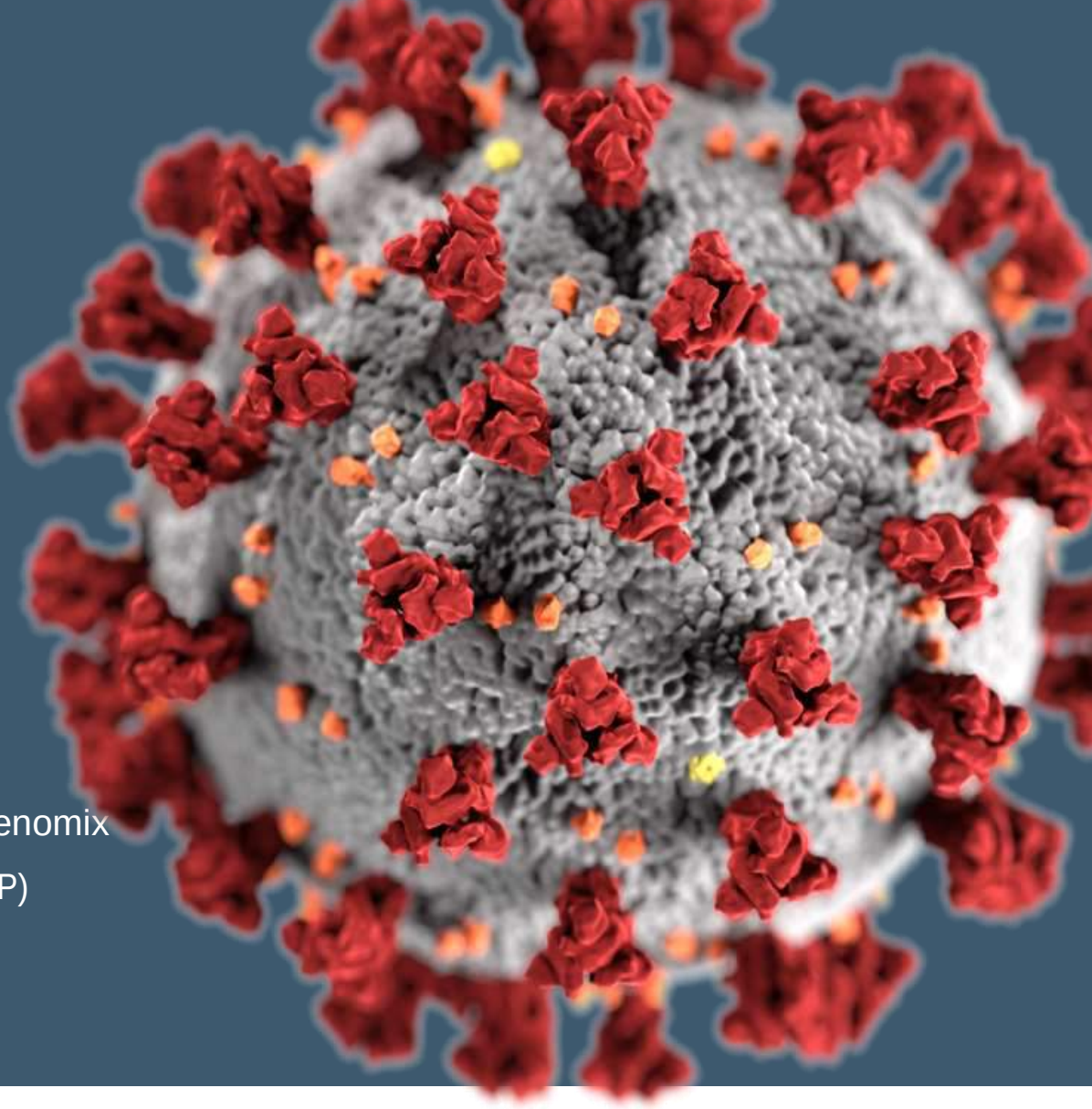
Técnicas para detectar COVID-19:

Cuáles, cómo y cuándo



Javier García-Planells, Ph. D.

Clinical Development & Scientific Advisor Rare Diseases Director, Igenomix

Presidente de la Asociación Española de Diagnóstico Prenatal (AEDP)

