2017; Oliver et al. 2015; Fu et al. 2020). In clinical practice, bioinformatics can effectively predict the prognosis of patients or the occurrence and development of diseases based on the integration of previous diagnosis and treatment data and sequencing data and provide guidance for the diagnosis and treatment of diseases. For diseases whose pathogenesis is not clear, bioinformatics can also provide strong guidance, which can effectively save time and avoid aimless experiments.

The clinical identification of disease subtypes has mainly relied on pathology and symptoms, but the use of molecular bioinformatics to identify molecular subtypes has just begun. The molecular subtypes of diseases can be associated with clinical phenotypes, which may indicate the causes of phenotypic changes and explain the different symptoms of the same disease at the molecular level. This paper introduces how clinical bioinformatics can integrate molecular networks into clinical practice and how bioinformatics can be used to reclassify disease and solve clinical problems in regional medicine.

13.2 Methods Suitable for Clinical Practice

Clinical bioinformatics is widely used, which can not only integrate phenotype and gene expression but also predict phenotype and even find etiology through gene expression. It could also focus on genes, regulatory elements, or microRNAs to find potential ways to treat diseases. The following are some bioinformatics methods that can be popularized in clinical practice.

13.2.1 Weighted Gene Co-expression Network Analysis (WGCNA)

Correlation network analysis is becoming more and more widely used in biological research. Weighted correlation network analysis (WGCNA) is a method used to describe the gene association patterns among different samples. It can be used to identify highly covariated gene sets and to identify alternative biomarker genes or therapeutic targets based on the connectivity of the gene sets and the association between the gene sets and phenotypes. Compared with the research method of focusing on differentially expressed genes, WGCNA can study thousands of genes with the greatest variation or all detected genes, form co-expression networks, and then conduct significant association analysis of phenotypes. This can either make full use of the information or obtain the important genes associated with the phenotype by screening the hub genes of the module and also provide reference and inspiration for the diagnosis and treatment of clinical diseases (Yin et al. 2018; Bai et al. 2020). WGCNA mainly include the establishment of gene co-expression network, formation of co-expressed gene modules, correlation of co-expressed gene modules with clinical data, correlations between modules and among genes within modules, and screening of hub genes according to gene significance and module membership (Langfelder and Horvath 2008), of which the WGCNA workflow is shown in Fig. 13.1a.

13.2.2 Identification of Disease Subtypes

Clinically, diseases are often classified according to their symptomatic characteristics. Consensus clustering provides a new way to classify molecular subtypes of diseases according to gene expression. Based on consensus clustering results, clinical phenotypes of different molecular subtypes were studied by statistical methods such as chi-square test and *T* test, or WGCNA was used to construct co-expression network to correlate molecular subtypes with clinical phenotypes, which is beneficial to more efficient and accurate diagnosis and treatment of diseases. The consistent clustering method takes sub-sampling from the gene expression matrix to determine the clusters with a specific cluster count (k). For the consensus value, the two items have the same cluster in the number of occurrences in the same subsample, which is calculated and stored in the symmetric consensus matrix for each k. There are many methods to determine the optimal clustering number *K* value of consensus clustering. The optimal cluster number can be determined by (principal component analysis) PCA method or by consensus CDF (Fig. 13.1b, c). However, no matter which method is used, the final clustering results need to pass the evaluation of clustering significance.

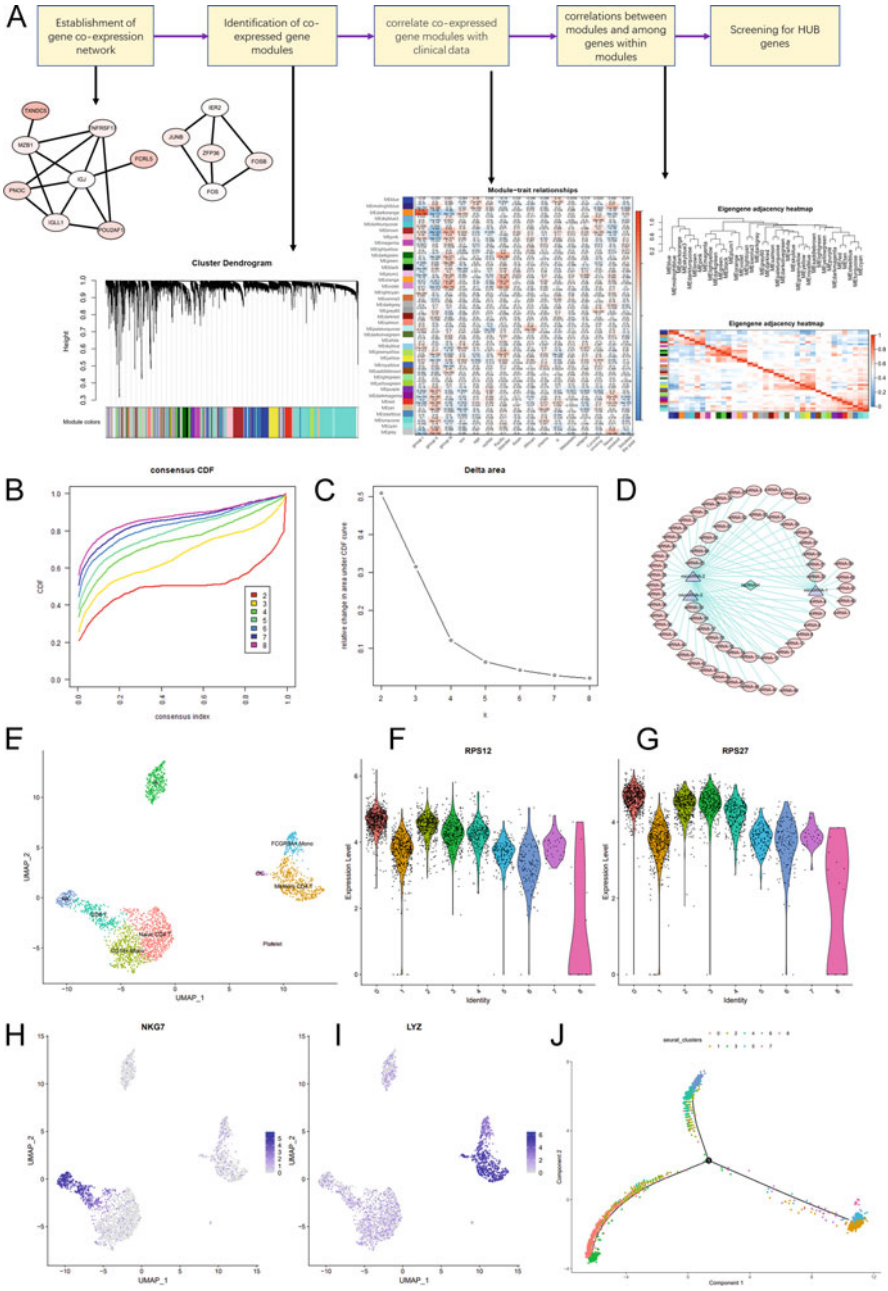

Fig. 13.1 Introduction to several bioinformatics methods. (**a**) The flowchart of WGCNA. First, the co-expression network was constructed, and then gene modules were formed, which were correlated with clinical phenotypes, and HUB genes were selected. **(b, c)** The method of consensus clustering to select *K* value. **(d)** A schematic diagram of the ceRNA network, which is usually composed of mRNAs, microRNAs, and lncRNAs. **(e, j)** Part of the results of single-cell sequencing analysis, and the analysis data came from the dataset PBMC3K provided by R package Seurat

In addition, before using consensus clustering to classify molecular subtypes of diseases, it is necessary to ensure that no batch effect exists; otherwise, the effect caused by batch effect needs to be eliminated.

13.2.3 The ceRNA Regulatory Network

Competitive endogenous RNA (ceRNA) has attracted much attention in academic circles in recent years. It represents a new regulation mode of gene expression. Compared with the mRNA-miRNA regulation network, the ceRNA regulation network is more sophisticated and complex, involving more RNA molecules, including mRNA, pseudogenes of coding genes, long non-coding RNAs and miRNAs, etc. ceRNA network provides a new way of studying transcriptome and can explain some biological phenomena more deeply. Common ceRNA networks generally contain differentially expressed mRNAs, microRNAs, and lncRNAs or circRNAs. Among them, the expression trend of mRNAs and lncRNAs was consistent, while the expression trend of microRNAs and mRNAs was opposite, and the same was true between microRNAs and lncRNAs. The regulatory relationships among microRNAs, mRNAs, and lncRNAs can be effectively predicted through the construction of the ceRNA regulatory network. It is helpful to excavate gene function and regulation mechanism at a deeper level and facilitate to understand many biological phenomena in a more thorough and comprehensive way (Fig. 13.1d).

13.2.4 Single-Cell Sequencing

Biomarkers are analyzed and mined based on genomics, proteomics, and transcriptomics in a large number of cell or tissue samples, of which the information always ignores the heterogeneity of the sample. In order to fully explore the heterogeneity of cells or tissues and explore the trajectory of cell differentiation, single-cell sequencing is essential (Wang and Song 2017). Techniques such as scRNA-seq and scATAC-seq are gaining popularity in scientific research.

By using Cell Ranger to process single-cell FASTQ files and mapping reads to the reference genome, we can obtain gene expression matrix, annotation information, and cell information. Data are imported into R packages such as Seurat (Satija et al. 2015; Durruthy-Durruthy et al. 2014) and Monocle (https://cole-trapnell-lab.github.io/monocle3/) (Trapnell et al. 2014) to create objects, and then principal component analysis (PCA), T-SNE, and other methods can be used to cluster cells, and marker of different clusters can be identified. In addition, cell types can also be identified based on marker identification results. For example, in the clustering results of PBMC samples, we can pick out the cell cluster with CD8a as marker and mark it as CD8+ T cells or pick out the cell clusters with GNLY and

NKG7 as marker and mark them as NK cells (Fig. 13.1e). It is worth noting that different single-cell sequencing methods have different ways of identifying cell types. For example, single-cell ATAC-seq can also identify and cluster similar cell types and states, but it generally uses the open promoter region as a signal of transcriptional activity.

