Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

CRISPR-Cas Technology: A Comprehensive Review on COVID-19 Research and Potential Application

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The outbreak of the COVID- 19 that was catalyzed by the SARS-CoV-2 virus negatively affected the global health system, and hence, there is a need to research the diagnosis, treatment, and prevention of the disease. This research paper explores the convergence of two cutting-edge technologies. Researchers combat COVID-19 using CRISPR-Cas gene editing and deep learning. The CRISPR-Cas technology has transformed the field of genetic modification by allowing for precise genome changes. Its potential in developing rapid and accurate diagnostics and targeted therapeutics against SARS-CoV-2 has garnered attention. This paper examines recent advancements in using CRISPR-Cas to detect viral RNA and proteins, focusing on its high specificity and potential for multiplex detection. Deep learning techniques have shown remarkable promise in analyzing complex biological data and making predictions. Deep learning with CRISPR-Cas integration technologies can enhance the design of effective guide RNAs for gene editing, predict potential off-target effects, and optimize delivery methods for therapeutic interventions. The paper comprehensively reviews the current state of CRISPR-Cas and deep learning applications in COVID-19 research. It highlights studies that utilize these technologies for drug discovery, vaccine development, and personalized medicine. Researchers discuss challenges and ethical considerations related to these technologies, emphasizing the need for robust experimental validation and responsible use. As research advances, this interdisciplinary approach could lead to breakthroughs in diagnostics, therapeutics, and our understanding of viral pathogenesis, setting a precedent for the future of precision medicine in infectious disease control.

Keywords: covid-19, the Gene editing tool, Cas proteins, CRISPR, guide RNA, Programmable sequence, Deep learning.

1. Introduction

SARS-CoV-2, which was accountable for the COVID-19 epidemic, has been present since it first surfaced in late 2019 and has had a massive global impact. In December 2019, the virus was discovered in Wuhan, China, and quickly spread throughout China and beyond the world. On March 11, WHO proclaimed COVID-19 a global epidemic., 2020, as the virus spread rapidly across continents. It belongs to the corona virus's family, known for causing respiratory infections in humans and animals [1]. Before the outbreak, humans had not previously identified this particular strain of coronavirus. The virus spreads mainly when an infected individual coughs, sneezes, talks, or primarily breaths; respiratory droplets occur. The tiny particles can land on human lips or noses or be inhaled and cause disease. Infection can be transferred by touching the part of the virus-infected surfaces, particularly the mouth, and then touching the face, nose, or eyes. COVID-19 symptoms may range from minor to severe and can emerge 2-14 days after exposure. Cough, fever, fatigue, muscle or body aches, sore throat, loss of taste or smell, shortness of breath, and headache are common symptoms. The infection can lead to acute respiratory distress syndrome (ARDS), pneumonia, organ failure, and death in extreme cases and those with a history of medical problems.

The pandemic's impact has been significant on a global scale. On March 11, 2020, the World Health Organization designated COVID-19 a pandemic, as the virus spread rapidly over the world [2]. Lockdowns, quarantine measures, social distancing, mask mandates, and travel restrictions rules were among the measures implemented by governments and health regulatory bodies to slow the virus's spread. Healthcare systems in many countries faced unprecedented challenges due to the sudden surge in cases. Hospitals and medical facilities struggled to provide adequate patient care, particularly in areas with high infection rates. Shortages of personal protective equipment (PPE), ventilators, and other medical supplies have highlighted the need for emergency preparedness and strengthened healthcare infrastructure. The scientific community was crucial in understanding and developing strategies to combat the virus. Sequencing the virus's genome was made possible through rapid global collaboration, enabling the development of diagnostic tests and vaccine candidates.

Various technologies, including mRNA and viral vector platforms, have been used to develop several vaccines. These vaccines underwent rigorous clinical trials and were granted emergency use authorization in record time, marking a significant achievement in vaccine development [3]. WHO launched worldwide vaccination campaigns to control the virus's propagation and minimize the severity of COVID-19 instances. However, challenges included ensuring equitable vaccine distribution, addressing vaccine hesitancy, and adapting to the development of novel viral varieties that could potentially evade immunity or alter the severity of the disease.