European Molecular Genetics Quality Network (EMQN) Assessor

Igenomix® foundation FORWARD THINKING

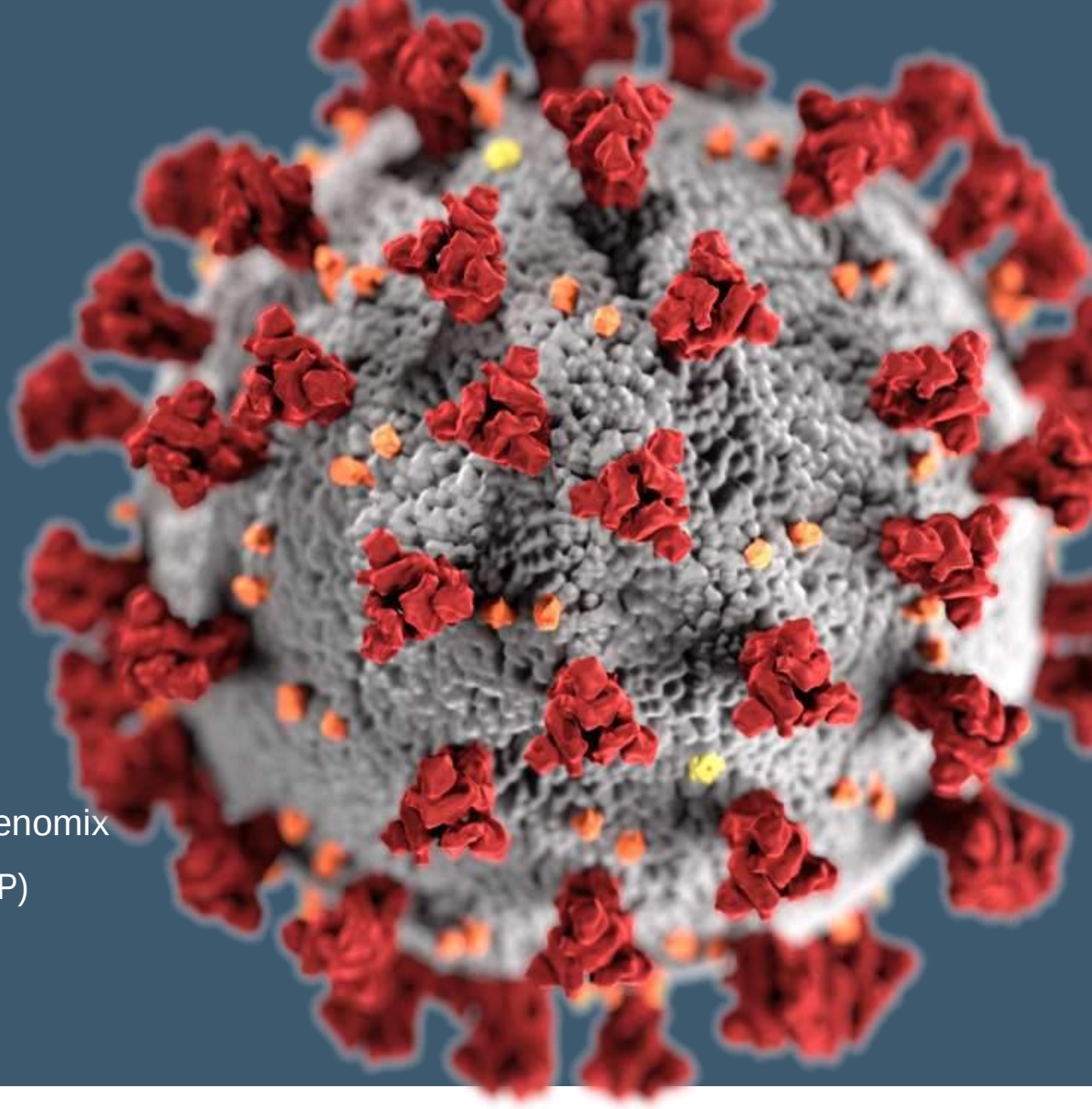
Valencia, SPAIN

7th April 2020

Igenomix foundation FORWARD THINKING

Técnicas para detectar COVID-19:

Cuáles, cómo y cuándo



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Outline

- SARS-CoV-2 virus
  - Features
  - Life Cycle
- COVID-19 Technologies
  - Which
  - How should we use them
  - When must we use them

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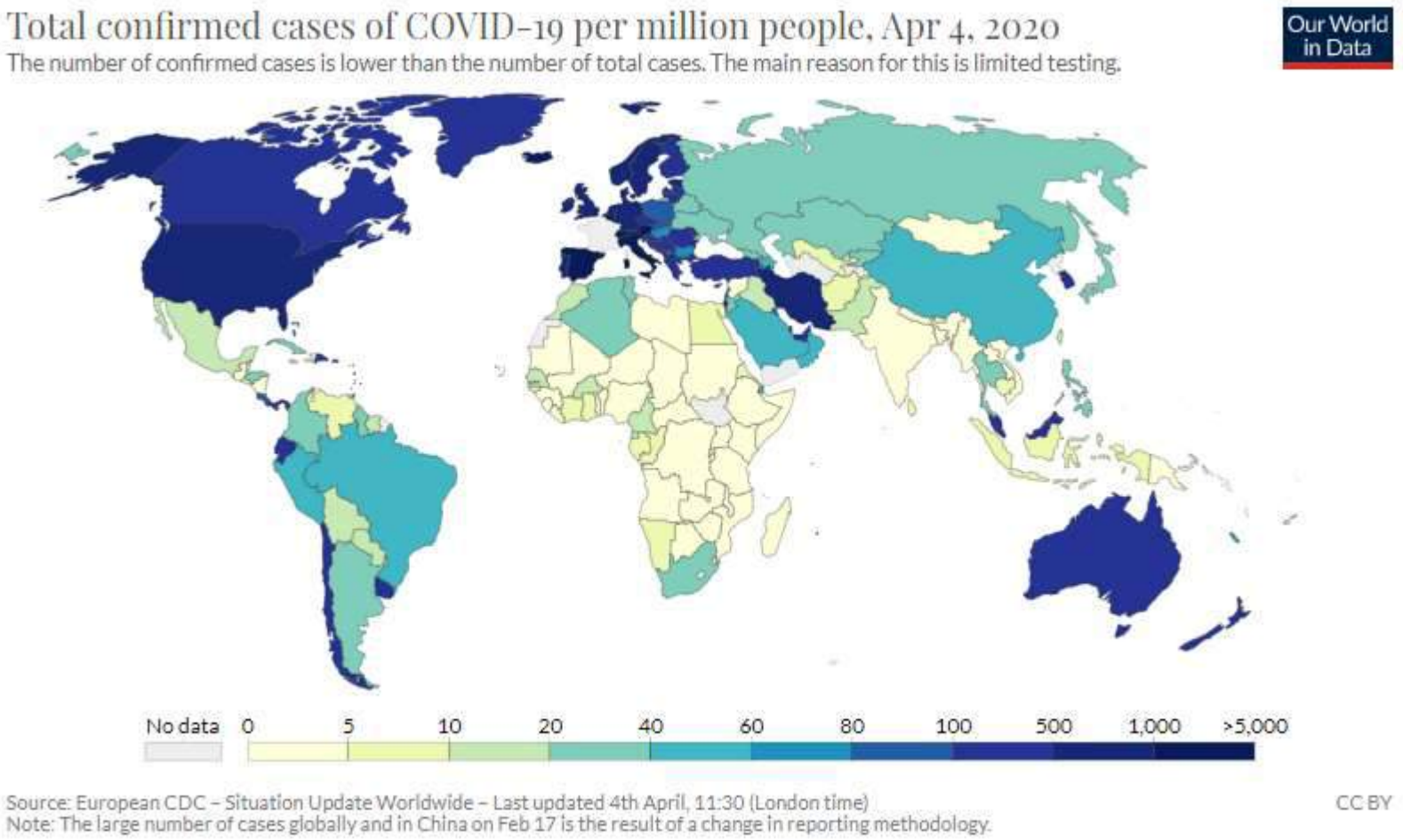
COVID-19 is the Coronavirus Disease caused by the **SARS-CoV-2 virus**, declared as a new **pandemic** by the World Health Organization (WHO) as of 11th March, 2020.



World Health Organization. Coronavirus disease (COVID-19) outbreak. https://www.who.int/emergencies/diseases/novel-coronavirus-2019
Gorbalenya, et al. Biorxiv. https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.full.pdf
Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/index-sp.html

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COVID-19 is the Coronavirus Disease caused by the **SARS-CoV-2 virus**, declared as a new **pandemic** by the World Health Organization (WHO) as of 11th March, 2020.

We need more knowledge to understand....