Based on the above analysis results, further pseudotime analysis can be performed. As the cell transitions between states, it undergoes a process of transcriptional recombination, in which some genes are silenced and others are activated. These states are often hard to characterize. Pseudotime analysis of single-cell RNA-seq can view these states without the need to purify the cells (Guerrero-Juarez et al. 2019) (Fig. 13.1j). The single-cell transcriptome analysis data was derived from the PBMC3K dataset provided by R package Seurat.

13.3 Example of Molecular Bioinformatics in Application

Data analysis based on presentation matrices usually requires normalization of the data. Just as the count value in RNA-seq is normalized to obtain the FPKM value, the microarray expression data also needs to be normalized, which can be determined by plotting a boxplot (Fig. 13.2a). If you are using a Series Matrix File on the Geo Dataset for analysis, another problem you may encounter is whether you need to perform log2 transformations on the data. It can be preliminarily judged from the value of each expression quantity in the expression matrix. The analysis results should not only conform to the set threshold but also be analyzed in combination with the actual situation.

13.3.1 mRNA-MicroRNA Interaction Network

We studied the regulatory networks of mRNA and microRNA in non-specific interstitial pneumonia (NSIP) based on two datasets of GEO dataset GSE110147 (Cecchini et al. 2018) and GSE32538 (Yang et al. 2013) (Table 13.1). The online differential expression analysis tool GEO2R (http://www.ncbi.nlm.nih.gov/geo/geo2r/) was used to analyze the differences in the two datasets (GSE110147 and GSE32538), respectively, to obtain the genes and microRNAs differentially expressed in NSIP. Cutoff values were adjusted p-value < 0.01 and $|\log FC| > 1.3$ (FC: fold change of expression between NSIP and normal tissue) for DEGs and adjusted p-value < 0.01 for DEMs. GO and KEGG analysis of DEGs was done by DAVID database (https://david-d.ncifcrf.gov/) (Kanehisa et al. 2016). The $p < 0.05$ serves as the cutoff value.

The regulatory relationship between mRNAs and microRNAs was predicted based on the miRWalk database (Dweep et al. 2011; Sticht et al. 2018). Protein-protein interaction (PPI) network was obtained from STRING (http://string-db.org/)

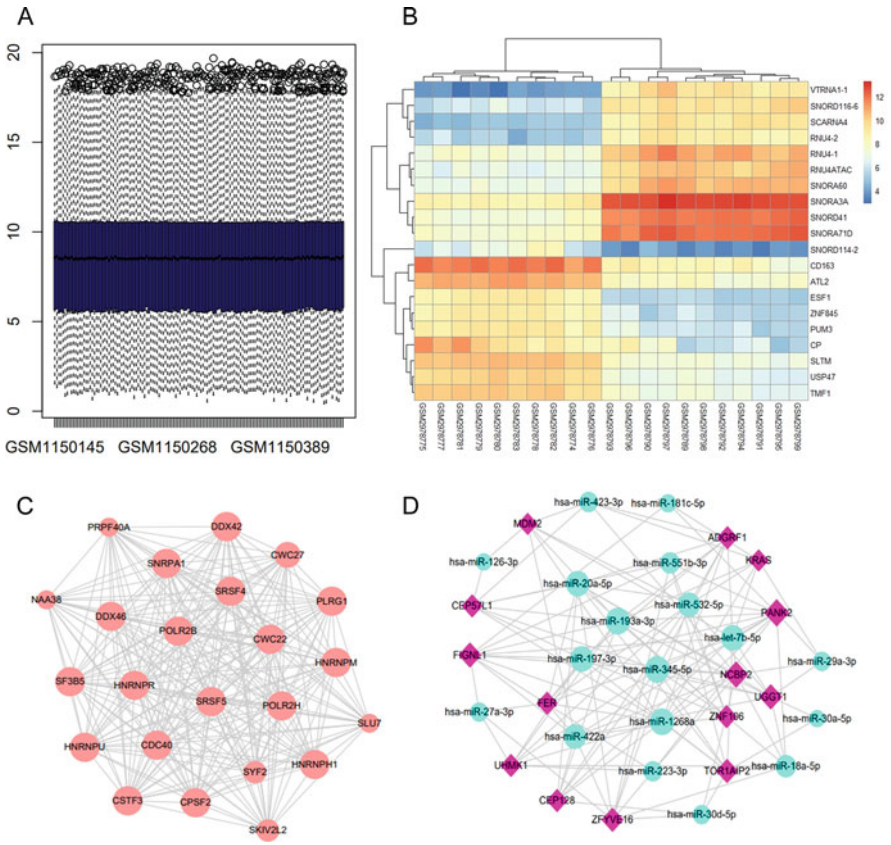

Fig. 13.2 NSIP-related differentially expressed genes and network analysis. (**a**) Boxplot of gene expression data, according to which the normalized of data can be roughly judged. (**b**) Heat map of the top 10 upregulated genes and the top 10 downregulated genes. According to the results of cluster analysis, 10 samples on the left were taken from NSIP patients, and 11 samples on the right were normal tissue controls. (**c**) Protein-protein interaction (PPI) network of differentially expressed genes with the highest score. (**d**) Interaction network between differentially expressed genes and differentially expressed microRNAs; 123 interactions between 18 DEMs and 14 DEGs were selected

Table 13.1 The situation of GSE110147 and GSE32538 in GEO database, respectively

GEO number	GSE110147	GSE32538
Experiment type	Expression profiling by array	Non-coding RNA profiling by array
Years	2018	2013
City	London	Aurora
NSIP	10	14
control	11	50

database (Szklarczyk et al. 2015). PPI network was drawn by Cytoscape (Su et al. 2014). The cutoff values were a combined confident score of >0.7 for the PPI network and a node degree of ≥10 for screening hub genes. We used the Molecular Complex Detection (MCODE) plug-in for Cytoscape to screen hub genes from the PPI network. As a result, there were 2099 differential expressed genes to be identified between NSIP and normal lung tissue samples, and these genes were potential disease-associated genes for NSIP. 450 genes were upregulated from normal to NSIP, and 1649 genes were downregulated. These genes maybe play key roles in disease onset of NSIP. The heat map of expression quantity of DEGs (the top 10 upregulated genes and the top 10 downregulated genes) was shown in Fig. 13.2b. In addition, we used to adjust p-value<0.01 as a threshold and identified 21 DEMs between NSIP and normal lung tissue samples.

The functional analysis was performed on GO and KEGG for the 2099 DEGs by DAVID database. In the result analysis, $p < 0.05$ was used as the threshold. The GO analysis revealed that the differential expressed genes were significantly enriched in immune response mechanisms, such as "innate immune response," "adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains," "adaptive immune response," "immunoglobulin-mediated immune response," "activation of plasma proteins involved in acute inflammatory response," "immunoglobulin production," etc. (Table 13.2a). Furthermore, by KEGG pathway analysis, the results indicated that DEGs were significantly enriched in tumor and cell cycle-related pathways, such as "Cell cycle," "p53 signaling pathway," or "Pathways in cancer" (Table 13.2b).

The molecular sub-network was identified by mapping the differential expressed genes into the PPI network, choosing the nodes in which the combined score is greater than 0.7 and the degree value is greater than 10. A sub-network with 131 nodes and 1009 edges was obtained from the network. By MCODE, a significant module containing 23 nodes and 246 edges was identified (Fig. 13.2c). We selected the ten genes with the highest degree (degree-value = 22): PLRG1, SRSF4, SNRPA1, HNRNPR, CDC40, DDX42, CWC22, HNRNPU, CPSF2, and CSTF3. Other genes in the significant module network are DDX46, HNRNP, HNRNPH1, SRSF5, POLR2H, POLR2B, SF3B5, CWC27, SKIV2L2, SYF2, SLU7, PRPF40A, and NAA38. Using adjusted p-value < 0.01 as the threshold for DEMs, 21 microRNAs were identified as differential expressed microRNAs between NSIP and normal tissue samples. With miRwalk3.0, a microRNA target gene prediction tool was obtained, and the score >0.95 serves as the cutoff. We predicted the target genes of 21 microRNAs and screened out the overlap between the target genes and the differentially expressed genes. A total of 3687 DEG-DEM interactions are obtained.

In addition, we drew DEG-DEM interaction networks by Cytoscape, calculated degree values of nodes, and further studied sub-networks with degree values ≥ 9. According to the interaction relationship, we further screened out the pairs of interaction relationship with opposite expression trend, selected a total of 123 interactions between 18 DEMs and 14 DEGs (Fig. 13.2d), and listed them in Table 13.3. In 14 target genes, MDM2, as a target gene of hsa-let-7b-5p, hsa-miR-126-3p,

Table 13.2 Shows the GO and KEGG analysis results of DEGs, in which Table 13.2(a) is the GO analysis results and Table 13.2(b) is the KEGG analysis results with the ten pathways with the lowest *p*-value

Category	Term	Involved in	*p*-Value
(a)			
GOTERM_BP_FAT	GO:0002252	Immune effector process	8.23E−04
GOTERM_BP_FAT	GO:0045087	Innate immune response	0.011
GOTERM_BP_FAT	GO:0002449	Lymphocyte-mediated immunity	0.015
GOTERM_BP_FAT	GO:0002250	Adaptive immune response	0.015
GOTERM_BP_FAT	GO:0016064	Immunoglobulin-mediated immune response	0.025
GOTERM_BP_FAT	GO:0002377	Immunoglobulin production	0.035
GOTERM_BP_FAT	GO:0002253	Activation of immune response	0.040
GOTERM_BP_FAT	GO:0002440	Production of molecular mediator of immune response	0.041
(b)			
KEGG_PATHWAY	hsa03040	Spliceosome	3.03E−04
KEGG_PATHWAY	hsa03018	RNA degradation	0.002
KEGG_PATHWAY	hsa04110	Cell cycle	0.003
KEGG_PATHWAY	hsa05222	Small cell lung cancer	0.007
KEGG_PATHWAY	hsa05218	Melanoma	0.007
KEGG_PATHWAY	hsa04510	Focal adhesion	0.008
KEGG_PATHWAY	hsa05016	Huntington's disease	0.009
KEGG_PATHWAY	hsa05200	Pathways in cancer	0.009
KEGG_PATHWAY	hsa05120	Epithelial cell signaling in *Helicobacter pylori* infection	0.012
KEGG_PATHWAY	hsa00190	Oxidative phosphorylation	0.020

hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-422a, hsa-miR-423-3p, and hsa-miR-532-5p, has been confirmed to be related to NSIP, but the regulatory effects of these four microRNAs on MDM2 in NSIP have not been reported in the literature. Studies have shown that compared with normal lung parenchyma, MDM2 in the epithelial cells of IPF and NSIP patients is significantly upregulated (Nakashima et al. 2005). In addition, CEP128 as a target gene of hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-20a-5p, hsa-miR-30d-5p, hsa-miR-345-5p, hsa-miR-422a, and hsa-miR-532-5p is an autoimmune thyroid diseases' pathogenic factor (Wang et al. 2019).

