

World Journal of *Clinical Cases*

World J Clin Cases 2021 October 16; 9(29): 8627-8952



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INDEXING/ABSTRACTING

The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJCC* as 1.337; IF without journal self cites: 1.301; 5-year IF: 1.742; Journal Citation Indicator: 0.33; Ranking: 119 among 169 journals in medicine, general and internal; and Quartile category: Q3. The *WJCC*'s CiteScore for 2020 is 0.8 and Scopus CiteScore rank 2020: General Medicine is 493/793.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Jia-Hui Li; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

October 16, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Healthcare practice strategies for integrating personalized medicine: Management of COVID-19

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Author contributions: Liu WY and Tung TH had full assessment for all of the data in the study and take responsibility for the integrity and accuracy of the data; Chien CW contributed to data interpretation and drafting the manuscript; all authors provided a critical review and approved the final manuscript.

Conflict-of-interest statement: The authors have no proprietary interest in any aspect of this review.

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Manuscript source: Invited manuscript

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Abstract

Personalized medicine is the tailor-made clinical treatment to the individual characteristics of each patient. It may be considered an extension of traditional approaches to knowing and treating diseases. Personalized medicine has the potential to change the way of identification and management of health problems. Coronavirus disease 2019 (COVID-19) is an infectious disease that primarily affects the patients' lungs. The first case of pneumonia of unknown cause was reported in Wuhan, China on December 31, 2019. As thus, we are quickly approaching the era of personalized medicine. This review discusses the practices currently used in the management of COVID-19 and how they relate to personalized medicine.

Key Words: Healthcare; Personalized medicine; COVID-19; SARS-CoV-2

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Core Tip: For patients with coronavirus disease 2019 (COVID-19), providing the most effective treatment is a task of paramount importance in personalized medicine. The pandemic of COVID-19 is the opportunity and challenge to change toward a more personalized approach taking patients' needs into consideration. Personalized medicine related research is ideally suited to dealing with infectious diseases; however, there has

Specialty type: Medicine, research and experimental

Country/Territory of origin: China

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

Received: February 17, 2021

Peer-review started: February 17, 2021

First decision: March 11, 2021

Revised: March 22, 2021

Accepted: August 18, 2021

Article in press: August 18, 2021

Published online: October 16, 2021

P-Reviewer: Dhaiban AK

S-Editor: Yan JP

L-Editor: Wang TQ

P-Editor: Li JH



been relatively little research in this area.

Citation: Liu WY, Chien CW, Tung TH. Healthcare practice strategies for integrating personalized medicine: Management of COVID-19. *World J Clin Cases* 2021; 9(29): 8647-8657

URL: <https://www.wjgnet.com/2307-8960/full/v9/i29/8647.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i29.8647>

INTRODUCTION

Since coronavirus disease 2019 (COVID-19) was first identified in December 2019 in Wuhan, the capital of China's Hubei province, it has spread to the whole China due to large-scale transportation, resulting in the ongoing 2019-2020 coronavirus pandemic. At this globalism time, the virus is likely to overwhelm most countries[1]. As of April 6, 2020, COVID-19 has already attacked 183 countries or regions in the world, with the epicenter swiftly transferring from China to Italy and America[2]. The areas influenced by COVID-19 are six times higher than those by severe acute respiratory syndrome (SARS)[3]. The methods of personalized medicine for COVID-19, including the pathogenesis of COVID-19 and the development and application of detection kits, have played a key role in countries' response to the outbreaks[4-7]. We are undergoing a transition from traditional medicine era to personalized medicine era. By development and amendment of the law, we are more able to stick to the principles of personalized medicine, face the challenges posed by it, and embrace the coming of the era of personalized medicine through certain strategies. Similarly, in other infectious diseases, personalized medicine methods also show unique advantages[8,9]. A number of studies have reported on the use of personalized medicine to treat the COVID-19 pandemic, such as the application of detection kits. Nonetheless, there has been relatively little research on the use of personalized medicine for the treatment of infectious diseases.

We believe that with the rapid development of molecular diagnostic technology and the increase of awareness of the cost-effectiveness of personalized medicine interventions, a review of the research and applications of personalized medicine in the field of infectious diseases will promote better management and treatment of such diseases.