... causes and reasons for its rapid spread and population differences

- Prevention

... the biology and pathophysiology of the disease

- Treatments and vaccines

.... how are we going to recover our activities and previous lifestyle

- Epidemiology

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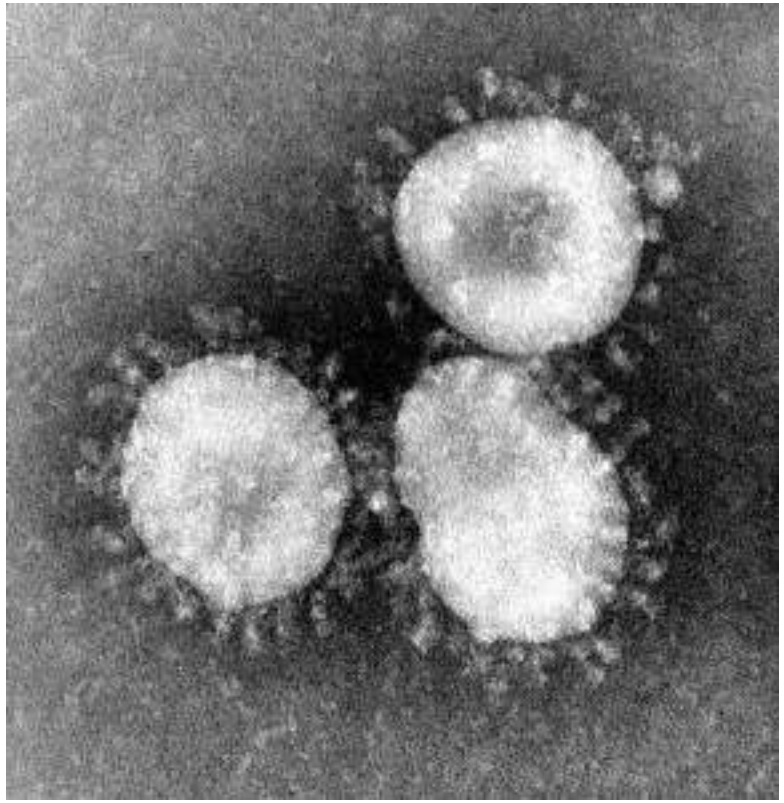
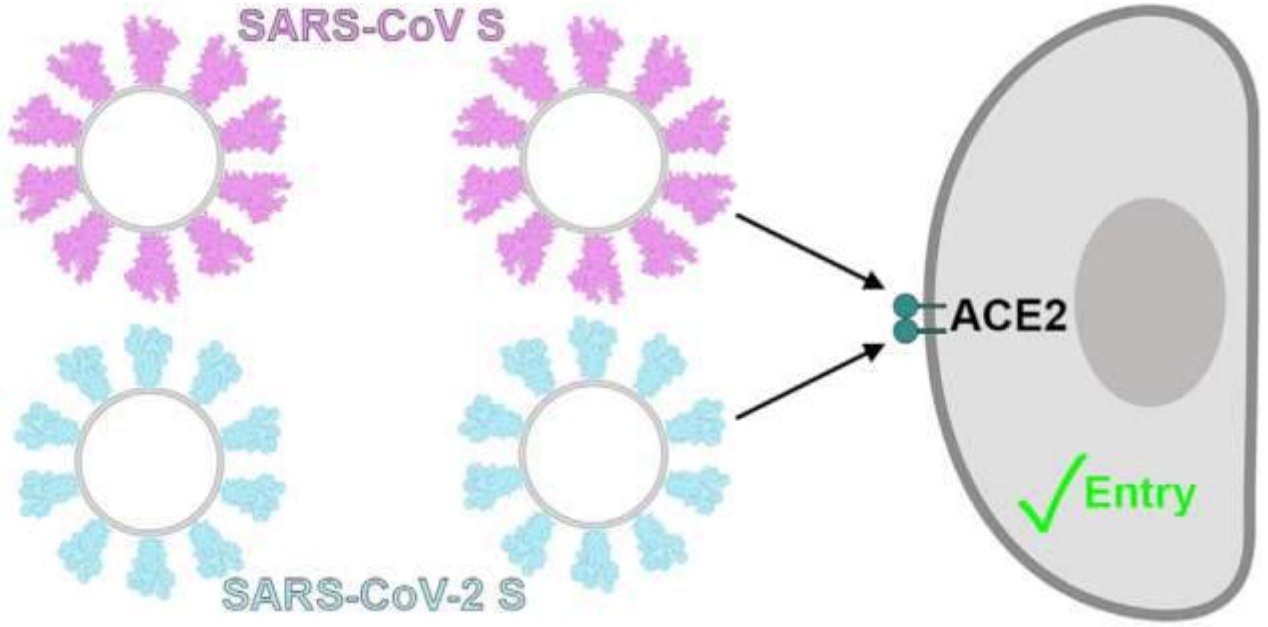
SARS-CoV-2 virus

SARS-CoV-2 is a single-stranded RNA, enveloped virus, belonging to the β-coronavirus family. This virus is able to enter the human cells by binding of its spike (S) protein to ACE2 enzyme.





ACE2 (Angiotensin converting enzyme 2) is expressed in the membrane of different cell types as a part of the renin-angiotensin (RAS) system, involved in the regulation of blood pressure.

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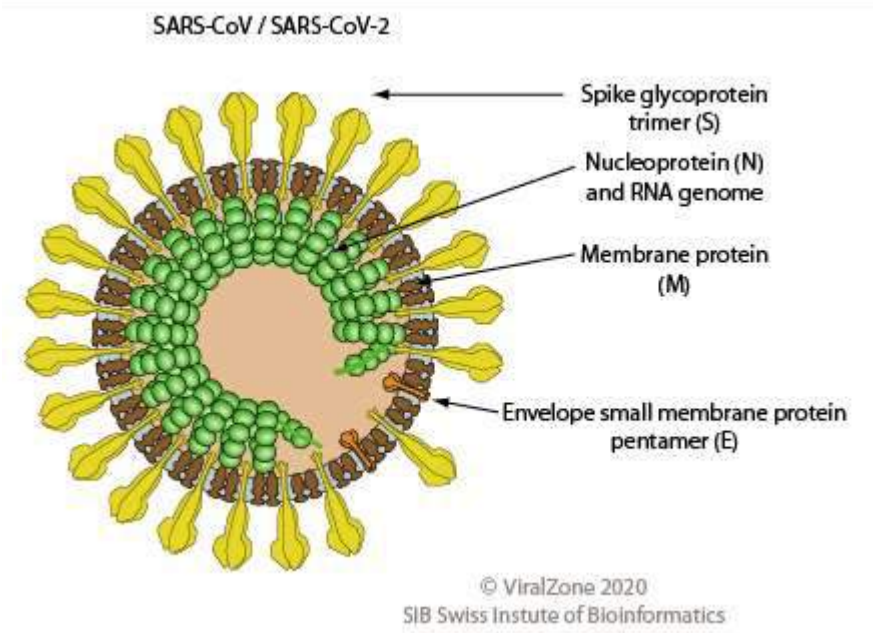
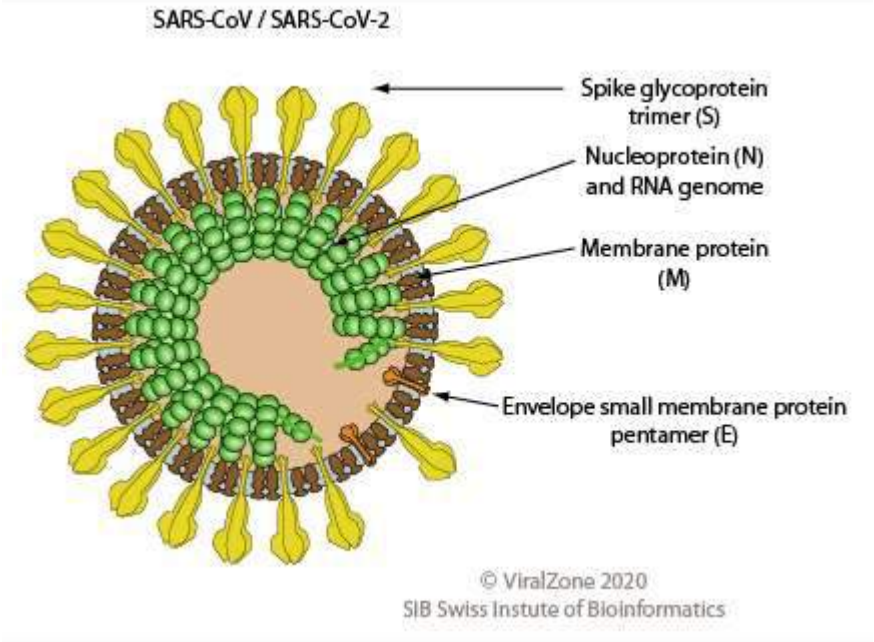
Walls et al. *Cell*. 2020.