Based on the above research results, we have identified the interaction relationship between 18 DEMs and 14 DEGs associated with NSIP, which has not been reported yet. Of the 14 NSIP-related DEGs, MDM2 has been shown to be related to NSIP in previous studies (Chen et al. 2017; Wurz and Cee 2019). Therefore, the interaction relationship between 18 DEMs and 14 DEGs selected in this study, especially 4 interaction relationships of MDM2, may provide new ideas for the research of NSIP.

Table 13.3 The list of microRNAs with differential expression and the predicted target genes with an opposing expression trend

Target genes	MicroRNA
ADGRF1	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-345-5p, hsa-miR-423-3p, hsa-miR-532-5p
CEP128	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-20a-5p, hsa-miR-30d-5p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-532-5p
CEP57L1	hsa-miR-126-3p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-345-5p, hsa-miR-423-3p, hsa-miR-551b-3p
FER	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-27a-3p, hsa-miR-422a, hsa-miR-532-5p
FIGNL1	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-181c-5p, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-223-3p, hsa-miR-27a-3p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-551b-3p
KRAS	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-181c-5p, hsa-miR-193a-3p, hsa-miR-29a-3p, hsa-miR-423-3p, hsa-miR-532-5p
MDM2	hsa-let-7b-5p, hsa-miR-126-3p, hsa-miR-1268a, hsa-miR-193a-3p, hsa-miR-422a, hsa-miR-423-3p, hsa-miR-532-5p
NCBP2	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-18a-5p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-223-3p, hsa-miR-29a-3p, hsa-miR-30d-5p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-423-3p
PANK2	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-181c-5p, hsa-miR-18a-5p, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-223-3p, hsa-miR-29a-3p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-551b-3p
TOR1AIP2	hsa-let-7b-5p, hsa-miR-1268a, hsa-miR-18a-5p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-30a-5p, hsa-miR-30d-5p, hsa-miR-345-5p, hsa-miR-551b-3p
UGGT1	hsa-let-7b-5p, hsa-miR-18a-5p, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-29a-3p, hsa-miR-30a-5p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-532-5p
UHMK1	hsa-miR-1268a, hsa-miR-18a-5p, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-223-3p, hsa-miR-27a-3p, hsa-miR-345-5p, hsa-miR-532-5p
ZFYVE16	hsa-miR-18a-5p, hsa-miR-20a-5p, hsa-miR-223-3p, hsa-miR-27a-3p, hsa-miR-30d-5p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-532-5p, hsa-miR-551b-3p
ZNF106	hsa-miR-18a-5p, hsa-miR-193a-3p, hsa-miR-197-3p, hsa-miR-20a-5p, hsa-miR-345-5p, hsa-miR-422a, hsa-miR-532-5p, hsa-miR-551b-3p

This table contains 14 genes and 18 microRNAs

13.3.2 Identification of Genes Associated with Open Regions of Chromatin and Super-enhancers in Lung Adenocarcinoma

In addition to the analysis of mRNA-microRNA interaction regulatory network, which can explain the causes of some gene expression changes, the causes of gene expression changes are often explored through the identification of enhancers, super-enhancers, and open regions of chromatin. The presence of super-enhancers and open regions of chromatin generally leads to the upregulation of the corresponding

genes (Buenrostro et al. 2015; Peng and Zhang 2018). Super-enhancers are generally identified by analyzing ChIP-seq processed with H3K27ac (Jiang et al. 2017). The general analysis flow of super-enhancer identification is shown in Fig. 13.3a.

The potential regulatory genes of the super-enhancer can be identified by annotating the genes in the upstream and downstream 50kb range of the super-enhancer. The image shows the results of ChIP-seq analysis of the lung adenocarcinoma cell line A549, Calu-3, and lung fibroblast cell line IMR-90 (Fig. 13.3b–d). Among them, the ChIP-seq data of A549 cell line was derived from the Encyclopedia of DNA Elements (ENCODE) Project (Consortium EP 2012); GEO Accession numbers are GSE91337 and GSM2421889. The ChIP-seq data of the Calu-3 cell line came from the GEO database; GEO Accession numbers are GSM1548075 and GSM1548073 (Fossum et al. 2014). ChIP-seq data for IMR-90 cell line was derived from the Encyclopedia of DNA Elements (ENCODE) Project (Consortium EP 2012); GEO Accession number is GSE16256 (Lister et al. 2009; Hawkins et al. 2010; Bernstein et al. 2010; Lister et al. 2011; Schultz et al. 2015; Micheletti et al. 2017; Rajagopal et al. 2013).

The process of ATAC-seq to identify open regions of chromatin is similar to that of ChIP-seq, but data quality control is required. ATAC-seq data for the A549 cell line came from the Encyclopedia of DNA Elements (ENCODE) Project (Consortium EP 2012); GEO Accession number is GSE114202. Differential expression results of lung adenocarcinoma and normal controls based on TCGA database (Tomczak et al. 2015), we finally screened out five genes: EFNA5, HAVCR1, ATP1B1, DUSP4, and IGF2BP3, among which DUSP4 and IGF2BP3 are associated with prognosis. Prognostic analysis results were obtained from UALCAN (http://ualcan.path.uab.edu/) (Chandrashekar et al. 2017) (Fig. 13.3l–p).

13.4 Disease Categories Based on Molecular Networks

In the past, clinical phenotypes have been an important basis for distinguishing disease subtypes. Now, the concept of molecular subtype provides a new research idea for the diagnosis and treatment of diseases. Here, we present a case study of molecular subtypes associated with immune genes in COPD. Chronic obstructive pulmonary disease (COPD) is a form of chronic bronchitis or emphysema characterized by blocked airflow. If not treated, it often develops into pulmonary heart disease or respiratory failure (Blanchette et al. 2014; Kim et al. 2017). With the increase of air pollution, the incidence of COPD is increasing, but its mechanism is still not fully understood. Currently, COPD is still diagnosed and treated based on simple clinical presentation (degree of airflow limitation, symptoms and frequency of exacerbations, etc.). With the popularization of the concept of precision medicine, it has become a general trend to treat patients according to their individual differences (Zhang et al. 2018; Hogg et al. 2004). Reclassification of COPD is essential for developing more effective new treatments or optimizing existing treatments. Therefore, it is necessary for bioinformatics technology and the existing large amount of

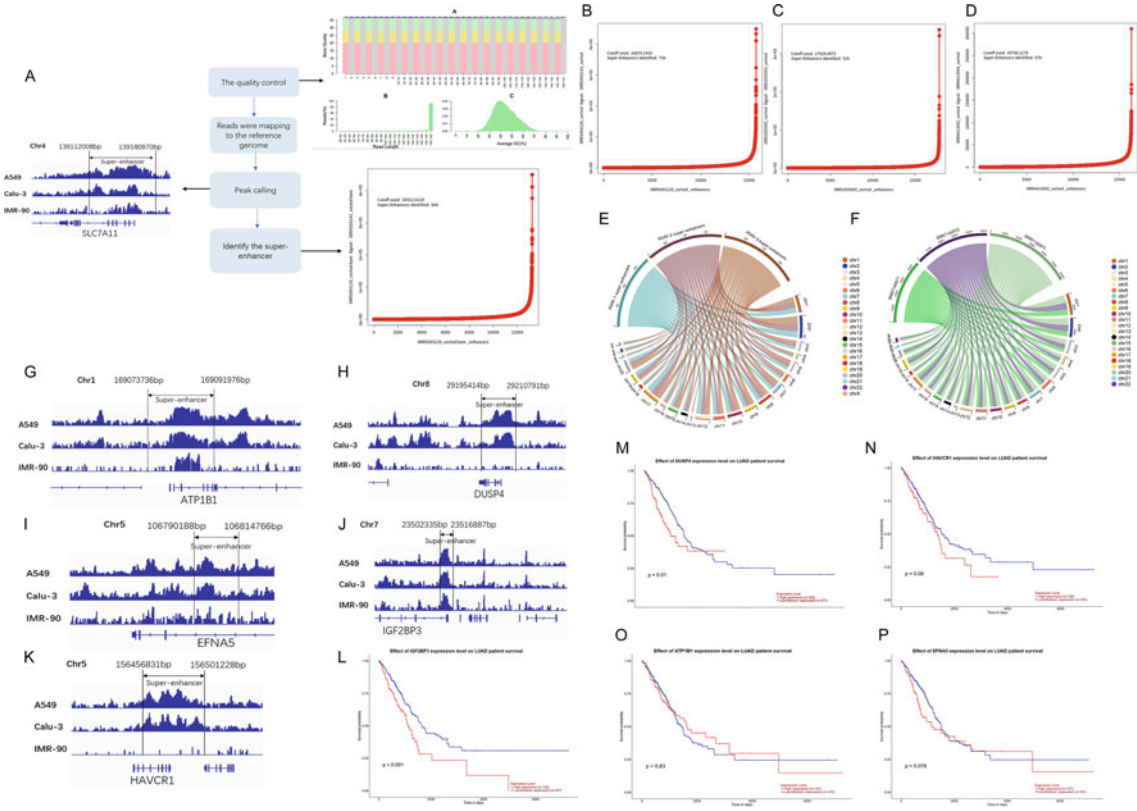

Fig. 13.3 Identification of genes associated with open regions of chromatin and super-enhancers in lung adenocarcinoma. (**a**) The process for identifying super-enhancers. (**b–d**) The identification results of super-enhancers in A549, Calu-3, and IMR-90 cell lines, respectively. (**e, f**) The distribution of super-enhancers and open regions of chromatin on chromosomes, respectively. (**g–k**) The H3K27AC signal near the five genes EFNA5, HAVCR1, ATP1B1, DUSP4, and IGF2BP3 in different cell lines. (**l–p**) Results of survival analysis of five genes. The result suggested that DUSP4 and IGF2BP3 were significantly associated with prognosis