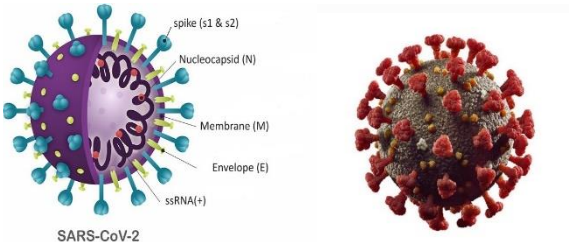

Fig 1: Structure of SARS-COV-2

Because of its unique self-replication phenomena, this organism's genomic sequence, which is a newly developing virus, is prone to mutation and recombination. During the pandemic's early stages, metagenomic techniques shared the whole viral genome sequence, and researchers determined its main proteins' three-dimensional structure. In fig:1, The SARS-CoV-2 genome's fourteen open reading frames (ORF) encode four structural proteins such as membrane (M), envelope (E), spike (S), and nucleocapsid (N), as well as nine auxiliary proteins. These proteins comprise the replicase complex, composed of sixteen nonstructural proteins. Cathepsin L and transmembrane protease serine 2 (TMPRSS2) are required to activate the two functional portions of the spike protein, S1 and S2[4]. While the spike protein of other human coronaviruses can bind to various cellular entry receptors like aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4), the receptor-binding domain (RBD) of the spike protein in SARS-CoV-2 binds to human cell receptors, Angiotensin-Converting Enzyme 2 (ACE2), and defines the tropism and pathogenicity of the virus. A mutation in RBD increases the virus's binding affinity to human ACE2 and, as a result, its transmissibility compared to SARS-CoV and MERS-CoV.

In the COVID-19 pandemic, notable biotechnological techniques include the development of novel and quick platforms for Virus infection detection, prevention, and treatment. As a result, learning more about the virus's biology and pathology will aid in diagnosis, therapy regimens, and vaccine development. Because of their conserved sequences, ORF1ab is one of the hotspot areas used for molecular identification of the SARS-CoV-2 virus, envelope protein gene (E), and nucleocapsid protein gene (N) sequences of the RdRP gene. Designing antiviral molecular therapy platforms must focus on the virus's cell entry pathway, which includes RBD, and the virus replication complex, which provides for RdRp. [5].

2. Evaluation of Cripsr-Based Diagnostic in covid-19:

Feng Zhang et,al, developed a diagnostic test called SHERLOCK that utilizes CRISPR-Cas technology. SHERLOCK can determine SARS-COV-2 RNA in patient samples of blood. The system uses the Cas13 enzyme to detect and cleave target RNA sequences, triggering a fluorescent signal that indicates the virus's existence. This technology offers rapid and sensitive testing without complex equipment. Cong L et.al, [7] a co-developer of CRISPR-Cas9, is involved in efforts to repurpose CRISPR for COVID-19 diagnostics. Her team at the Innovative Genomics Institute has developed a platform called STOP Covid, which stands for SARS-CoV-2 Testing with an Optimized PCR-CRISPR. This platform combines the sensitivity of PCR (polymerase chain reaction) with CRISPR's ability to recognize the virus's genetic material. Doudna JA, et.al [8] A CRISPR-based platform can detect viral RNA in patient samples. It combines CRISPR-Cas13a with oligonucleotide probes to achieve precise and sensitive detection of SARS-CoV-2. Julia Joung,et. al. [9]. It is a technique that combines CRISPR-Cas12 with nanopore sequencing to detect viral RNA sequences. It offers a sensitive and rapid method for diagnosing COVID-19. Mammoth Biosciences, a business co-founded by CRISPR pioneer Jennifer Doudna [10], is developing a CRISPR-based diagnostic tool to identify COVID-19. The technique is called DETECTR which means DNA Endonuclease-Targeted CRISPR Trans Reporter, uses the Cas12 enzyme to cleave target RNA sequences and release a fluorescent signal, enabling virus detection. Sherlock Biosciences, co-founded by Feng Zhang, has developed a CRISPR-based diagnostic test is known as INSPECTR which means INternal Splint-Pairing Expression Cassette Translation Reaction, uses a modified Cas12 enzyme to detect viral RNA. Producing a signal detectable by a lateral flow strip, akin to the mechanism in a pregnancy test by Clare L. Fasching et.al. [11]. Elizabeth A et.al [12] Researchers at the Diagnostics Development Hub (DDH) in Singapore have been using CRISPR-Cas technology to develop a rapid and portable COVID-19 diagnostic test. The CARMEN test (Cas13-based, Amplification-Free, Multiplexed Detection of RNA) uses CRISPR-Cas13 to detect viral RNA in patient samples. Anastasiya Kostyusheva et.al.[13] Mammoth Biosciences and Agilent collaborated to develop a CRISPR-based diagnostic test for COVID-19. This test, named DETECTR BOOST SARS-CoV-2 Reagent Kit, SARS-CoV-2 RNA in patient samples is detected using CRISPR technology. James P. Broughton, et.al. [14] researchers have also developed a CRISPR-Chip diagnostic method. This approach combines CRISPR-Cas-based detection with microfluidics and electronics to enable rapid and sensitive determination of SARS-CoV-2 RNA. V. Edwin Hillary et.al. [15] Researchers have explored using CRISPR-Cas12a enzymes combined with electrochemical sensing to detect specific viral RNA sequences. This approach can detect SARS-CoV-2 precisely and sensitively. Chenshuo Wu et.al. [16] Researchers have used CRISPRi to selectively silence genes in human cells to study how different genes affect the virus's ability to infect host cells. This method helps identify potential therapeutic targets. Weijia Lin, et.al [17] Researchers have used CRISPRa to activate specific genes in human cells that could interfere with the virus's replication. This approach helps understand host-virus interactions and identify potential antiviral factors. STOP is a CRISPR-Cas13-based method that targets SARS-CoV-2 RNA sequences. It employs an orthogonal PAM (Protospacer Adjacent Motif) system to increase the specificity of RNA detection by Yongzhong Jiang et.al. [18]. Robin Augustine et.al.[19] Researchers have proposed using LAMP which means Loop-mediated isothermal amplification coupled with CRISPR-Cas12 as a sensitive and precise method for determine the SARS-CoV-2 RNA. LAMP amplifies target RNA, and CRISPR-Cas12 detects the amplified product. Vladimir Chulanov et.al. [20] Researchers have developed CRISPR-STOP. This method detects the presence of SARS-RNA by inducing the polymerization of specific oligonucleotides upon identification of viral RNA. It leads to the formation of a colorimetric or fluorescent signal. BEAMing-CRISPR method combines CRISPR technology with BEAMing (Beads, Emulsions, Amplification, and Magnetics) to detect specific mutations in the virus's genome. It enables the identification of viral variants and potential drug-resistance mutations used by Wenjie Lu, Jiazheng Li et.al. [21].