EPIDEMIOLOGY, DIAGNOSIS, TREATMENT, AND PROGNOSIS OF COVID-19

Epidemiology

At the end of December 2019, pneumonia cases of previously unknown etiology were observed in Wuhan, China. On January 7, 2020, the causative pathogen was identified as COVID-19. On March 21, 2021, the global number of confirmed COVID-19 cases is 122.8 million and the total death toll is 2.7 million[10]. This human-to-human transmission rate of the novel coronavirus is significantly high, which results in a wide spectrum of clinical manifestations in infected patients [11]. Although the higher absolute number of deaths related to COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appears to have a lower fatality rate when compared to SARS-CoV or Middle East respiratory syndrome (MERS) coronavirus [12]. There is increasing evidence that many cases of COVID-19 are asymptomatic with its global outbreak, but they can transmit the virus to others[13]. Estimates of the incident asymptomatic infections could clarify the epidemiological potential of COVID-19 transmission and help understand the true universality of the disease[13, 14]. It is essential to detect asymptomatic infections for early prevention and control of COVID-19 worldwide[15].

The spread of COVID-19 has been rapid. The transmission of the current outbreak is far higher than that of SARS, due to the high binding affinity of the SARS-CoV-2 to human angiotensin-converting enzyme2 (ACE2), the main cell receptor of the coronavirus[16]. In the early stages of infection, the effective reproductive number of

the SARS-CoV-2 was estimated at 2.9, whereas it was 1.77 for the SARS virus[17]. Multiple transmission pathways also contribute to the widespread transmission of the virus. Direct, aerosol, and contact transmissions are the three main transmission pathways of the SARS-CoV-2[18]. Major cities, such as Paris, Madrid, Milan, London, and Moscow, have become centers of infection due to their dense population and the high mobility of travelers.

Many patients with COVID-19 experience flu-like symptoms, including cough, fever, fatigue, anorexia, myalgias, sputum production, and shortness of breath[19]. Most people experience only mild symptoms; however, COVID-19 can also cause severe acute respiratory syndrome (ARDS), which often leads to intensive care unit admission and death[20]. Respiratory failure from ARDS is the primary cause of mortality; however, other patients suffer from non-respiratory symptoms, such as kidney failure, due to the viral invasion of organs with high ACE2-expressing cells. Damage to male gonadal function has also been reported in some cases[21,22].

Diagnosis

Reverse transcriptase-polymerase chain reaction (RT-PCR) is the most widely used method for the confirmation of COVID-19 diagnosis. Initial conclusions related to the sensitivity of RT-PCR from pharyngeal swabs ranged from 66%-80%, depending on assumptions made about patients with conflicting diagnostic data as computed tomography (CT) results were not often aligned with those of RT-PCR[23]. A global shortage of qualified test kits is a serious problem; however, CT imaging and blood tests can also be used for testing. When combined with RT-PCR, they can improve the accuracy of diagnosis. Epidemiological analysis of the patients' travel and contact histories can also be very helpful in pre-screening. Table 1 shows the three major diagnostic measurements for COVID-19[23,24].

RT-PCR is used to test for the presence of viral RNA. The fact that the virus infects the human body through the respiratory tract means that samples for testing must be obtained from that area of the body[25]. One study assessing the rate of positive RT-PCR among confirmed patients reported that bronchoalveolar lavage fluid specimens achieved the highest true positive rate of 93%, followed by sputum (72%), nasal swabs (63%), fibrobronchoscope brush biopsy (46%), and pharyngeal swabs (32%)[26]. It is also recommended that clinicians obtain samples from the lower respiratory tract to avoid false negatives and false positives. Nonetheless, RT-PCR results are not 100% accurate (*i.e.*, they occasionally present false negative results); therefore, individuals who receive negative results should still self-quarantine for at least 72 h after receiving their results[27].

The limited sensitivity of RT-PCR makes CT a valuable supplementary method to improve the accuracy of diagnosis. CT images cannot be used as direct diagnostic evidence on their own; however, they can be used to guide the initial diagnoses. In the diagnosis of COVID-19, chest CT scans vary considerably in terms of diagnostic efficacy with a sensitivity of 97%, specificity of 25%, and accuracy of 68%[28]. Considering their high sensitivity and low specificity, CT images should be best used in combination with RT-PCR.