SARS-CoV-2 virus



SARS-CoV-2 Genome

A virus is "simply a piece of bad news wrapped up in protein,"
Jean and Peter Medawar, 1977



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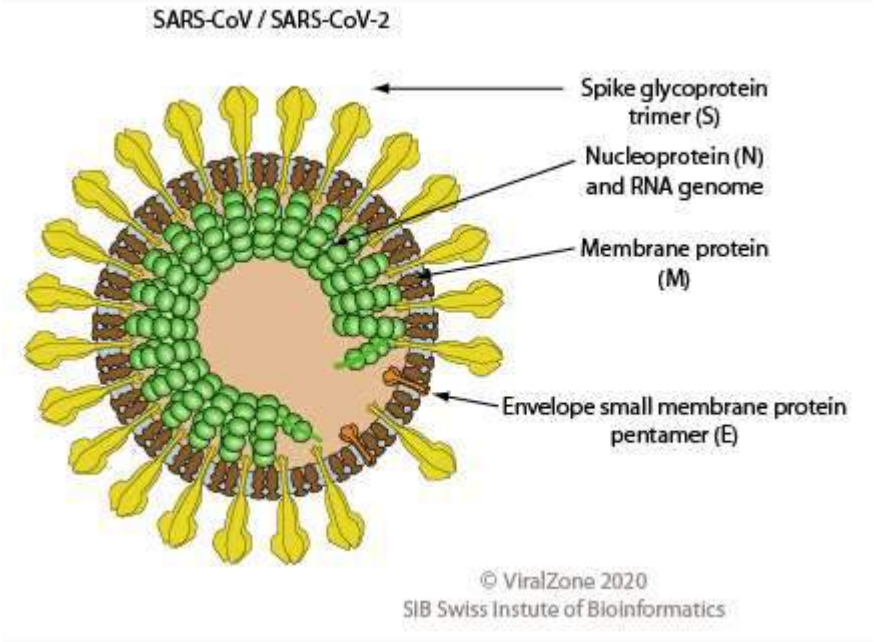

Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome

NCBI Reference Sequence: NC_045512.2

GenBank Graphics

>NC_045512.2 Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome

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5th January 2020

SARS-COV2 Genome: ss-RNA: 29903 nt
Human Genome: ds-DNA: 3300×10^6 nt

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SARS-CoV-2 Genome

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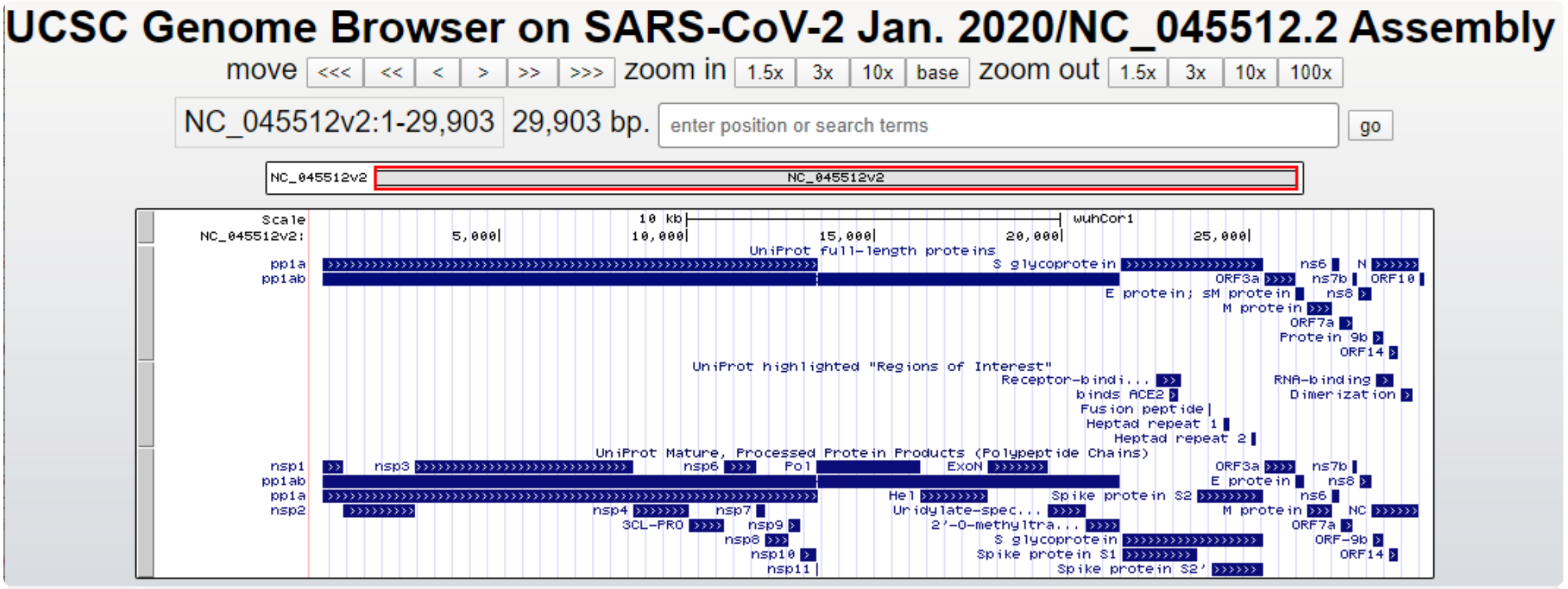