Table 1. Some CRIPSR-based methods for prediction of COVID-19

Author and year	TITLE	Merits	Dataset used	Method used	Limitations
Guishan Zhang et.al. [22]	C-SVR Crispr: Prediction of CRISPR/Cas12 guide RNA activity using deep learning models	Using the indel frequency score before starting an experiment saves time and money.	gRNA sequences	CNN and SVR	The data size is tiny.
Hayden C. Metsky et.al. [23]	CRISPR-based surveillance for COVID-19 using genomically comprehensive machine learning design	A program that implements our strategy using the most recent viral genomes from databases. ADAPT runs at scale and is entirely automated.	865-nt-target sequence	Deep CNN with ADAPT	However, current design paradigms, which demand curating incoming data, take time and effort.
Michael F. Cuccarese1 et.al. [24]	Functional immune mapping with deep-learning enabled phenomics applied to immunomodulatory and COVID-19 drug discovery.	Active COVID-19-associated SARSCoV-2 and cytokine storm infection phenotypic models the discovery of drugs with proven clinical efficacy, and the identification of numerous new drug repurposing prospects	HUVEC cells, Macrophage, HRCE, BV-2 cells.	DenseNet -161	Phenomics reveals chemicals that operate via cell-autonomous processes when analyzing a cell type in isolation. The development of coculture models may uncover compounds that intervene in multicellular processes.
Aubin Samacoits et.al. [25]	Machine Learning-Driven and Smartphone-Based Fluorescence Detection for CRISPR Diagnostic of SARS-CoV-2	The ability to increase data openness and educate the general audience about current infectious disease diagnosis and population-based surveillance so that private citizens and government authorities can take the required precautions to stop, intervene with, or facilitate ongoing endemics.	15 nasal swab Samples	Logistic Regression	Accuracy and specificity were slightly lower compared to earlier research using comparable CRISPR-Cas diagnostic technologies.
Muhammad Sher Afghan et.al. [26]	Reviewing methods of deep learning for diagnosing COVID-19, its variants, and synergistic medicine combinations	To examine alternative COVID-19 versions, a fully automatic DL-driven system leveraging available resources is proposed.	CT scan images	CNN	Imbalanced data set.
Dalia Ezzat, Aboul Ella Hassanien et.al. [27]	An enhanced deep learning architecture based on gravitational search optimization for the detection of COVID-19 disease	This method simplifies and speeds up the examination of chest X-rays obtained through different COVID-19 diagnostic protocols.	Chest X-RAY images	CNN	Researchers propose enhancing the image quality to improve its diagnostic ability fo r COVID-19.
Pwadubashiyi Coston Pwavodi et.al. [28]	Crispr biosensing and AI-driven tools for detection and prediction of Covid-19	Researchers have designed POC which means point-of-care diagnostic kit that is sensitive, easy to use, quick, inexpensive,	Chest X-RAY images	CNN	Biosensors based on CRISPR that are more precise and sensitive