high-throughput data to redefine and interpret large amounts of multi-level information. Two new research strategies (systems biology and network medicine) have the potential to provide new perspectives on the pathology of COPD. Our research has found that the immune-based COPD classification can be used as an auxiliary reference for clinical treatment, which is helpful to the advancement and development of precision medicine.

Common detection items of COPD patients are FEV1 (forced expiratory volume in 1 second) (Chuang and Lin 2019), FVC (forced vital capacity) (Chuang and Lin 2019), emphysema (F-950), DLCO (Hao et al. 2019), etc. DLCO tests the lung's ability to diffuse carbon monoxide. FEV1 is the rapid exhalation of air within 1 s after inspiration to total lung volume. FVC is the maximum amount of breath that can be exhaled as soon as possible after inhaling as much as possible. Emphysema (F-950) is the index involved in quantifying emphysema on CT images by using the density mask method to calculate voxel fraction of the lung (Radder et al. 2017). These indicators play an important role in the clinical diagnosis of COPD.

Although many articles have reported the influence of immune genes and pathways on COPD, the study on the classification of COPD according to the immune gene expression mode of patients' lung tissues has not been reported. COPD is a complex disease driven by a combination of genes; because the gene combinations of different patients are very different, COPD are wildly heterogeneous. Immune-based COPD classification may be used as an auxiliary reference for clinical treatment, which is conducive to the advancement and development of precision medicine.

The expression data of COPD (GSE47460) (Peng et al. 2016; Anathy et al. 2018; Kim et al. 2015; Yu et al. 2018; Tan et al. 2016) were downloaded from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds/). We excluded whole lung homogenate samples with interstitial lung disease and at risk and selected 139 COPD whole lung homogenate samples with different gold stages for analysis. Download the immune gene list from the ImmPort database (https://www.immport.org/: SDY1205, DOI: 10.21430/M37N6PJEQT) for research.

Combined with the list of immune genes, all the immune gene expression data in the expression data were taken for consensus clustering by using R package ConsensusClusterPlus (Wilkerson and Hayes 2010). According to the results of the first consensus clustering, we pre-classified the samples into 2 categories, 68 subtype I and 71 subtype II (Fig. 13.4a). By using R package Limma (Ritchie et al. 2015) for differential gene analysis of the 2 subtypes (Fig. 13.4b), 158 different immune genes were obtained. According to the screened 158 immune genes, consensus clustering was carried out for the second time, and the result of 69 subtype I and 70 subtype II was obtained (Fig. 13.4c). 134 immune genes were differentially expressed between the 2 subtypes. Through the third consensus cluster analysis of the 134 different immune genes, the final subtype grouping was obtained, including 70 subtype I and 69 subtype II. A total of 131 immune-related differentially expressed genes were found between the 2 subtypes.

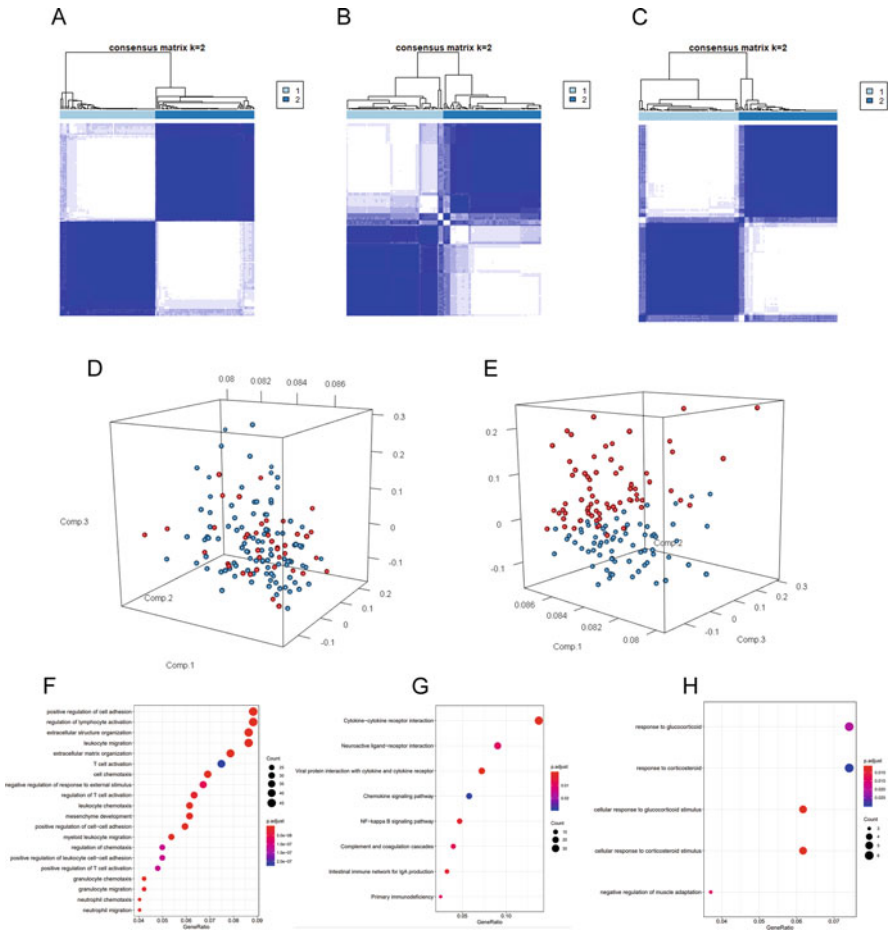

Fig. 13.4 Molecular subtype analysis of chronic obstructive pulmonary disease. (**a–c**) The result of thrice consensus clustering. (**d**, **e**) Principal component analysis (PCA) of immune-related genes. PCA results confirm that the molecular subtypes obtained in this study are not caused by batch effect. (**f**, **g**) GO and KEGG enrichment analysis results of differentially expressed genes between subtype I and the control group. (**h**) GO enrichment analysis result of differentially expressed genes between subtype II and the control group, but there is no significant enrichment KEGG pathway

The R package SigClust (Huang et al. 2012) was used to evaluate the clustering results, and the clustering significance *p*-values of the two subtypes obtained were shown in Table 13.4. The *p*-value of the third cluster is the smallest.

In general, the series matrix file of GEO database has preprocessed the data. But we are still trying to verify whether there is a batch effect in the data. To ensure that the intergroup differences we analyzed were not due to batch effect, we queried the sample data one by one from the GEO database and obtained the batch information of 139 COPD samples we used. First, we performed principal component analysis

Table 13.4 shows the clustering significance between the two subtypes of the third consensus clustering

	Subtype I	Subtype II
Subtype I	1	6.175072e−05
Subtype II	6.175072e−05	1

Table 13.5 Chi-square test results between clinical data and subtypes

		Subtype I	Subtype II	df	X-squared	*p*-value
Gold stages	Gold I and II	38	50	1	4.1916	0.04063
	Gold III and IV	32	19			

The results showed that gold staging is significantly correlated with the two subtypes

(PCA) on the total expression data of 139 COPD samples and on the immune genes differentially expressed between subtypes I and II in the third consensus cluster. Batch or subtype information was labeled in the three-dimensional scatter plot to verify whether the differential gene expression between different subtypes was caused by batch effect. In addition, we did the same for 131 differentially expressed immune genes in the third consensus cluster. Ensure the consistency of clustering results and intergroup differences are independent of the batch effect. As shown in Fig. 13.4d–e, the clustering results of labeled batch information are inconsistent with the clustering results of labeled subtype information, which proves that the subtype we obtained is not caused by batch effect.

To determine the differences between different subtypes and the normal control group, we set $p < 0.01$ and fold change $= 0.5$ which were used as thresholds to obtain differentially expressed genes between subtypes, and functional enrichment analysis was performed on the results. Functional enrichment analysis was performed using R package clusterProfiler (Yu et al. 2012). As shown in Fig. 13.4g, subtype I was significantly enriched in immune-related pathways, while subtype II was not. This seems to indicate that the immune subtype I identified is more immune-dependent than the immune subtype II.

In combination with clinical data, we investigated the relationship between two immune subtypes and clinical data. We performed chi-square tests on gold stages in the two subtypes. Results showed that the proportion of gold III and gold IV patients in subtype I patients was significantly higher than that in subtype II patients (Table 13.5).

We used R package WGCNA (Langfelder and Horvath 2008) to further investigate the genes that play a key role in the division of molecular subtypes. All the genes in the dataset were included in the analysis so as not to miss out on key information. The results showed that the turquoise module was significantly correlated with the molecular subtypes (Fig. 13.5c). According to gene significance and module membership (Fig. 13.5d), we screened out 11 key genes for subtype classification (Fig. 13.5e–g).

