SARS-CoV-2 and COVID-19: An Evolving Review of Diagnostics and Therapeutics

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Abstract

Since late 2019, Coronavirus disease 2019 (COVID-19) has spread around the world, resulting in the declaration of a pandemic by the World Health Organization (WHO). This infectious disease is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Research on the virus SARS-CoV-2 and the diease it causes is emerging rapidly through global scientific efforts. The development of diagnostics, treatments, and vaccines will be critical to mitigating the impact of the virus. Here we present a collaborative effort to organize and consolidate the rapidly emerging scientific literature related to SARS-CoV-2. We present information about the virus in the context of what is known about related viruses and synthesize studies emerging about the diagnosis and treatment of COVID-19 alongside literature about related illnesses. A broad scientific effort to understand this pandemic and related viruses and diseases will be foundational to efforts to predict possible interventions. This text is an evolving and collaborative document that seeks to incorporate the ever-expanding body of information related to SARS-CoV-2 and COVID-19.

Where to Contribute

Introduce Yourself (GitHub Issue) https://github.com/greenelab/covid19-review/issues/17

Community Chat (Gitter Room) https://gitter.im/covid19-review/community

More Info (GitHub Readme) https://github.com/greenelab/covid19-review#sars-cov-2-and-covid-19-an-evolving-review-of-diagnostics-and-therapeutics

Introduction

General Background

On January 21, 2020, the World Health Organization (WHO) released its first report concerning what is now known as the Coronavirus disease 2019 (COVID-19) [1]. This infectious disease came to international attention on December 31, 2019 following an announcement by national officials in China about 44 cases of a respiratory infection of unknown cause. The first known cases were located in Wuhan City within the Hubei province of China, but the disease spread rapidly beyond Wuhan within China and subsequently around the world. At the time of the first situation report [1], 282 confirmed cases had been identified, primarily in China, but also 1-2 exported cases had been identified in several neighboring countries (Thailand, Japan, and the Republic of Korea). One week later, 4593 confirmed cases had been identified, spanning not only Asia, but also Australia, North America, and Europe [2]. On March 11, 2020, WHO formally classified the situation as a pandemic [3]. By WHO Situation Report 61, released on March 20, 2020, 266,073 confirmed cases had been reported worldwide, with cases on every continent except Antarctica [4]. At this time, over 11,000 deaths had been reported worldwide.

[Note: Maybe add a graph here, update as new reports come out.]

COVID-19 is caused by the newly identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a coronavirus, a family of RNA viruses known to cause respiratory and intestinal infections in humans and other species. Infectious diseases of global concern have previously been associated with coronaviruses, including Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) [5,6]; however, neither of these reached pandemic status, owing to proper containment procedures (SARS) or intrinsic limitations in virus transmission (MERS). Additionally, there are four endemic human coronaviruses that rarely progress beyond the mild symptoms associated with the common cold [6]. The precise identity of SARS-CoV-2 virus was unknown until approximately January 12, 2020, when Chinese officials released its genetic sequence to aid in worldwide efforts to diagnose the disease [1]. As researchers worldwide work to characterize SARS-CoV-2 and COVID-19, information about the transmission and life cycle of the virus as well as the diagnosis and treatment of the disease is emerging rapidly. In this review, we seek to consolidate information about the virus in the context of related viruses and to synthesize what is known about the diagnosis and treatment of COVID-19 and related diseases. This is a real-time, collaborative effort that welcomes submissions from scientists worldwide.

Coronaviruses: What are they, and what do we know about SARS-CoV-19?

Coronaviruses are RNA viruses that... [Summarize relevant mechanisms for cell entry & address evidence for/against ACE2 being important]

The origin of the SARS-CoV-19 virus is not yet fully understood. Genomic analyses and comparisons to other known coronaviruses suggest that SARS-CoV-19 is unlikely to have originated from a laboratory – either purposely engineered and released, or escaped – and instead evolved naturally in an animal host [7]. Among known coronaviruses, SARS-CoV-19 has the closest overall sequence similarity to RaTG13 (~96%) found in a *Rhinolophus affinis* bat [8], while the receptor binding domain (RBD) is highly similar to that of viruses found in pangolins [9]. This suggests that SARS-CoV-19 may have originated in viral reservoirs of similar hosts, however current evidence cannot discriminate an origin of the virus before or after zoonotic transfer to humans [7].