		and able to perform detection wide range of specimens without requiring technical expertise.			
Triveni C5erukuri Suvarna et.al. [29]	Real-Time Deep Intelligence Analysis and Visualization of COVID-19 Using FCNN Mechanism	For the researcher using conventional methods, database management for deep virus analysis is crucial.	SARS-COV-19 Indian dataset	FCNN	Researchers have developed a bio-inspired algorithm that utilizes RNA, DNA, and biological data, but its implementation using software tools may be complex.
Thomas Beder, Antonella Vera-Guapi et.al. [30]	Machine learning on large-scale perturbation screens for SARS-CoV-2 host factors identifies β-catenin/CBP inhibitor PRI-724 as a potent antiviral.	Machine learning enables the concentration and expedition of the identification of host-dependent elements and prospective host-directed antivirals.	CACO-2 cell line	LASSO Regression	When we built the computational technique, we used screening data from the first four screens as the basis for the machine-learning procedure.
Zexu Li, Yingjia Yao et.al. [31]	A deep learning-based drug repurposing screening and validation for anti-SARS-CoV-2 compounds by targeting the cell entry mechanism	deep-learning techniques to test antiviral drugs through drug repositioning, targeting the entry mechanism for SARS-CoV-2 compounds.	A549, HEK293FT, A375, Huh7 cells and HCT116	DTINet, DeepCPI, DeepPurpose	Data Availability and Quality, Model Interpretability

3. Inferences from the Survey:

- Designing efficient and selective guide RNAs (gRNAs) has improved CRISPR systems, reducing off-target effects and enhancing genome editing precision.

- Integrated deep learning models like Lasso Regression, FCNN, DTINet, DeepCPI, DeepPurpose, and hybrid CNN frameworks have improved gRNA activity prediction accuracy.

- Accurate predicting gRNA efficiency and specificity is a significant challenge, with various machine learning algorithms used.

- The complexity of gRNA design and the need for precise on-target and off-target predictions are key challenges.

- CRISPR/Cas systems have numerous applications, but off-target mutations and delivery difficulties limit their therapeutic application.

- Further research is needed to improve the safety and efficacy of CRISPR/Cas systems, including developing complex computational models and investigating new Cas proteins.

- Addressing regulatory and ethical concerns is crucial for future use in therapeutic settings.

4. Result and Analysis

This technology employs a range of strategies, such as FCNN, DTINet, DeepCPI, DeepPurpose, and data augmentation techniques. Specific metrics used to assess the efficacy of these models include Accuracy (AUC), Precision, F1 score, and Recall.

4.1 Accuracy (AUC)

Accuracy is an important indicator for evaluating the performance of a classification model since it provides a rapid glimpse of how well the model performs in terms of correct predictions. This is determined as the ratio of correct predictions to total input samples.

$$Accuracy = \frac{TP+TN}{TP+TN+FP+FN} \quad (1)$$

Methods	Accuracy
Mobile Net [32]	96.78
Dark CovidNet [33]	98.08
CNN-SA [34]	95
Coro Net [35]	89.6
Deep Bayes-Squeeze Net [36]	98.3
GSA-Dense Net121 Cov19 [37]	98.3