Through bioinformatics and computational analysis, we have determined the possible set of mutations associated with immunity, as well as genes, cell types,

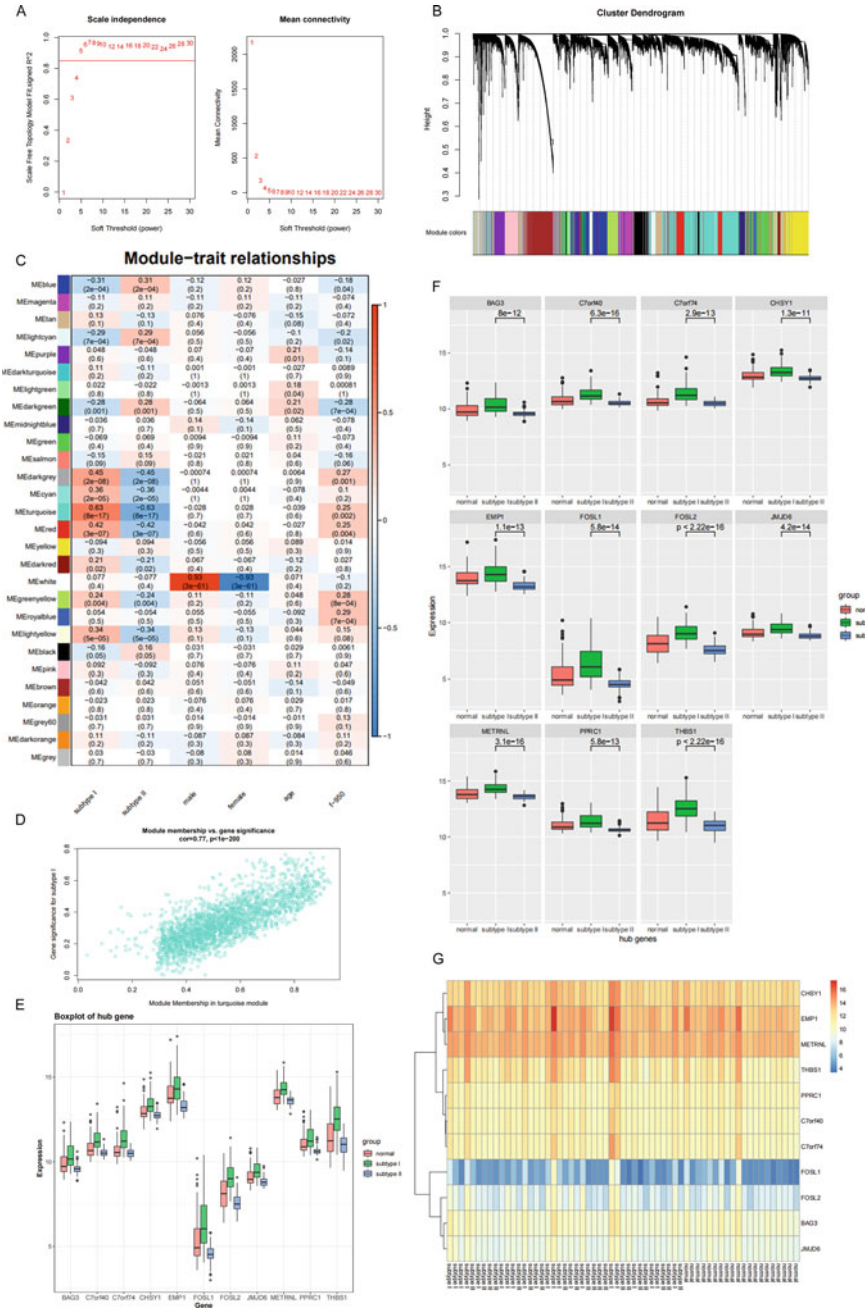

Fig. 13.5 Weighted gene co-expression network analysis and HUB gene screening. (**a**) The horizontal axis is soft threshold (power), and the vertical axis is the evaluation parameter of scale-free network. The higher the value is, the more the network conforms to the non-scale feature. (**b**) Gene clustering results. (**c**) Results of association between gene co-expression modules and clinical phenotypes. Correlation coefficient of threshold setting is greater than 0.5, and *p*-value is less than 0.05. (**d**) Correlation between genes and modules and phenotypes in turquoise module.

and biological pathways. Our analysis provides further support for the genetic susceptibility and immune heterogeneity of COPD. We identify the characteristics in each subtype of COPD, which may provide new insights into the biological mechanisms to promote the progress. Studying the use of these endotypes and biomarkers may be helpful for the diagnosis and treatment of COPD and the development of precision medicine.

13.5 Conclusion

Gene sequencing technology helps doctors diagnose patients with symptoms that have no clear cause. But the large amount of data generated is often difficult to get answers quickly. The use of molecular bioinformatics solved this problem. Most diseases are not caused by a single genetic defect but are caused by the interaction of a variety of different genes. Gene expression products such as RNA and proteins interact with other proteins and metabolites in the cell to form a signal regulation network of the disease. Gene mutation did not occur at exactly the same place, but some mutations occur in genes on the same signaling pathway. Gene expression can be changed by the environment, and when changed, specific disease subtypes or endotypes can be formed. Many interventions in the experimental model cannot be completely reproduced on the human body, and therefore molecular bioinformatics provides a way to explore the molecular complexity of a particular disease, to identify disease pathways and modules, and to explore the molecular connections between the different phenotypes. Therefore, molecular bioinformatics has the potential to discover new disease genes, reveal the biological importance of disease-associated mutations, and identify complex diseases, drug targets, and biomarkers (Agusti et al. 2017). The rapid development of molecular bioinformatics provides new ideas for the diagnosis and treatment of diseases. Molecular bioinformatics is defined as a treatment tailored to the individual needs of patients, which distinguishes specific patients from other patients with similar clinical manifestations based on genes, biomarkers, phenotypes, or psychosocial characteristics. Bioinformatics can often reduce research costs and be quick and effective, by computing a large number of sample data, summarizing rules, and associating phenotypes. It helps the precision medicine enter the primary medical system.

For primary hospitals, the simplification of methods is more conducive to the promotion of bioinformatics technology. As bioinformatics tools become more and more accessible, information learning loses some of its complexity and is easier to master quickly through short training. The transition from clinical practice to precision medicine is a more effective and safer way to treat patients than existing

Fig. 13.5 (continued) Genes with GS greater than 0.4 and Mm greater than 0.9 were selected as hub genes. (**e**–**g**) The difference and significance of hub genes' expression in the two subtypes and the control group

treatment methods. For the primary medical institutions, it has more development prospects. Most of the training and research related to bioinformatics take place in high-income areas and resource-rich medical institutions, while in primary medical institutions, bioinformatics technology cannot be popularized due to the limited funds and talents. It is becoming more and more urgent to assist primary medical institutions to train professionally talents in the field of bioinformatics. Our article offers an important perspective: molecular bioinformatics can be used in hospitals, and the basic approach we describe is clinically achievable. By learning the methods involved in our research, the personnel of primary medical institutions can use existing resources to re-analyze the published data which helps to re-understand the disease. In addition, the increasing popularity of cloud resources and the availability of online training materials provide excellent opportunities for researchers in primary medical institutions with limited resources. Researchers in primary medical institutions can use cloud resources to analyze large omics datasets, which can reduce the differences caused by equipment shortages to some extent (Mangul et al. 2019). The development of bioinformatics in primary medical institutions is conducive to discovering local related genetic abnormalities.

According to biomedical and life sciences researches, bioinformatics is essential for science to explain treatments and high-throughput omics data meaningful. In the process of disease recognition, diseases are often diagnosed and treated according to phenotypes. Using molecular biological information technology to classify ovarian cancer, it was found that the FGF pathway, a pathway related to tumor proliferation and angiogenesis, plays a significant role in one of the subtypes of ovarian cancer (Hofree et al. 2013). The subtype of liver cancer that overexpress seven hub genes may lead to reduced overall survival in patients (Li et al. 2021). According to the data searched from the public database, bladder cancer is divided into two main molecular subtypes, basic type and differentiated type, and it is found that basic type tumors are associated with a shorter survival period (Volkmer et al. 2012). Cancer involves not only individual mutations but also dysregulation of multiple pathways governing fundamental cell processes such as cell proliferation and apoptosis (Kreeger and Lauffenburger 2010). Increased researches have successfully integrated that database with the molecular to map the signal network of cancer. Through the use of bioinformatics analysis in the molecular signal network, we can subdivide a set of tumor mutation into different subtypes via their biological and clinical information. These subtypes are different from those classified by other clinical markers that are well known to be associated with survival. The subtypes may provide new insight for biological mechanisms driving disease progression.

As molecular bioinformatics become integrated into clinical treatments (Seiler et al. 2017), molecular subtype will become critical for determining the intrinsic feature of many diseases. Heterogeneity is a major challenge to promote precision medicine. If molecular bioinformatics is applied to clinical practice, the treatment and prognosis of diseases will be improved to a new height. We hope that the integration of molecular bioinformatics and multi-omics data will enable patients to receive more accurate, effective, and safe treatments.

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Chapter 14
Being "on a Mission" at Work: How to Make Mission Statements Effective in the Healthcare Sector

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Abstract The identification of the mission in organizations is crucial, providing a purpose and giving transcendent meaning to each person's work, among other benefits. But often mission statements are not carried out and have few practical results. This chapter aims to shed light on why it happens and how to make missions effective. We focus on the health sector and particularly on hospitals. We conclude that (i) a mission should be a real service—with a logical fit to truth and good—which generates value for its stakeholders; (ii) to kindle a "sense of mission" among the whole company, employees need to internalize the mission, aligning their values with those of the company; (iii) mission needs to be implemented in all organizational dimensions so that the purpose can translate into action, suggesting the need to use an operative tool (dynamic mission); and (iv) it is essential that *motor mission* (the personal motivation while connected to the accomplishment of the company's formal and dynamic mission) becomes a true end goal of the company's members. Finally, we discuss how "motor mission" is activated by transcendent motivation. This motivation goes well beyond contractual theory and becomes the key to make missions effective.