Mechanisms of Coronavirus-driven Disease in Humans

Coronaviruses are known to cause respiratory illnesses in humans through the following possible mechanisms...

Presentation of COVID-19

Information is rapidly becoming available about the wide range of symptoms that can be associated with COVID-19 as well as the range of symptom severity, onset from exposure, and possible risk or protective factors...

Vaccines for Viruses: Strategies for and challenges to development

What information is needed to develop a vaccine? How have vaccines for other viruses such as H1N1 been developed?

Diagnostics and Therapeutics for Viruses

Two major concerns within diagnosis include the detection of current infections in individuals with and without symptoms, and the detection of past exposure without an active infection. In the latter category, identifying whether individuals can develop or have developed sustained immunity is also a major consideration.

Within therapeutics, some possible efforts include efforts to identify strategies for the management of symptoms as well as the development of antivirals...

In this review, we seek to consolidate information about efforts to develop strategies for diagnosis and therapeutics as new information is released by the scientific community.

Pathogenesis

Mechanism of Host Infection by SARS-CoV-2

This section would also be great for the introduction of zoonotic diseases which has been shown to be the origin of SARS-CoV2.

Primary Transmission and Viral Entry

[How does SARS-CoV-2 enter human cells?] [What cells are primary infection sites for SARS-CoV-2?] [What structural aspects allow for viral entry]?

Viral Replication, Spreading and Transmission

[Basic introduction into replication cycle] [What is the basic reproductive rate] [What are the routes of transmission]

Immune Response to SARS-CoV-2

[Cellular responses to SARS-CoV-2 infection] [What is causing neutropenia and lymphopenia observed in COVID-19 patients] [Antibody production against SARS-CoV-2 by patient who recovered vs patient who did not recover] [Cytokines and other soluble factors contribution to immune response]

Systems level approaches for understanding SARS-CoV-2 pathogenesis

[Sandipan Ray volunteered to lead this section]

Diagnostics

Current Strategies for Diagnosing COVID-19 and Similar Viral Infections

Given the heterogeneity of symptom presentation across patients with COVID-19, the development of standardized protocols for testing samples for SARS-CoV-2 is urgent. Following the release of the genetic sequence of the virus by Chinese officials on January 12, 2020, the first tests for detecting the virus were released on XX, 2020. These tests used the following approach to identify the active virus in patient samples... However, many countries have struggled to acquire the tests required to keep pace with the epidemic. [Why is it so difficult to scale up testing? What are some of the considerations?]

Possible Alternatives to Current Practices for Identifying Active Cases

[Are there other approaches that have worked for diagnosing other viruses at a rapid pace in large numbers of people?] [What are some approaches people are currently testing for detecting live viruses, especially SARS-CoV-2?]

Detection of Past Exposure and/or Sustained Immunity

[What are approaches that allow us to detect past exposure for other viruses?] [What efforts are underway to develop similar approaches for SARS-CoV-2?] [What is sustained immunity and what are the indicators?]

Limitations to Implementation of Large-Scale Testing

[Right now, reagent supply is an issue. Are there others concerns that are likely to emerge?]

Stratgies and Considerations for Determining Whom to Test

[If it's not possible to test everyone, what strategies exist for selecting who to test?] [Are these strategies likely to change over time? Presumably there are different stages of managing spread vs mitigating severity once it's already at high prevalence?]