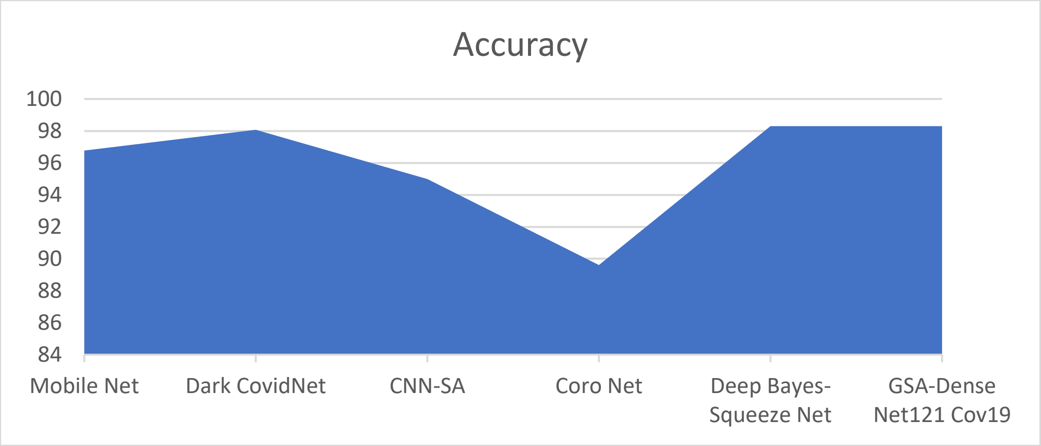

Fig.2 Accuracy analysis

F1 Score

It is the ideal balance of memory and precision. The range is [0,1]. This measure typically indicates how exact (it properly classifies how many instances) and robust (it does not miss any significant number of cases) our classifier is.

Methods	F1 Score
Dark CovidNet [33]	96.51
CNN-SA [34]	95
Coro Net [35]	89.8
Deep Bayes-Squeeze Net [36]	98.3
GSA-Dense Net121 Cov19 [37]	98

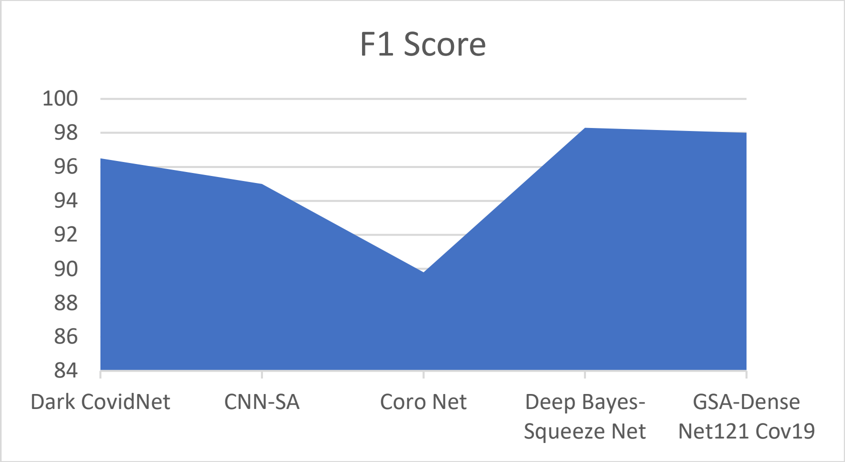

Fig.3 F1 score analysis

Precision

Another metric is known as Precision. It is a performance measure that indicates how many of the model's positive predictions are right. It is determined as the number of true positive predictions divided by the no of true positives and false positives.

$$Precision = \frac{TP}{FP+TP} \tag{2}$$

Methods	Precision
Mobile Net [32]	96.46
Dark CovidNet [33]	98.03
CNN-SA [34]	95
Coro Net [35]	90
Deep Bayes-Squeeze Net [36]	98.3
GSA-Dense Net121 Cov19 [37]	98.5

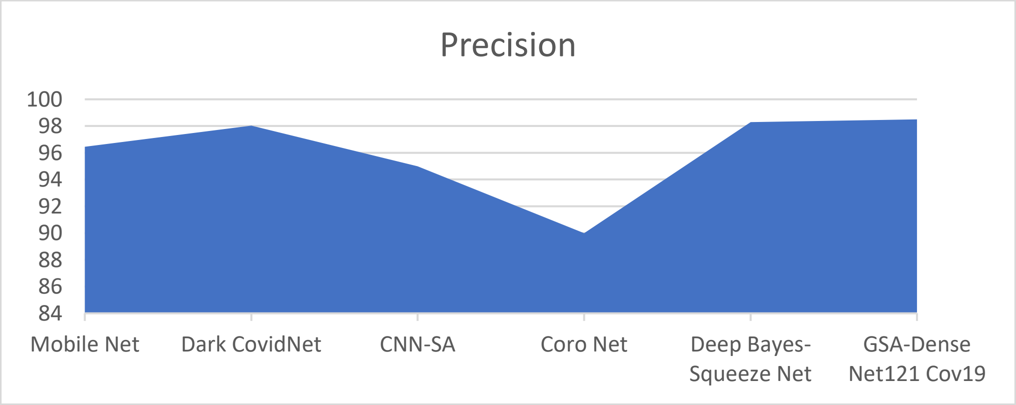

Fig.4 Precision analysis

Recall

It is known as sensitivity or True Positive Rate, is a model's ability to correctly detect positive cases. It is derived by dividing the number of genuine positive predictions by the total number of positive cases (true positives and false negatives combined). This can be expressed properly using the recall formula.