Keywords Managing people · Management by missions · Motivation · Healthcare management

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14.1 Introduction: Mission in Organizations

This chapter briefly covers mission in organizations and its importance and content, focusing on the health sector. Presented with scarce practical results from mission statements in several organizations, in which the health sector is not spared, we outline some ideas—based on existing literature—on how to kindle the "sense of mission" of each worker and in doing so align the diverse participants of the company, to make the mission effective.

14.1.1 The Concept of Mission

The concept of mission is rich in nuances and is used with different content and meanings. Mission has been present in business management for about half a century and is currently one of the main business tools in companies all over the world (Cardona and Rey 2005). In fact, it is rare to find a company or institution without a mission; however, mission is one of the most misunderstood business tools (Bart and Hupfer 2004).

At the root of defining mission, there is Peter Drucker's question (1986, p. 56): "What is our business and what should it be?" This is linked with Frankl's (1959) contribution, although not in organizational terms, that the search for meaning and the need to be a part of something with a broader purpose than oneself is a basic human impulse. A timeless statement, actually, already studied by ancient philosophers.

Campbell and Yeung (1991) consider that the response to Drucker develops into two schools of thought. One sees mission as a purely strategical tool, which defines and describes business basics and their relationship with the market. The other school sees mission in ethical and philosophical terms, as a cultural binder which makes it possible for an organization to function as a collective unit. This culture based on norms and values influences people's behavior: in their way of working and pursuing the goals of the organization; besides that, it allows for employees to understand and interpret phenomena in a similar manner and to express themselves in a common language. According to these authors, both schools of thought can and should synthesize in the same description of mission, since this includes both strategy and cultural aspects.

This is possible to align with Rey's (2011) work, which refers several ways of understanding the concept of mission, ranging from a more confined perspective (value the business offers the client) to a broader group of elements which, other than serving certain stakeholders, includes the company's global view.

It is out of the scope of this study to review the literature on the concept of mission in detail, but it is important to clarify the meaning with which it will be used in this chapter.

Mission is the "what for" of a company. Mission is the purpose of a company, the essence of a business, the contribution to the main stakeholders (Rey and Mas-Machuca 2013): clients, investors, and workers (Cardona and Rey 2005). Naturally, a company's mission is closely related and interdependent on the essence of the organization or company (what the company is, that means, its nature or identity). Therefore, mission is, concisely, "a contribution that characterizes the identity" of the company (Cardona and Rey 2009, p. 2).

It is more of a contribution, not a position.[1] A contribution which "is, in the first place, a service, a specific way to solve real problems of people, groups or society at large. Yet not all contribution is mission. Missions are those contributions which characterize identity, give meaning to the existence of a company, department, team or professional" (Cardona and Rey 2005, p. 63).[2]

Mission can be described through several elements, which include purpose and value, but also strategy and behavior, as referred to in "The Ashridge Mission Model," a reference in the 1990s (Campbell and Nash 1992).

Finally, it is important to differentiate between mission and two other concepts associated: values and vision. We consider values as principles: criteria which guide decision-making on the most appropriate behavior in each situation, indicating how to fulfill the mission (Cardona and Rey 2005). Vision is considered as a future image the company would like to achieve (Senge 1998).

14.1.2 Mission Statement

To make a company's mission more explicit, a mission statement can be made, which is a formal, written document, and tries to capture the sole and permanent purpose of the organization, to serve as a reference for organization's planning and goal setting (Ireland and Hitt 1992). It is also a message to others and a process of self-communication (Bartkus and Glassman 2007).

> Mission describes who the organization is and what it does. It is a statement of purpose, not direction. Effective mission statements commonly define what business the organization is in, its beliefs about how business should be conducted, the markets and customers it serves, and the unique value it contributes to society at large. Rarely do mission statements change significantly over time (Levin et al. 2000, p. 93).

[1] For example, a company being market leader in its sector is a position, not a mission.

[2] For example, a business which produces cell phones may, using its own resources, promote various charitable actions to fix a house for the homeless, but this (laudable) contribution is not its mission as a cell phone producer. On the other hand, it can be included in its mission to keep in mind, *in the process of producing cell phones*, to facilitate the inclusion of excluded members of society such as the homeless. Both are contributions in favor of the homeless. The latter is intrinsic to the business and therefore part of its mission. Values such as justice and solidarity are not something *added* to the business activity, but are an invaluable reference for it.

Therefore, it seems that missions which are broader and qualitative and reflect the organization's purpose are more attractive than those which reflect quantifiable measurements of production or finance (Paarlberg and Lavigna 2010).

14.1.3 Mission and Stakeholders

A mission statement is a good map of the relationship between the company and its different stakeholders. Among the main ones, it is common to identify clients, investors, and employees or workers; it is becoming more common to add the community where the company exercises its activity or general society to this list, as the importance of social corporative responsibility has grown over the last years (Rey 2011).

The ideas which underlie the stakeholder theory (mainly described in "Strategic management: a stakeholder approach" by Freeman (1984) have become more widely accepted in business and in various fields of management science. Currently, it is clear that companies will only be able to compete successfully if they earn the trust of all active participants in their business (Regojo 2014). Understanding and meeting the needs of different stakeholders maximizes efficiency of organizational interrelationships (Evans 2012).

This is not void of possible conflict of interests. One may question at times if it is reasonable to exclude legitimate interests of a key stakeholder, for example, to withhold a service from clients; or to lack action for the development of workers; to not generate dividend for investors; or even to not have a positive impact on society in general. In order to establish priorities among the stakeholder's ambitions, what a company is and what its main ends are must be clear. This is necessary not only in theory but in the particular case of each company.

It is also necessary to keep in mind "the consideration of the person as a subject who possesses dignity and can never be treated as means to an end" (Canals and Fontrodona 2006, p. 39). A company that did not generate value, did not serve society, and did not develop people could possibly not call itself a company (Llano Cifuentes 1997).

To conclude, taking into consideration the balance of different stakeholders implies that, on the one hand, these are people or groups with legitimate interests in substantial or procedural aspects in business activity and, on the other hand, that the interests of all parties have intrinsic value. This is that each stakeholder deserves consideration on his own and not simply due to being able to satisfy the interests of another group (Donaldson and Preston 1995).

14.1.4 Mission's Added Value and the Sense of Mission

Each mission—if it is authentic and achievable—generates value by definition. The definition of mission already includes the added value the mission imparts to society and, as by reflex, to the organization and its members. This definition—made explicit in the mission statement—also includes the genesis of many relevant advantages not only from the ontological point of view but also for the company's organization. Let us expand on this. Fonseca Pires (2017) extensively compiles the advantages that one would expect from a mission statement in the management of an organization, referencing several studies.

These advantages can be summarized, from an outside point of view, as an instrument of institutional communication, making the identity and goal of the company known to clients, suppliers, authorities, and the general public. Thereby the organization's goals are made clear and attract the resources necessary for their operation.

From an internal point of view, we can highlight three key points:

(a) *Inspiring and motivating all that are part of the organization*, providing *purpose* and *direction* in their intervention and collaboration in the business, and giving *meaning to their work*.

This can be called kindling a sense of mission in each element of the business, that is, emotional commitment [perhaps interior, because it does not just imply feelings] of people to the company's mission, which happens when there is an adjustment between the organization's values and individual's values (Campbell and Yeung 1991). If the employees consider the organization's mission as something important and consistent with their own values, it is more likely that they will identify with it and incorporate organizational goals (Weiss and Piderit 1999).

This implies the existence of a true and coherent mission in the business. The more attractive, participative, and valuable the mission is to the workers, the more they will support the business, affiliate themselves, and feel motivated to work well in it (Rainey and Steinbauer 1999). The more "satisfaction" the employees feel for the mission and the more intelligible, clear, and valuable it is to them, the more they will feel personally committed (Bart et al. 2001). The greater the perception of the company's loyalty to the declared mission, the greater the synchronization of the workers with it (Suh et al. 2010).

Thus, the meaning of mission is not just "something good" but "something necessary" because it takes on a relevant role in the development of employees' motivation (Rey and Mas-Machuca 2013), which reflects in benefits for the workers and the entire company.[3]

[3] If we said until here that true and coherent mission can kindle a sense of mission and motivation in workers, in Sect. 14.4 of this chapter, we will look at how, at the same time, it is only possible to fulfill the mission of the company with people that possess a particular kind of motivation.

Finally, from this first point, responsibility and self-control from the workers arise, avoiding excessive formal mechanisms of external control and its financial costs.

(b) *Focusing and guiding the strategy and decision-making.*

The existence of a clear mission that is known to all enables and shines light on strategic options. On this, Drucker (1986) defended that a business is not defined by its names or statutes, but instead by its mission, and that the strategy requires knowing beforehand "what is our business and what should it be": one clear definition of the company's mission—setting of priorities, strategies, plans, and job allocation—makes the establishment of realistic and clear goals feasible.

By pointing in the same direction which transcends the individual and his needs, as well as those of the department, the mission statement enables the process of coherent decision-making in all levels of the company, especially in high-level management, whether they are strategic, critical, or current decisions. It also avoids dispersing into other causes, which might be noble, but are not part of the business's mission. It also serves to justify the allocation of resources, regardless of the level of decision.

The fact of a mission transcending the individual also stresses that those that lead the business are not the source of authority, but that this derives from the ideas stated in the mission. The mission becomes more important than the boss (Senge 1998).

(c) Finally, we can add—although this subheading also has an external reach—that mission provides a *balance between the competitive interests of the stakeholders* (clients, society, shareholders, workers), guaranteeing that their legitimate interests are not ignored.