Therapeutics

Given the rapid predicted spread of the disease, the development of therapeutics will be critical to mitigating its effect on health and the mortality rate. Typically, therapeutics can take a few forms. First, the treatment and reduction of symptoms can result in the reduction of the severity and risk associated with an active infection. Second, the development of antiviral drugs can drive a reduced recovery time for patients by inhibiting the development of the virus once an individual is infected. Finally, vaccines present a strategy for bolstering the immune response of the populus broadly to the virus, resulting in a lower rate of infection. All three of these strategies have been valuable elements of responses to other viruses, including coronaviruses, and are being investigated by researchers at present. Additionally, there have been suggestions within the scientific community that nutraceutical or dietary supplement interventions may prime an individual's immune system to prevent or lessen the impact of RNA virus infections [**???**,10]. In the following sections, we critically appraise the literature surrounding the repurposing of existing treatments and development of novel therapeutics for the prevention, mitigation, and treatment of coronavirus infections.

Treatment of Symptoms

Possible background needed: -COVID-19 is characterized by... -The most severe and concerning symptoms are typically... -The symptoms most often regarded as the proximal cause of death from COVID-19 are... -Other diseases with similar symptoms include XYZ but these diseases may be different because... -Given what we know about the mechanisms of the virus and why it produces the symptoms we see, are there drugs or categories of intervention that might be relevant?

So far, some strategies for reducing the severity of symptoms have included...

Symptom Management Approach 1

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the symptom management approach.

Antivirals

Antivirals are an emerging category of drugs. Unlike antibiotics, they do not kill viruses. Rather, they inhibit the proliferation of a virus. Categories may include therapies that inhibit viral proteins, inhibit viral entry, and more Antivirals have been used to treat XYZ diseases through [what mechanisms or approaches are used?]

Add a subcategory (using ####) for each category of antiviral treatment

Antiviral Approach 1

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the antiviral approach.

Vaccines

Vaccines, widely recognized as one of the most significant advances in human health during the 20th century, can be used to bolser both individual and herd immunity to a virus by promoting the development of antibodies without infection. [Are vaccines available for other coronaviruses or related viral illnesses?] [What are some of the challenges to developing a vaccine? What needs to be taken into account about how the virus works?] [Are there any challenges or opportunities unique to coronaviruses and/or SARS-CoV-2?] [What are some approaches being tested or considered?]

Vaccine Approach 1

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the vaccine approach.

Neutralizing Antibodies

Monoclonal antibodies targeting viral antigens have shown therapeutic efficacy against viruses like Ebola and SARS CoV [11,12]. The first human neutralizing antibody against SARS-CoV-2 targeting the trimeric spike (S) glycoproteins has been developed [13].

Neutralizing Antibody Approach 1

Brief background on the therapeutic.

Anticipated Mechanism

Why it may be useful

Current Evidence

A list of current studies and their results, using carefully the information requested in the therapeutic paper tickets.

Summary

Summarize the state of the neutralizing antibody approach.

Nutraceutical Internventions

Additional Items

Competing Interests

Author	Competing Interests	Last Reviewed
Halie M. Rando	None	2020-03-22
Casey S. Greene	None	2020-03-22
Michael P. Robson	None	2020-03-23
Simina M. Boca	None	2020-03-23
Nils Wellhausen	None	2020-03-22
Christian Brueffer	None	2020-03-25

Author Contributions

Author	Contributions
Halie M. Rando	Project Administration, Writing - Original Draft, Methodology
Casey S. Greene	Conceptualization, Software
Michael P. Robson	Software
Simina M. Boca	Methodology
Nils Wellhausen	Writing - Original Draft
Christian Brueffer	Writing - Original Draft

Formatting Examples

This manuscript is a template (aka “rootstock”) for Manubot, a tool for writing scholarly manuscripts. Use this template as a starting point for your manuscript.

The rest of this document is a full list of formatting elements/features supported by Manubot. Compare the input (`.md` files in the `/content` directory) to the output you see below.

Basic formatting

Bold text

Semi-bold text

Italic text

Combined *italics and* ***bold***

~~Strikethrough~~

1. Ordered list item
2. Ordered list item
    a. Sub-item
    b. Sub-item
        i. Sub-sub-item
3. Ordered list item
    a. Sub-item

- List item
- List item
- List item

subscript: H_2O is a liquid

superscript: 2^{10} is 1024.

unicode superscripts^{0123456789}

unicode subscripts$_{0123456789}$

A long paragraph of text. Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua. Ut enim ad minim veniam, quis nostrud exercitation ullamco laboris nisi ut aliquip ex ea commodo consequat. Duis aute irure dolor in reprehenderit in voluptate velit esse cillum dolore eu fugiat nulla pariatur. Excepteur sint occaecat cupidatat non proident, sunt in culpa qui officia deserunt mollit anim id est laborum.