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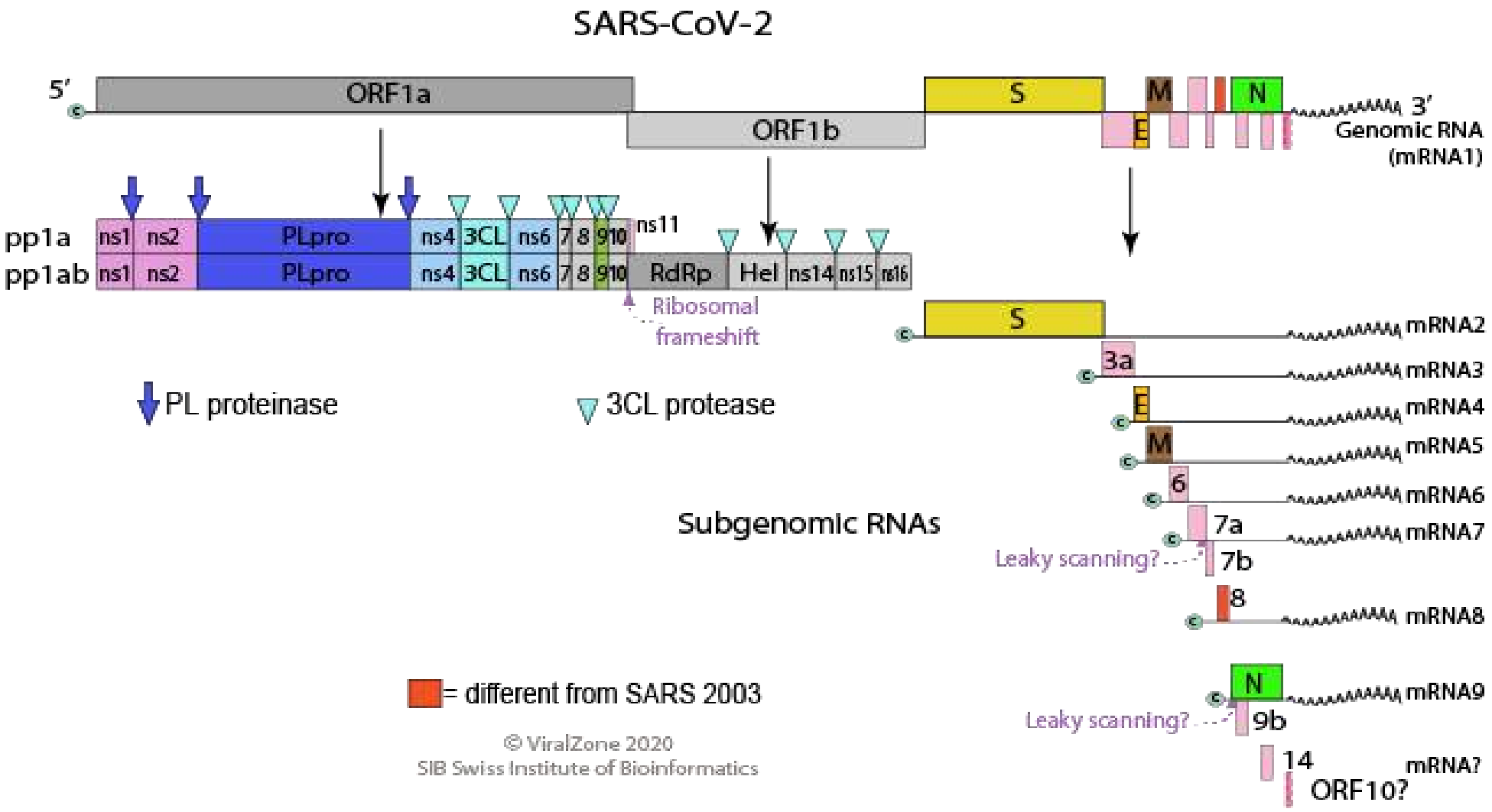

Andersen et al. *Nature Medicine*. 2020

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SARS-CoV-2 Life Cycle

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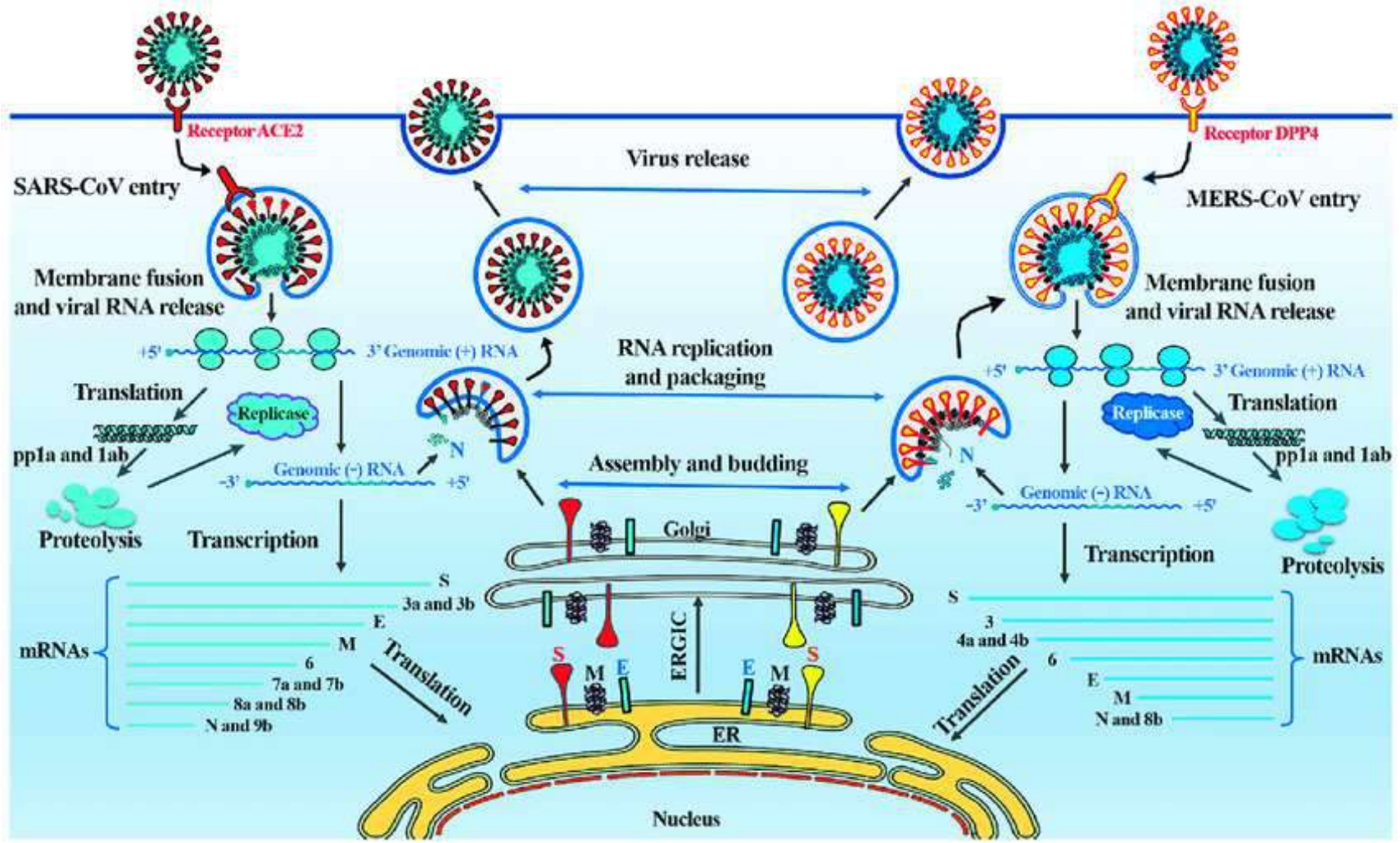