At present, blood tests are viewed as a feasible method for diagnosis, albeit as a complementary measure. The specific IgM antibody for the SARS-CoV-2 tests positive results within 3-5 d after infection, and during the recovery period, IgG antibody titers are at least 4 times higher than those during the acute period. Thus, the following blood test results are necessary to confirm an infection with SARS-CoV-2: (1) IgM and IgG antibodies are positive; and (2) serum IgG antibodies change from negative to positive, or the titer of IgG antibodies during recovery is at least 4 times higher than that during the acute period[29,30].

Treatment

Patients with a mild clinical presentation (absence of viral pneumonia and hypoxia) do not necessarily require initial hospitalization[31]. It is recommended that they remain at home, as most will recover without specific treatment. Patients with severe symptoms require medication and close monitoring during inpatient clinical management. There are no drugs approved specifically for the treatment of COVID-19. This means that physicians should adjust their medication plan according to the condition of each patient. Remdesivir, favipiravir, tocilizumab, and chloroquine are widely used to treat COVID-19; however, the efficacy of these drugs still needs to be demonstrated through clinical trials. In case of complications, such as respiratory distress, hypoxemia, or shock, supplemental oxygen therapy should immediately be administered. Intubation or high-flow nasal cannula oxygen therapy is recommended for patients with acute hypoxemic respiratory failure. If neither is available, non-

Table 1 Three major diagnostic measurements for coronavirus disease 2019

	RT-PCR	CT	Blood test
Accuracy	66%-80%	68%	Unknown?
Testing time	4-6 h	10-15 min	Less than 10 min
Advantage	Most accurate	Convenient and intuitive	Quick
Disadvantage	Global shortage; unstable accuracy; need to be sent to qualified labs	Very low specificity	Not applicable for patients with low level of antibodies

RT-PCR: Reverse transcriptase-polymerase chain reaction; CT: Computed tomography.

invasive positive pressure ventilation is considered an emergent alternative[32]. The WHO suggests the use of extracorporeal membrane oxygenation for patients with refractory hypoxemia. Severe patients also face the risk of co-infection. As soon as possible, empiric antimicrobials should be administered for the treatment of all pathogens that likely cause severe acute respiratory infection or sepsis[33].

Remdesivir is one of the most promising drugs for the treatment of COVID-19. Despite the fact that it was initially developed to treat Ebola, the efficacy of remdesivir in treating Ebola has yet to be proven in clinical trials. In pre-clinical animal models involving monkeys infected with the MERS virus, all of the animals that were not treated with remdesivir became very sick, whereas those treated with remdesivir presented no symptoms or signs of lung damage. Furthermore, virus volume was significantly lower in treated animals than in untreated ones[34]. Due to the biological similarity between the SARS-CoV-2 and MERS virus, remdesivir is viewed as a potential treatment for COVID-19. Preliminary results have already revealed that the recovery time of patients who received remdesivir was 31% faster than those who received placebo[35].

Drugs such as favipiravir and tocilizumab have also shown potential in clinical trials. Favipiravir is an antiviral drug with a mechanism similar to that of remdesivir, but with far lower potency, as demonstrated in pre-clinical trials[36]. Researchers conducting ongoing clinical trials in China have reported that favipiravir is effective in some patients; however, further data will be required to demonstrate its efficacy. The fact that IL-6 is a key factor triggering the cytokine storm of COVID-19 has prompted interest in the monoclonal antibody tocilizumab, which targets the IL-6 receptor. Recent published results on 14 patients (9 severe and 2 critical cases) with diffuse lesions in both lungs prior to treatment have reported that tocilizumab has positive effects in terms of fever reduction. Specifically, the temperature of 11 patients dropped to normal levels within 24 h, and the effect lasted up to 9 d[37].

In addition, chloroquine, abidor/darunavir, and other drugs are also being tested for use in the treatment of COVID-19. Chloroquine is a widely used antimalarial drug. During an *in vitro* study, chloroquine was shown to kill the SARS-CoV-2; however, its efficacy in humans has not yet been proved. The very low potency of abidor/darunavir in *in vitro* studies suggests that benefits may only be derived from doses high enough to produce unanticipated side effects.