Putting each sentence on its own line has numerous benefits with regard to editing and version control.

Line break without starting a new paragraph by putting
two spaces at end of line.

Document organization

Document section headings:

Heading 1

Heading 2

Heading 3

Heading 4

A heading centered on its own printed page

Horizontal rule:

`Heading 1`'s are recommended to be reserved for the title of the manuscript.

`Heading 2`'s are recommended for broad sections such as *Abstract*, *Methods*, *Conclusion*, etc.

`Heading 3`'s and `Heading 4`'s are recommended for sub-sections.

Links

Bare URL link: https://manubot.org

Long link with lots of words and stuff and junk and bleep and blah and stuff and other stuff and more stuff yeah

Link with text

Link with hover text

Link by reference

Citations

Citation by DOI [14].

Citation by PubMed Central ID [15].

Citation by PubMed ID [16].

Citation by Wikidata ID [17].

Citation by ISBN [18].

Citation by URL [19].

Citation by tag [20].

Multiple citations can be put inside the same set of brackets [14,18,20]. Manubot plugins provide easier, more convenient visualization of and navigation between citations [15,16,20,21].

Citation tags (i.e. aliases) can be defined in their own paragraphs using Markdown's reference link syntax:

Referencing figures, tables, equations

Figure 1

Figure 2

Figure 3

Figure 4

Table 1

Equation 1

Equation 2

Quotes and code

> Quoted text

> Quoted block of text
>
> Two roads diverged in a wood, and I—
> I took the one less traveled by,
> And that has made all the difference.

Code `in the middle` of normal text, aka `inline code`.

Code block with Python syntax highlighting:

```
from manubot.cite.doi import expand_short_doi

def test_expand_short_doi():
    doi = expand_short_doi("10/c3bp")
    # a string too long to fit within page:
    assert doi == "10.25313/2524-2695-2018-3-vliyanie-enhansera-copia-i-
        insulyatora-gypsy-na-sintez-ernk-modifikatsii-hromatina-i-
        svyazyvanie-insulyatornyh-belkov-vtransfetsirovannyh-geneticheskih-
        konstruktsiyah"
```

Code block with no syntax highlighting:

```
Exporting HTML manuscript
Exporting DOCX manuscript
Exporting PDF manuscript
```