Song et al. *Viruses* 2019

SARS-CoV-2 Life Cycle

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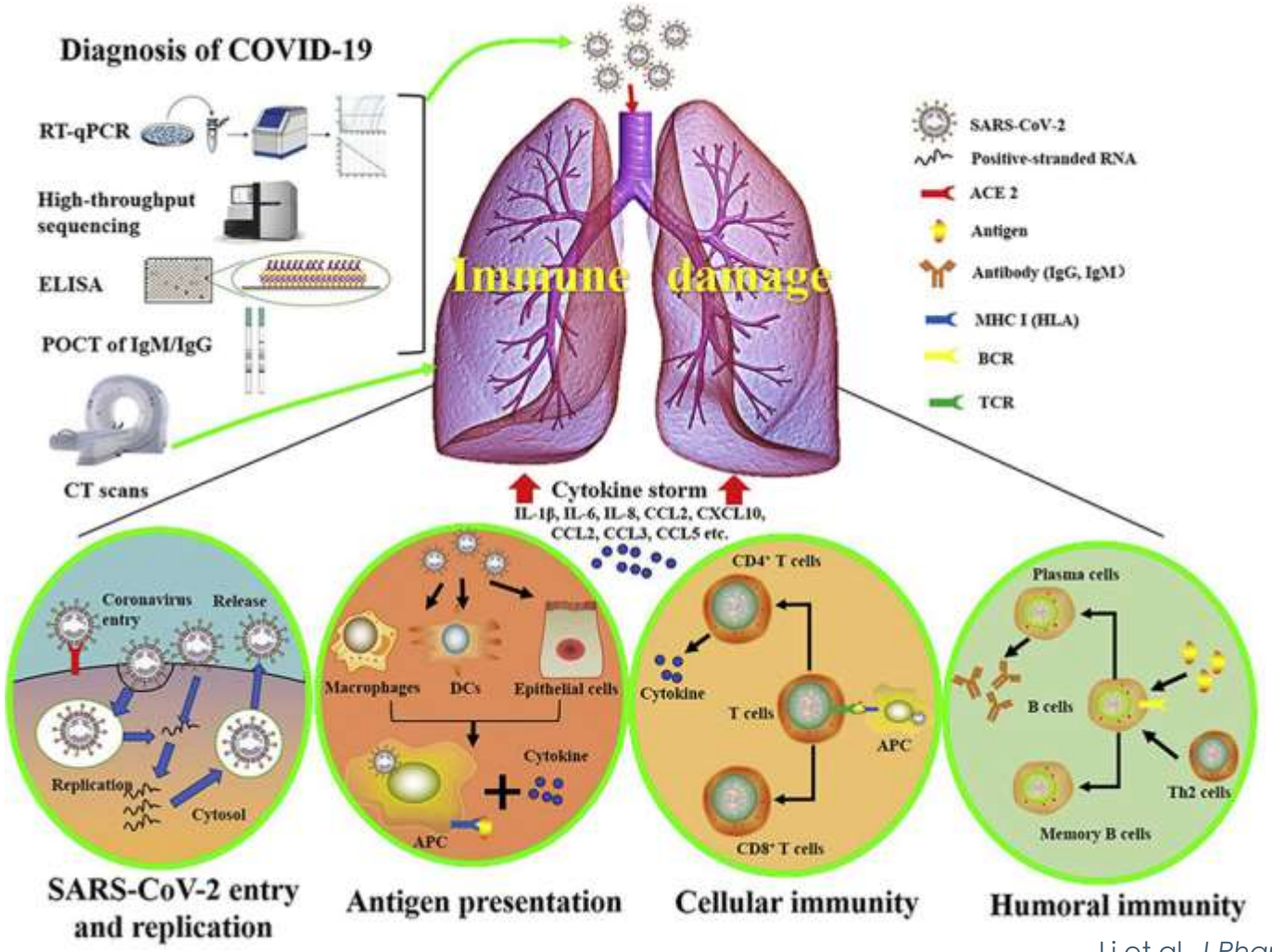

Li et al. *J Pharm Anal* 2020.

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Technologies

...for SARS-COV2 detection

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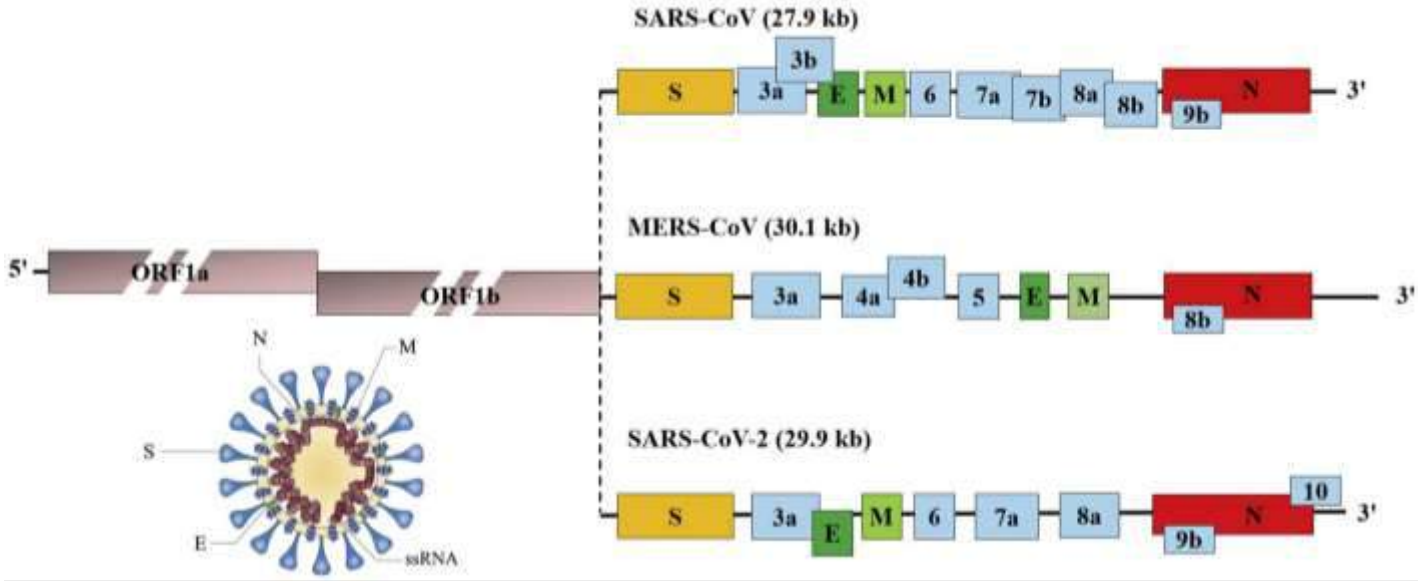
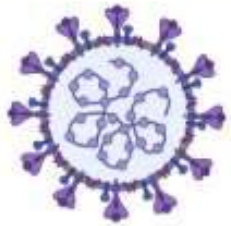
COVID-19 Technologies



Li et al. *J Pharm Anal* 2020.