To conclude, the impact of a mission statement on better financial performance does not yet seem very clear, although some authors point toward this. Mission seems to influence behavior and attitude more directly than reaching goals (Campbell and Yeung 1991): the mission statement influences behavior, commitment, and satisfaction in workers more than financial revenue (Bart et al. 2001). It is intuitive, however, that this impact on behavior, commitment, and satisfaction can also contribute to financial improvement.

14.2 Missions in the Healthcare Sector

14.2.1 Importance

The context above allows us to have a global view of the importance and impact of management by missions. We can look at this model in the health sector specifically, taking into account its nature and particularities.

About 20 years ago, Bart (2000) indicated that the mission statement was growing in importance in modern health organizations and that the development

of an adequate mission statement is one of the most critical strategic tools to attain (and evaluate[4]) the success of an organization in the health sector.

In fact, a correct formulation of a mission statement helps the hospital—especially in moments of greater pressure and uncertainty—to identify and focus on its main and critical capacities; to allocate scarce resources appropriately while promoting, in times of budget restrictions, efficiency and effectiveness; to react to new strategies, reorganizing them toward the purpose[5]; and to redress the low morale of employees, inspiring and motivating them (Bart 2000). Mission also establishes relevant organizational orientations to help put professionals on the same page—especially physicians (Lindgren et al. 2013)—with an organizational purpose (Lee and Cosgrove 2014). Another reason is that the health sector is constantly changing (legislation, technology, financing, etc.) and has diverse characteristics, which can lead to the members of the organization losing sight of the purpose of the institution. Due to all of this, it is essential that, for directors and workers alike, a robust mission statement be made which can be referred to in times of uncertainty (Forehand 2000).

14.2.2 The Specific Content of Mission Statements in Healthcare Sector

Taking this into account, what content should be present in the mission statement of a health institution, specifically in that of a hospital? In the work of Fonseca Pires (2017) we have been following, there is another compilation of studies, which analyzes the most frequent content in hospital mission statements.

Here we limit ourselves to briefly naming what stands out from these studies as main points in the content of the hospital mission statement: Firstly the identity of the hospital, which end up to primarily feature the "reason" and "great aspiration" of the hospital. Next, the identification of the stakeholders, of the services provided, and of the client-patients served; patients emerge as main stakeholders in hospitals and providing appropriate and excellent care for them is of utmost importance in the hospital mission statement; also, a concern with workers in the content of hospital mission statements has the tendency to be higher than in other industries; shareholders are referred as well as the sustainability and survival of the hospital (resources); suppliers, although with a lesser presence; society in general. Finally, the competitive orientation: relative position and level of differentiation with which the organization hopes to attract and keep patients.

It is also important to refer a minor presence of components such as "financial goals" and "competitive strategy and position," although some studies (Bolon 2005)

[4] Bart (2007).

[5] This is the current debate surrounding the pandemic in 2020/2021, which frequently refers that hospitals have given undue priority to patients with Covid-19, in detriment to other patients with serious illnesses.

did not find significant differences in the content of mission statements in a sampling of 52 American for profit and non-profit hospitals.[6]

Last, and generally, research indicates no significant differences in the main content in mission statements in organizations in the United States and Europe (Bartkus et al. 2004). Also, workers in health institutions in diverse cultural environments and countries seem to have a common idea on organizational attributes necessary for providing quality healthcare (Flynn and Aiken 2002).

14.3 Making the Mission Effective

In many cases, the mission becomes a declaration without practical consequences. After years of developing missions in the company—also in the health sector (Graber 2009; Katongole et al. 2015)—many companies admit not having effectively introduced them into the organization (Cardona and Rey 2005) or their implementation having been difficult or even impossible (Fairhurst et al. 1997; Warner 1995).

Even if many companies state their mission, behavior of employees is not necessarily congruent with this purpose (Wang 2011). Other than this, the positive influence of the mission statement seems to be limited to managers, seemingly very reduced among other members of the organization (Vandijck et al. 2007; Vardanyan and Kaur Grewal 2015).

Fonseca Pires (2017) presents literature that highlights the insufficiency of a formalization of meaning and purpose in a mission statement if it is not accompanied by proper implementation. Within the list in this work, we draw attention to a few reasons that could be behind the failure to carry out a mission statement practically.

These reasons are: the lack of truth or incongruity of the mission (which solely exists to morally legitimize something whose true objective is another, less noble, although well-known by the managers and workers of the company), which makes it empty or even hypocritical; the oversight of mission (lack of capability of the managers in identifying what is truly the company's mission, with which the workers truly identify); the merely institutional existence of mission (it exists because it is supposed to exist, for bureaucratic reasons); a mistaken evaluation by directors (because they use inappropriate criteria, based more on budget than on stakeholder satisfaction); the lack of specificity, ambiguity, being outdated, or even the impossibility of the mission; lack of transmission and of fluid communication about mission on all levels of the company; the existence of aspects of mission in broader guidelines of the company, but its scarce presence in more current character procedure.

[6]Even though none of the groups showed reluctance in referring to concepts such as "quality of assistance," some reluctance was noted in "for-profit" hospitals in mentioning financial aspects in their mission statement.

This being said, *what is needed to make mission effective?*

1. It needs to be supported by an *implementation plan*, because as we have seen it doesn't automatically flow in the organization (Desmidt et al. 2008): once the mission is identified, it is the task of high-level management and, afterward, of each director not only to promote the “sense of mission” of each person but to consider how he will do so, whether through training, coaching, goal-setting, processes, etc.
2. It is necessary that the mission be taken on by workers as part of their convictions and values, that is, it *needs to be internalized* (Marimon et al. 2016).

   Other than this, the *implication of several stakeholders* (directors, managers, workers, patients, investors, etc.) in the design and development of the mission statement has an important role to achieve an effective mission, conquering a *belonging and ownership* which leads to having workers more dedicated to the mission, with more energy to see it completed and more permeable to its influence (Bart 2000).
3. The more the *mission is true* (not just in terms of transparency—of doing what it says it does—but also in terms of the mission being in conformity with truth and good, in other words, that it seeks to satisfy a real need of society), the more pronounced is the internalization of mission and the feeling of belonging to the company. Mission, to be effective, should have a foundation, a content or base, which is logical, fitting for reality (Bart et al. 2001).
4. To achieve a robust *alignment between mission and other organizational dimensions*: this is achieved by making mission's implications reach operational and strategic planning, cost control, leadership, goal-setting, and, especially, the results evaluation system (Bart and Tabone 1998). Yet it would also be desirable to have this present in the processes of selection and recruitment, in the description of job openings (Crotts et al. 2005), in training sessions. On the whole, to achieve a clear connection between mission and action in all that the company does.

   The purpose and mission must be translated into action. Otherwise, it is reduced to words that never become reality; mission should be present in systems such as goal-setting, allocation of resources and job openings, structure definitions, and operative decisions (Drucker 1986); mission should translate into policies and directives of attitudes and behaviors which help people decide what to do in their everyday work (Campbell and Yeung 1991, p. 14).

   As such, it is important to bring the mission closer to all levels of organization, conferring meaning to each specific context (Cardona and Rey 2005), to the policies established, to systems created, to traditions started, to stories told, that is, to everything workers do, because the organization should base itself on its workers—on their attitudes and actions—to secure the effective fulfillment of mission (Crotts et al. 2005).
5. *In order for mission to fulfill its purpose, high-level management should transform it into an operating tool*. All aspects of performance which are implicit in the mission statement should translate into specific goals, measurable, acceptable,

realistic, and timely (Doran 1981), so that the results may be reliably evaluated (Bart and Hupfer 2004).

To connect the individual with mission so that each worker may acquire a profound sense of mission, capable of uniting and unifying head, hands, and heart (Huber et al. 2003), and to transform intentions into specific goals which make connection between mission and objectives more evident (Paarlberg and Lavigna 2010; Warner 1995), it is necessary to establish mechanisms that allow to concretize, analyze, and evaluate the mission according to indicators or evidence (Rey 2011).

In this sense—the need for an operative model—Cardona and Rey (2005) propose a process through various departments, teams, and people in organization. Each division, department, or workstation should reflect and specify a formal declaration which makes explicit its "why." This unfolding of the company's mission in "participated missions" will confer meaning to different levels and functional areas of an organization.

We can summarize this section with Rey's (2011) proposal (see also Rey and Bastons 2018), which points to three dimensions which he calls "minimal conceptual model" of mission: formal mission, dynamic mission, and motor mission:

(a) *Formal mission* is the explicit declaration of the ends of the company identified as such by members of the organization, defined and communicated through the *mission statement*; there it is translated into the "why," the purpose of the company. It describes the basic commitment of the business with certain ends.
(b) *Dynamic mission* is the level of accomplishment of the formal mission, the "why" of the company expressed quantitatively (the operative tool referred to in point 5), guided to establish mechanisms which reinforce the integration of mission in management systems as a way to evaluate the company's performance and set goals.

    Directors will not be able to see the extent of the fulfillment of the mission if their components do not translate into measurements (Bart and Hupfer 2004). Naturally, the measurements of various tangibles and intangibles are not void of problems and have a high level of subjectivity (Kaplan and Norton 2004); but quantification is useful, and, according to Crotts et al. (2005), it is necessary and serves as a message of alignment, or lack thereof, with the organization's mission.
(c) *Motor mission* is the personal motivation of members of the organization as linked to the accomplishment of the company's formal mission and not to be confused with the personal motivation related to his own benefit. It is the result of considering mission from a teleological perspective, in which mission becomes the end goal of the actions of the business's members. It differs from the other two dimensions of mission—formal and dynamic—because it develops exclusively within people.

Motor mission is what makes formal mission and dynamic mission become authentic, something genuinely sought after and desired as a true end goal for people and for the organization and not just a declaration of interests or the appropriate

result of an activity. It is understood that only if a formal mission exists in the company, known and motivating to workers, can there be motor mission.