Prognosis

There is no sequelae for patients with mild symptoms, which account for 80% of confirmed cases[38]. The survival of patients with severe symptoms depends on age and complications. One observational study conducted in Wuhan Jin Yin Tan Hospital reported that the average age of non-survivors was higher than that of survivors. Non-survivors were also more likely to develop ARDS and to receive mechanical ventilation. Damage to other organs, such as acute kidney injury, cardiac injury, and liver dysfunction, has also been observed in most critically ill patients[39].

According to research from the Suzhou Hospital of Nanjing Medical University, ACE2 is highly expressed in renal tubular cells, Leydig cells, and cells in seminiferous ducts, which suggests that the virus binds directly to ACE2 positive cells. There have also been reports of damage to testicular tissue; however, these findings have to be verified through clinical research[40]. Nonetheless, the threat should not be disregarded and physicians ought to consider assessing the fertility of patients in clinical follow-ups.

Pregnant women do not appear to be more susceptible or vulnerable to COVID-19; however, physicians should be aware that at least one report has provided evidence of fetal compromise and preterm rupturing of membranes due to COVID-19. Note however that there is no evidence demonstrating that the virus is teratogenic[41].

INTEGRATING PRINCIPLES, CHALLENGES, AND STRATEGIES FOR PERSONALIZED MEDICINE INTO EVIDENCE-BASED COVID-19 HEALTHCARE

Over time, the necessity of a more precise and effective clinical treatment resulted in the development of a scientific field currently known, that is, personalized medicine [7]. Providing the most effective treatment is a task of paramount importance in personalized medicine for patients with COVID-19. However, the abilities of some developing countries to organize regional predictive, preventive, and personalized pandemic monitoring systems are questionable[42]. The pandemic of COVID-19 is the right occasion and challenge for both research and healthcare professionals to change toward a more personalized approach taking patients' needs into consideration. Researchers are enthusiastic about the potential of personalized medicine in the treatment of COVID-19; however, many barriers have to be overcome to realize the benefits.

Principles

Privacy: Large databases of genetic information are essential to the advancement of personalized medicine; however, the collection of data depends on patients agreeing to share their genomic information[43,44]. This will only be possible when they understand the benefits that this can bring for themselves (personalized treatment) as well as society as a whole (new forms of therapy).

Security: Safety and effectiveness have always been the primary criteria guiding the development of medicine; however, some personalized medicine methods (*e.g.*, gene therapy) impose particularly acute risks. Operational rules must be followed strictly to avoid risking patients, clinicians, and society as a whole[45].

Innovation: Practitioners of traditional medical practice and personalized medicine alike are seeking to realize the goal of early discovery, early isolation, and early treatment. The COVID-19 pandemic has prompted extensive research in nucleic acid detection, which has produced notable improvements in accuracy, precision, and speed[46].

Challenges

Awareness: A profound lack of educational resources pertaining to personalized medicine makes it very difficult to make patients aware of the personalized treatment options open to them. Most medical practitioners are also unaware of critical advances made possible by researchers in personalized medicine (*e.g.*, genomics)[47]. Few experienced physicians have the time to update their knowledge on state-of-the-art personalized medicine technologies and outdated medical school curricula hinder the development of next generation physicians[48,49].

Patient empowerment: Physicians often fail to consider the wishes of patients and their family members when making treatment choices. It is important to keep patients informed of everything that is happening to them and make them aware of their options[50,51].

Value recognition: The medical establishment relies far too heavily on trial-and-error. Even in the treatment of acute patients, clinicians are accustomed to repeating the cycle of prescribing and abandoning treatments until they discover the correct diagnosis or an effective treatment plan[52]. In addition, not all molecular variants are clinically actionable, and physicians may lose the incentives for adoption of personalized medicine therapies. Consequently, clinicians do not pan out when conducting scrutinization due to the reason that payers fail to appreciate state-of-the-art diagnosis. Despite the enormous funding for genomics (\$3 billion per year), a lack of profitable business models makes it difficult for healthcare organizations to take advantage of the new progress[53].