Figures

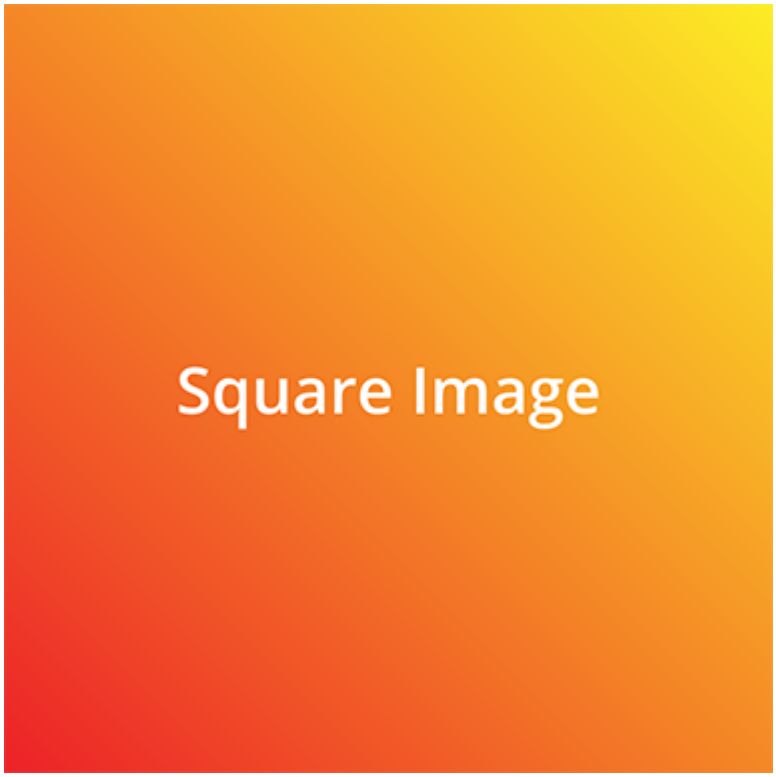

Figure 1: A square image at actual size and with a bottom caption. Loaded from the latest version of image on GitHub.

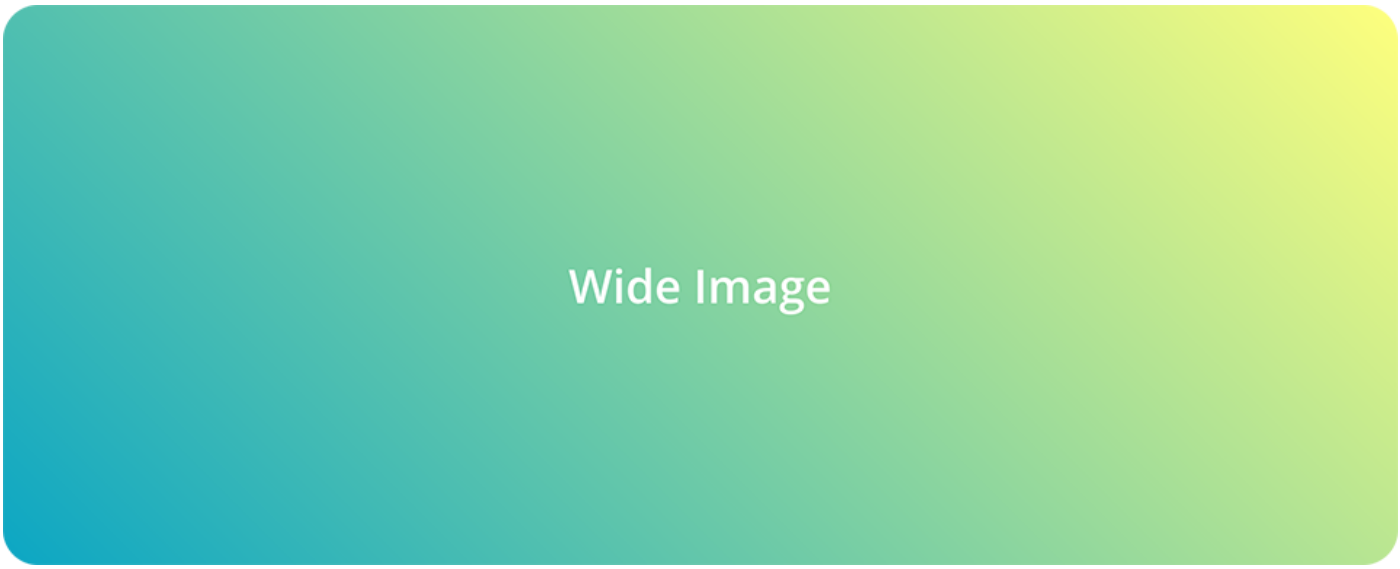

Figure 2: An image too wide to fit within page at full size. Loaded from a specific (hashed) version of the image on GitHub.

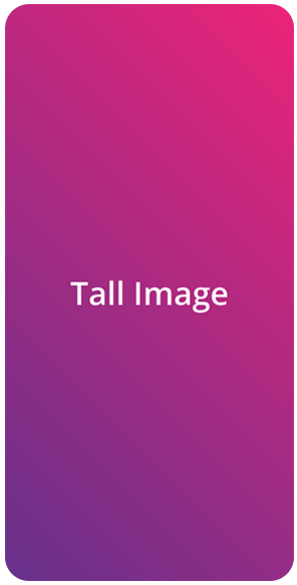

Figure 3: A tall image with a specified height. Loaded from a specific (hashed) version of the image on GitHub.