Motor mission can have different levels in function of people’s motivation in relation to the company’s mission (Rey 2011). Therefore, “motor mission” is activated by motivation, which we will look at now. It is a specific kind of motivation.

14.4 Mission and Motivation

For mission to be achieved and the “sense of mission” kindled in the organization, motivation is required. This is particularly relevant in the health sector. Likewise to technical value, motivation is one of the key factors to achieve good service by healthcare professionals and, in this way, an appropriate quality of the service provided and higher efficiency and equity, three results which are obtained through the worker’s effort and dedication (Franco et al. 2002).

In fact, providing healthcare is highly labor-intensive, and, at the same time, the performance of the healthcare professionals depends heavily on their motivation (Franco et al. 2002; Lambrou et al. 2010), in the sense that it promotes attendance, diligence, flexibility, and playing a role with true willingness.

It is necessary to discover what motivates each professional, as well as know how the manager can successfully motivate his team and the whole organization. Because of this, “Leaders of health care organizations are increasingly interested in ways to attract, retain, and gain commitment from their employees. This interest is created in part because high turnover rates and the lack of commitment negatively affect the provision of care and the bottom line in their organizations” (Morrison et al. 2007, p. 98).

Fonseca Pires (2017) lists literature on the motivation of healthcare professionals. From his work, among other topics beyond the scope of this chapter, it is apparent that some studies point to, as the main motivational factors, the deepest aspects of the worker and his identification with the healthcare sector, such as vocational and service aspects, or the search for meaning and purpose (more important in female workers). For others, the autonomy and professional achievements are considered crucial to promote workers’ motivation. It is also mentioned that in so-called “magnetic” hospitals (named after their ability to attract and retain good professionals), the most important motivational factors are participative decision-making, continuous development, and professional training and professional flexibility.

Among demotivating factors, studies are cited which refer to the lack of recognition and commitment, the heavy workload,[7] inadequate supervision, lack of

[7] On this topic, the exploratory work on the Portuguese reality of Afonso et al. (2019) might be of interest. One of the conclusions is that a high percentage of physicians have a workload which is superior to what they consider harmful to their work-family balance.

professional opportunities, lack of equipment and resources, lack of time to be able to do the job well, low salaries, and lack of job conditions.

So, what is motivation? It can be defined as the impulse that incentivizes the person's will to do certain things. Motivation shouldn't be confused with mere enthusiasm. Motivation has a more stable and consistent character.

A motivated person feels active and with energy to reach a certain end (Ryan and Deci 2000a). Motivation is hugely valued in organizations because it encourages action (Ryan and Deci 2000b).

The theoretical framework of human motivation allows us to identify two main categories that are conceptually different (Benkler 2011; De Dreu 2006): the self-referential, of personal interests, and that which transcends the "me" and is oriented to service, contribution, and altruism.

Self-referential behavior focuses on pleasure, satisfaction, and one's own development, whereas service-oriented behavior relies on meaning and altruistic purpose as a lever for effort (Grant et al. 2008; Perry et al. 2010).

Altruistic or transcendent motivation (which in this chapter we can also call *pro-stakeholder motivation* (Bastons et al. 2016) in the sense that it is linked to the business's mission and the stakeholders' legitimate interests) relies more on attitudes which look beyond the interest of oneself or of the group, projecting itself on broader entities (Vandenabeele 2007), reaching the community, the state, and humanity (Rainey and Steinbauer 1999). "It is motivation encouraged by consequences that a person's action can have on meeting the needs of another or of other people" (Pérez López 1996, p. 10), a type of motivation that "transcends the individual's needs and centers itself on 'others'" (Rey 2011, p. 85).

It is important to clarify that these motivations might not be mutually exclusive and frequently coincide in a healthy way. This depends on the meaning with which the terms are used. Self-interest—understood as "one's own good," well-directed so as to not degenerate into self-referentiality, or selfishness—is not only legitimate, as it is commonly necessary for motivation in the social and transcendent sense to materialize. At the same time, altruistic motivation always benefits the person who fosters and performs it, not in a benefit necessarily associated with satisfaction or results (because, on the contrary, it is usually accompanied by sacrifice which requires "stepping out of oneself"), but in an ontological benefit which, insofar as it fulfills oneself and corresponds to his nature, has a very strong motivational strength when duly activated (Olaso 1996). Frankl (1959) also states that the search for meaning and the need to belong to something larger than oneself is a basic impulse of the human being.

It is about being directed toward the needs of others, which confers a sense of contribution to actions (Bastons et al. 2016), overcoming the limits of contractual theory (Dodlova and Yudkevich 2009). This attempt to transcend the ordinary [or better said, to transcend *in* the ordinary], the quest for an opportunity that will fill existence with meaning, is also motivating because it enlarges the meaning of work (Campbell and Yeung 1991). The "relevance of these kinds of motivation in the organizational context is generally due to the fact that the majority of actions performed in an organization—from top to bottom—are actions which impact

others, and therefore can be performed with transcendent motivation" (Rey 2011, p. 85).

Since the company's mission statement is directed toward the stakeholders' needs (Blair-Loy et al. 2011) and not to one's own interest, *motivation based on mission is therefore altruistic, transcendent and pro-social, and not self-referential* (Rey and Mas-Machuca 2013). At the same time, and for the same reasons, this type of motivation leads more easily to the fulfillment of the mission. In fact, Rey's (2011) studies confirm the influence of transcendent motivation (or *pro-stakeholder*) in the development of commitment of workers to the company's mission.

In any case, one must take into account that an altruistic motivation directed to those who are not stakeholders has the value of contribution, but does not fit into the company's mission; also, altruistic motivation that is directed toward only one of the stakeholders is not in line with the mission, because as we have seen, this is fulfilled with the contribution due to all main stakeholders. Motivation based on mission is the only one that respects, defends, and values legitimate interests of different stakeholders and achieves in entirety the organization's mission.

In this way, the concept of *pro-stakeholder motivation* is defined—the impulse of the person based on the desire to seek the benefit of the company's legitimate stakeholders. Also, this type of motivation has a huge potential, because many actions in the organization—not only from high-level management but also from employees—have direct impact on stakeholders. On the other hand, it indicates valuing the mission as representative of a contribution or service to the stakeholders (Bastons et al. 2016).

Pro-stakeholder motivation is thus the "motor" dimension of mission which internalizes it, the key to make the mission effective.

Fonseca Pires (2017) develops an extensive theoretical and empirical work where he concludes, among other things, that in the context of health institutions, a *pro-stakeholder motivation* applied to main stakeholders—patients, colleagues, institution, and society—can be very important to achieve cooperation of various professionals (such as physicians, nurses, and managers), which becomes another way in which motivation influences the achievement of mission because to attain it, especially in a health institution, also requires integration and interprofessional cooperation.

14.5 Conclusions

The identification of mission in organizations is increasingly more frequent and popular. It is normally formalized in mission statements. The added value to having this defined and communicated depends on the inspiration and motivation of all who are part of the organization, providing a purpose and giving transcendent meaning to each person's work; allowing for focus and guiding strategy and decision-making; harmonizing and balancing legitimate interests of each stakeholder; and facilitating institutional communication, among others.

Health institutions, particularly hospitals, are also a target for this tendency, and the convenience of a mission statement is great in a sector of constant change, with diverse characteristics, but at the same time anchored with intemporal values such as care and attention to the patient.

However, many times, mission statements are not carried out and have few practical results. At times, what drives the organization—often in misaligned or even contradictory ways—are other interests, commonly particular and unrelated to the mission. This can be due to several problems: if the identification of the mission is incongruent, false, ambiguous, wrong, or a mere institutional symbol, but also due to lack of communication, implementation, and evaluation.

How to make mission more effective in an organization? This chapter sought to give some hints in that direction, particularly focused on health organizations. Among the main ideas, we draw attention to the following:

Firstly, an organization's mission—other than being appropriately written, *formal mission—should be true (i.e., having a logical foundation, fitting for reality*). Mission is the "why" of an institution, its purpose, a service which generates value for its main stakeholders, a contribution which characterizes its identity (Cardona and Rey 2009, p. 2).

If an institution does not have a social or transcendent meaning clearly defined, it is easier to transform into a mere balance of particular interests of its members and in the influence of external agents upon it. Developing into a solely utilitarian framework, the proclivity for opportunism increases, which makes cooperation to achieve the common good—particularly important in health—more difficult (Fonseca Pires et al. 2016).

Secondly, *mission needs to be internalized and taken on by the workers and to involve the stakeholders in a way that generates belonging and identification with the mission.*

It is essential to kindle a "sense of mission" in the company's workers, which leads to align their values with those of the business. This alignment, not void of sacrifice insofar as it frequently requires giving up other personal interests, is not in any way totalitarian, in the sense of giving up one's own pursuit of happiness; the sense of mission awakens in the point of contact between human nature (and by its eagerness in transcending and contributing to the common good), the values freely accepted by each person, and the company's values and vision which are the groundwork for its mission. The sense of mission can be promoted through training, coaching and tutoring, goal-setting, processes, etc.

Thirdly, it is very important to reach an *implementation of the mission in all the organizational dimensions*, so that the purpose can translate into action. Consequently, *high-level management needs to use an operative tool*, to establish mechanisms which can put into practice, measure, analyze, and evaluate mission through indicators or evidence (*dynamic mission*).

Finally, for formal mission and dynamic mission to be authentic, it is essential that *motor mission*, which is personal motivation of members of the organization while connected to the accomplishment of the company's formal mission, becomes the end goal of the company's members, after being properly internalized.

“Motor mission” is activated by motivation, but not any kind of motivation. It is altruistic or transcendent motivation (which does not cancel an *ordered* self-referential motivation), directed toward the needs of others (in this case the stakeholders), characterized by urging the will to act in a certain way by the consequences that action can have on meeting the needs of others. This motivation goes beyond contractual theory and becomes the key to making mission effective.

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