Infrastructure and information management: The adoption of personalized medicine will require profound changes in the dissemination of information. Massive amounts of multi-modal information associated with private genomic and molecular profiles must be translated into data that is usable in all clinical settings. Personal tailored devices and wards related to its use call for all-around coordination of various organizations; however, regulatory oversight attributed to the lagging policies and guidelines would trigger great concern about the efficacy and safety of personalized medicine options. Extensive repercussions from perspectives of different stakeholders aggravate the requirement of personalized medicine infrastructure[54].

Reimbursement patterns: Regardless of whether healthcare costs are covered by Medicare or private insurance schemes, it is difficult to implement an appropriate payment mechanism for personalized medicine-related molecular diagnostics, those tests designated for research or investigational purposes only, as well as utility of molecular information[55]. Until 1985, the United States used the prospective “RVU–CPT–ICD coding systems” to reimburse personalized medicine diagnostic tests [56]. Given that the assay is associated with a CPT code, like complicated DNA sequence-based experiment it could get over \$4000 per test in reimbursement. At the same time, the test providers could seek extensive payment from center for Medicare services (CMS; Baltimore, MD, United States), or private health insurers for an averaged recoup no more than \$1500[57]. Unfortunately, it is also the seemingly accurate CPT codes that begin to collapse this system into bins. “Code stack” assigned for one genetic test confuses the payers about what they are paying for, while laboratories are not unanimously consistent with the CPT coding because legitimate insurance policy permits limited CPT codes[58].

Strategies

Awareness of personalized medicine: One survey by the United States National Institute of Health found that educated Americans were more willing than their less educated counterparts to undergo personalized medicine treatment. Nonetheless, most Americans do not grasp how pharmacogenomics works or how it could affect them. It is important to establish educational programs and communication initiatives to raise the awareness of personalized medicine among the general public[59].

It is also important for all practitioners (medical schools and caregivers) to keep abreast with developments in personalized medicine. Institutes specializing in genetics or genomics could work with medical schools. The Healthcare Center for Genetics and Genomics has already been established at Harvard Medical School and medical colleges in the Boston area[60]. The American center for disease control and prevention has also set up centers for genomics and public health with the aim of developing genomics educational programs for public health workers[61].

Patient empowerment: Third-party institutions could be tasked with the management of sensitive information, such as personal genomic data. Jefferson Health is currently working with Color Genomics to manage genetic data collected from Jefferson employees[62]. Legal constraints will eventually have to be implemented to guarantee the security of personalized medicine related data. Healthcare organizations should also provide patients with complete schedule, plans, and procedural profiles, followed by detailed explanations of their treatment choices.

Value recognition: Patients with acute or malignant diseases cannot afford the time-consuming process of trial-and-error diagnosis and treatment. Lung cancer is a good example. Only 43% of patients with cancer of the lung or bronchus and 15% with advanced non-small-cell lung cancer (NSCLC) survive for 1 year after diagnosis[63]. The standard first-line treatment for NSCLC is chemotherapy. However, there is mounting evidence that targeted drugs are also effective in advanced NSCLC patients who have a mutation in a gene known as epidermal growth factor receptor (EGFR). Tyrosine kinase inhibitors (TKIs) include Tarceva, a Genentech drug approved by the FDA in 2004, and Iressa, an AstraZeneca drug available in Japan since 2002 and in Australia since 2003[52]. Although the FDA approved Tarceva in 2004 only as a second-line therapy for all NSCLC patients, there is growing evidence that TKIs, as a class, are an effective first-line treatment for those with the EGFR mutation. Personalized medicine provides an unprecedented opportunity to identify the disease identity and cause without the potential to encounter serious toxicity due to specific characteristics of the individual patient, thus saving luxury time.