The highest

- Sensitivity
- Specificity

Flu	COVID-19	SARS	MERS
			
Influenza virus	SARS-CoV-2	SARS-CoV	MERS-CoV

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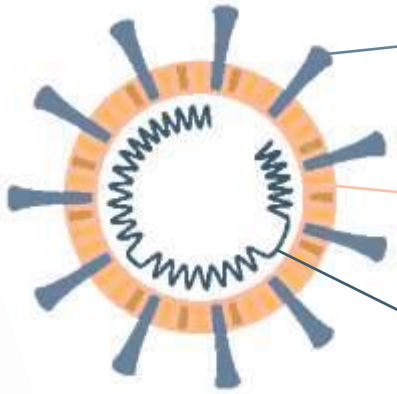
COVID-19 Technologies



Spike (S) protein

Envelop proteins (N protein)

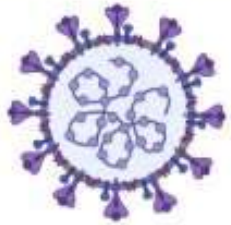
RNA

Technologies

- Immunoassays
- RT-PCR
- RNA NGS sequencing

The highest

- Sensitivity
- Specificity

Flu	COVID-19	SARS	MERS
Influenza virus	SARS-CoV-2	SARS-CoV	 MERS-CoV

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COVID-19 Technologies

Technologies for SARS-CoV-2

Immunoassay

- Antigen Detection
- Antibodies (IgG and IgM) detection (ELISA and PoC)

RNA detection and analysis

- RT-PCR
- Next Generation Sequencing (NGS)

COVID-19 Technologies

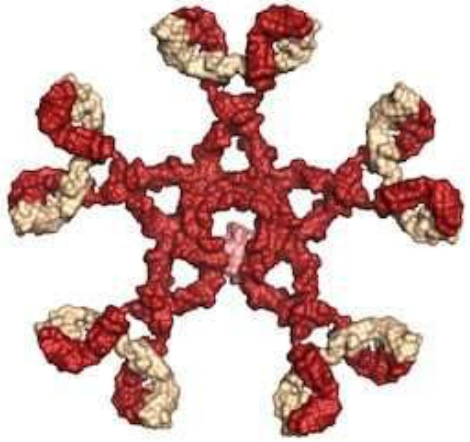
Immunoassays and Immune response

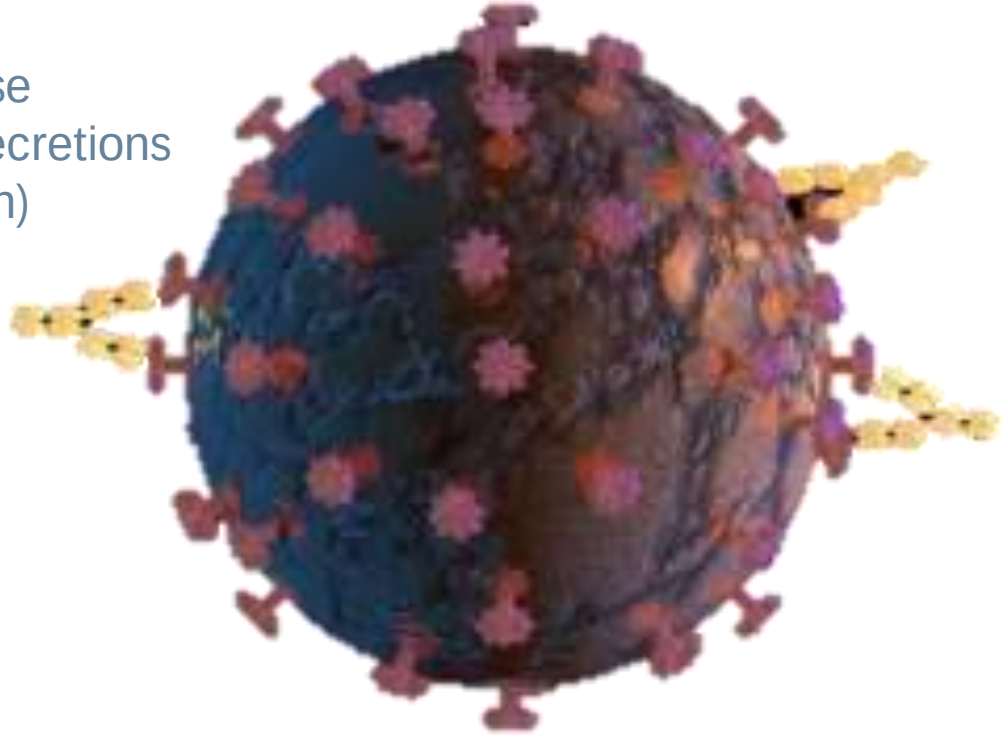
When a person is infected with a pathogen, its immune system reacts to this infection building antibodies against this antigen

Specific recombinant antigens and antibodies are targeted to S and N SARS-CoV-2 proteins

Antibodies: Immunoglobulines

- **IgM** is the first antibody produced during an immune response
- **IgA** is involved in primary defense and frequent in mucosal secretions
- **IgG** is produced in a delayed response (delayed immunization)





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COVID-19 Technologies

Immunoassays

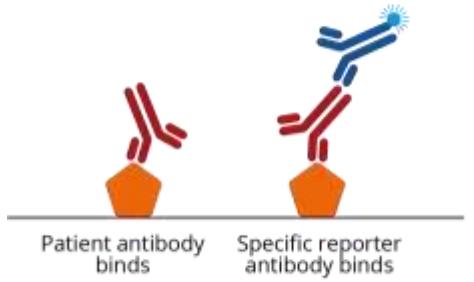
(SEIMC guidelines)

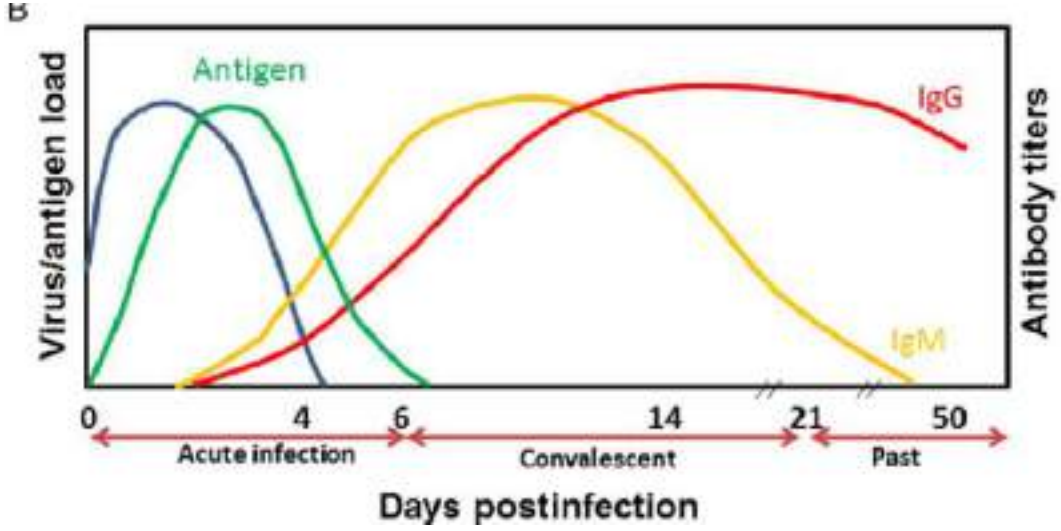
- Antigen Detection

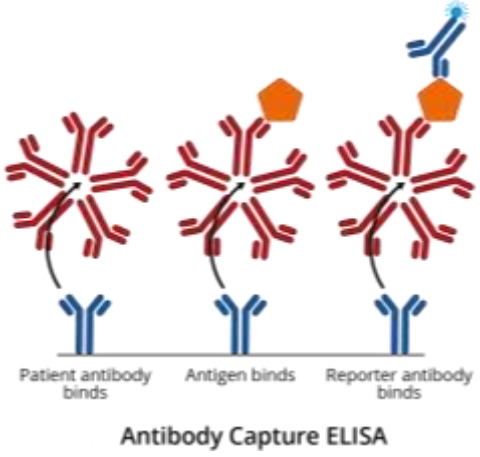
  Overall sensitivity is very low < 50% (SEIMC), are not (yet) recommended for COVID 19 acute phase

- Antibody (IgG and IgM) Detection (ELISA or Point of Care)

  Kinetic of immune response starts around day 5-6 postinfection
  High sensitivity after day 10 postinfection
  High variability among the kits in the market (Try fist!!!)