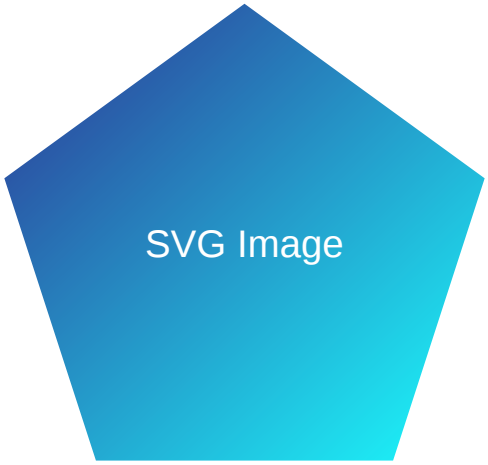

Figure 4: A vector `.svg` image loaded from GitHub. The parameter `sanitize=true` is necessary to properly load SVGs hosted via GitHub URLs. White background specified to serve as a backdrop for transparent sections of the image.

Tables

Table 1: A table with a top caption and specified relative column widths.

Bowling Scores	**Jane**	**John**	**Alice**	**Bob**
Game 1	150	187	210	105
Game 2	98	202	197	102
Game 3	123	180	238	134

Table 2: A table too wide to fit within page.

	Digits 1-33	**Digits 34-66**	**Digits 67-99**	**Ref.**
pi	3.14159265358979323 846264338327950	28841971693993751 0582097494459230	78164062862089986 2803482534211706	`piday.org`
e	2.71828182845904523 536028747135266	24977572470936999 5957496696762772	40766303535475945 7138217852516642	`nasa.gov`

ged cells using the `attributes` plugin.

	Colors	
Size	**Text Color**	**Background Color**
big	blue	orange
small	black	white

Equations

A LaTeX equation:

$$\int_0^\infty e^{-x^2} dx = \frac{\sqrt{\pi}}{2} \tag{1}$$

An equation too long to fit within page:

$$x = a + b + c + d + e + f + g + h + i + j + k + l + m + n + o + p + q + r + s + t + u + v + w + x + y + z + 1 + 2 + 3 + 4 + 5 + 6 + 7 + 8 + 9 \tag{2}$$

Special

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Adding arbitrary HTML attributes to an element using Pandoc's attribute syntax:

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Adding arbitrary HTML attributes to an element with the Manubot `attributes` plugin (more flexible than Pandoc's method in terms of which elements you can add attributes to):

Manubot Manubot Manubot Manubot Manubot. Manubot Manubot Manubot Manubot. Manubot Manubot Manubot. Manubot Manubot. Manubot.

Available background colors for text, images, code, banners, etc:

`white` `lightgrey` `grey` `darkgrey` `black` `lightred` `lightyellow` `lightgreen` `lightblue` `lightpurple` `red` `orange` `yellow` `green` `blue` `purple`

Using the Font Awesome icon set:

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Light Grey Banner
useful for *general information* - manubot.org

Blue Banner
useful for *important information* - manubot.org

Light Red Banner
useful for *warnings* - manubot.org

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Daniel S. Himmelstein, Vincent Rubinetti, David R. Slochower, Dongbo Hu, Venkat S. Malladi, Casey S. Greene, Anthony Gitter
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Travers Ching, Daniel S. Himmelstein, Brett K. Beaulieu-Jones, Alexandr A. Kalinin, Brian T. Do, Gregory P. Way, Enrico Ferrero, Paul-Michael Agapow, Michael Zietz, Michael M. Hoffman, … Casey S. Greene
Journal of The Royal Society Interface (2018-04-04) https://doi.org/gddkhn
DOI: 10.1098/rsif.2017.0387 · PMID: 29618526 · PMCID: PMC5938574

21. **Open collaborative writing with Manubot**
Daniel S. Himmelstein, Vincent Rubinetti, David R. Slochower, Dongbo Hu, Venkat S. Malladi, Casey S. Greene, Anthony Gitter
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DOI: 10.1371/journal.pcbi.1007128 · PMID: 31233491 · PMCID: PMC6611653