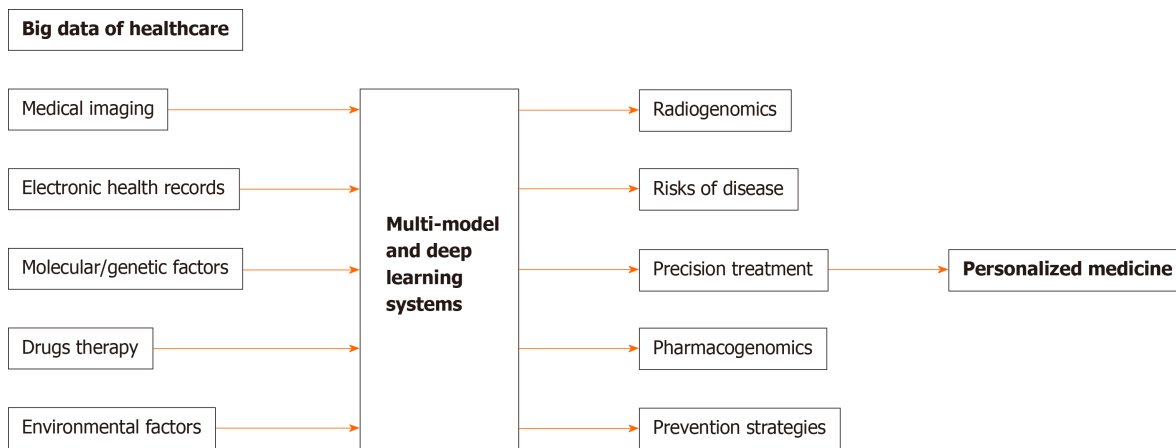


Figure 1 Multi-modal deep learning architectures could play a key role in advancing personalized medicine.

In 2011, Myriad Genetics, the third largest independent laboratory in the United States, reported \$101 million in net income (down from US\$152 million in 2010)[63]. Insight Pharma analysis reported that the overall market for gene sequencing now generates revenue exceeding US\$1 billion per year[64].

The Health Care Working Group of the Personalized Medicine Coalition is comprised of representatives from 49 organizations involved in healthcare delivery, including 19 academic health centers, 12 community healthcare systems, 16 healthcare delivery support organizations, and two physician groups.

Infrastructure and information management: Well-designed information systems make it possible to share data between clinics and research organizations. The problem of integrating multi-modal data (particularly paper-based records) of physicians was first addressed in 2006 with the National Electronic Medical Records project, which provides a uniform set of standards for data structure, transfer, and protection with \$125 million[65]. Deep learning algorithms using artificial neurons in multilayered computational structures are able to learn from existing databases to assist in the organization and interpretation of new data. They are ideally suited to the management of large medical databases[66,67]. **Figure 1** shows that the multi-modal deep learning architectures could play a key role in advancing personalized medicine [68].

Reimbursement patterns: Inconsistencies in the coding of genetic tests are confusing for all stakeholders. Substituting CPT codes with test code as Palmetto GBA, a wholly owned subsidiary of Blue Cross Blue Shield of South Carolina and a Medicare contractor in several states, did in November 2011[69]. Distinguished from CPT codes assigned for accurate sequence, test code offers a clearer elucidation of the assays to payers in the comment field of each claim to avoid a front-end rejection. In sight of this new code tracking tightly to assays conducted, assessment and payment can be simplified.

CONCLUSION

This review examines the epidemiology of COVID-19 as well as the diagnosis methods, treatment, and prognosis. We also examine the current state of personalized medicine and its applicability in coping with the COVID-19 pandemic. Effective therapeutic regimens should be explored and evaluated in a very limited period to minimize the consequences of this epidemic. New diagnostic approaches with higher sensitivity and specificity should be applied and could be the next generation of diagnosis.

Personalized medicine reflects a desire on the part of medical practitioners to escape from the "one-drug-fits-all" approach to medicine by focusing on the individual characteristics of the patient. Transitioning from traditional medical practice to personalized medicine will require amendments to existing laws. In order to apply personalized medicine methods in COVID-19 healthcare, we believe that we should adhere to ethical and practical principles to ensure safety and effectiveness; at the same time, we need to meet the challenges that personalized medicine may bring from different

aspects. The public must also be better informed with regard to personalized medicine, and patients should be empowered to participate in the decision-making process. Stakeholders must be reminded of the value of personalized medicine to promote construction of infrastructure related to the management of information. It will also be necessary to revamp systems used to fund personalized medicine related diagnostics and research.

Personalized medicine related research is ideally suited to dealing with infectious diseases; however, there has been relatively little research in this area. Personalized medicine related methods can be used to quickly diagnose pathogens that are difficult or impossible to cultivate. They can also be used to assess the pharmacogenetic characteristics of patients to guide treatment decisions and reduce the risk of side effects. Recent advancements have also made these technologies more convenient, more efficient, and less expensive.

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