$$Recall = \frac{TP+FN}{TP} \tag{3}$$

Methods	Recall
Mobile Net [32]	98.66
Dark CovidNet [33]	95.13
CNN-SA [34]	95
Coro Net [35]	89.92
Deep Bayes-Squeeze Net [36]	98.3
GSA-Dense Net121 Cov19 [37]	98.5

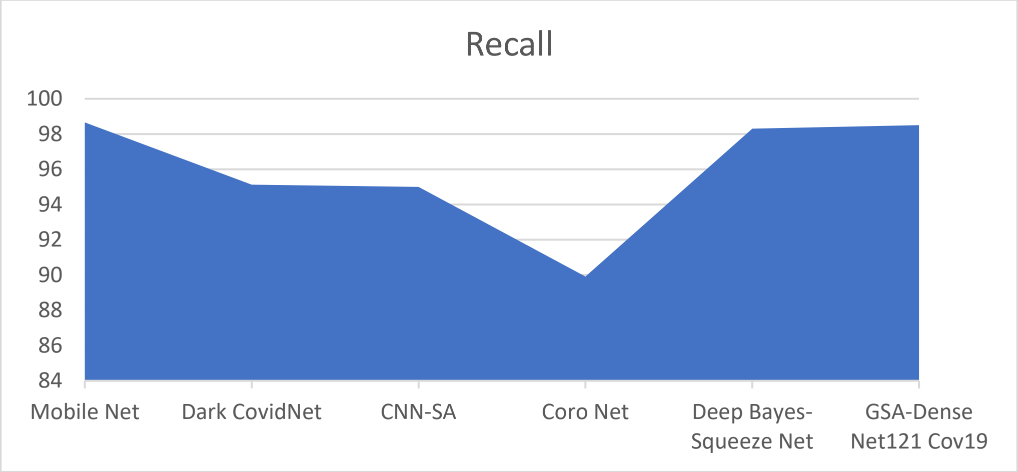

Fig.5 Recall analysis

5. Issues in COVID 19 using Crispr Technology

This part lists some of the problems that require resolution in future work:

CRISPR-Cas systems can lead to unintended genetic changes, requiring deep learning integration for prediction and design of guide RNAs.

Accurate guide RNA design is crucial for successful CRISPR applications, with deep learning algorithms aiding in predicting efficient and specific guide RNAs.

Training deep learning models requires high-quality data, crucial for predicting viral mutations and assessing implications.

Deep learning models can be complex and difficult to interpret, necessitating methods for understanding the rationale behind specific predictions.

Ethical concerns arise from applying CRISPR and deep learning to COVID-19 research.

Integrating information from genomics, transcriptomics, proteomics, and other omics data poses challenges in data pre-processing, alignment, and analysis.

Models developed for one strain or variant may not generalize well to others, necessitating training data for broad applicability.

Implementing CRISPR and deep learning technologies can be resource-intensive, limiting the technology's reach.

Rapid COVID-19 virus evolution necessitates continuous updates to deep learning models.

Clinical applications involving CRISPR and deep learning must adhere to rigorous regulatory and safety standards.

6. Limitation and future perspectives

While CRISPR-Cas technology holds promise in the fight against COVID-19, there are challenges to consider. Ensuring the specificity and accuracy of CRISPR-based diagnostics is crucial to avoid false positives or negatives. Delivering CRISPR components to target cells within the body remains a technical challenge. Researchers must tackle ethical and regulatory concerns while developing CRISPR-based therapies and interventions.

7. Conclusion

CRISPR-Cas technology underscores the remarkable strides in understanding the virus and developing innovative tools to combat it. Integrating CRISPR-Cas technology into COVID-19 research has opened avenues for faster, more precise diagnostics, therapeutics, and vaccine development. CRISPR-Cas holds immense promise in revolutionizing our approach to combating infectious diseases like COVID-19, from enhancing viral detection sensitivity to facilitating gene editing for potential treatments. However, while the potential is vast, continued research, collaboration, and ethical considerations are essential to fully realize the benefits of CRISPR-Cas technology in the battle against existing and future pandemics.

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