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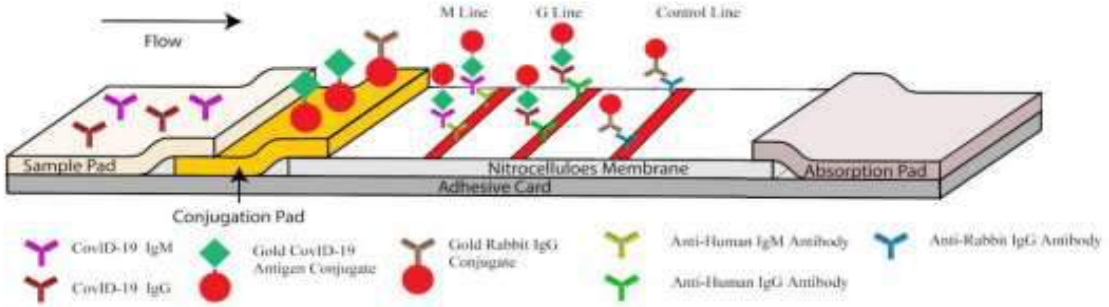
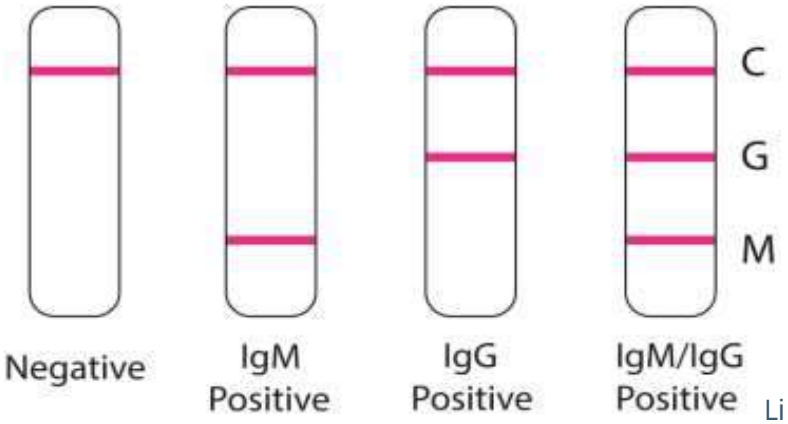
COVID-19 Technologies

Immunoassays

- Antibody (IgG and IgM) Detection (Point of Care)

  Reverse detection of antigens by lateral flow





Li et al. *J Med Virol*. 2020

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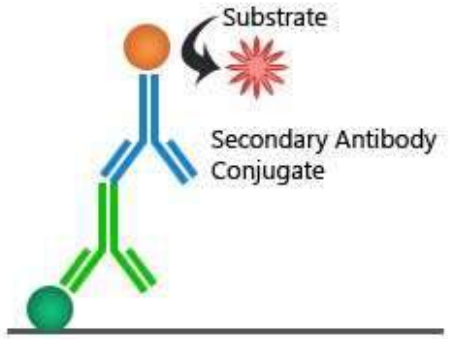

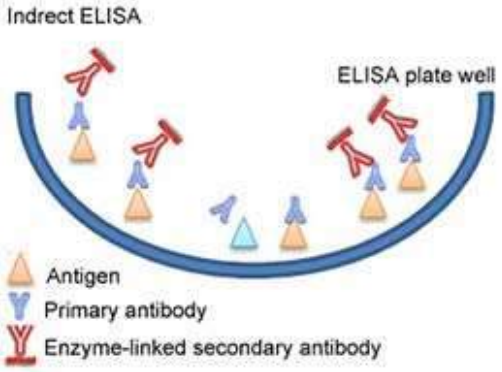

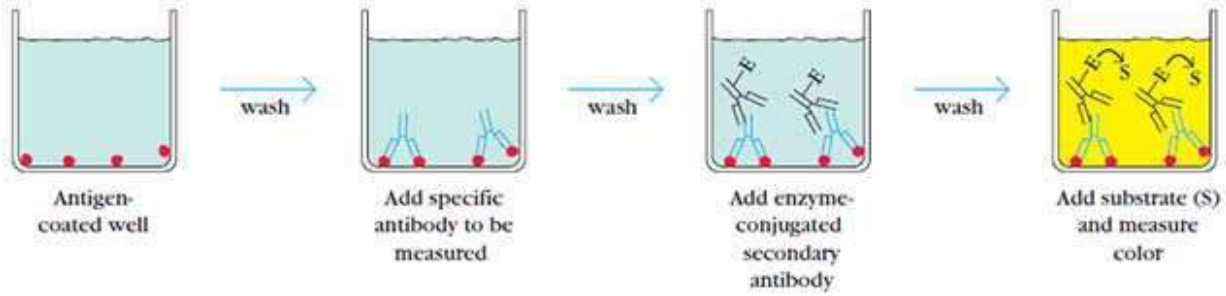

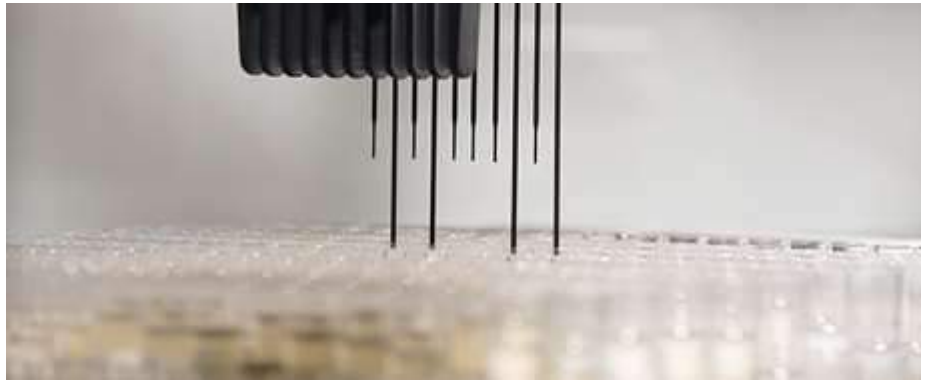

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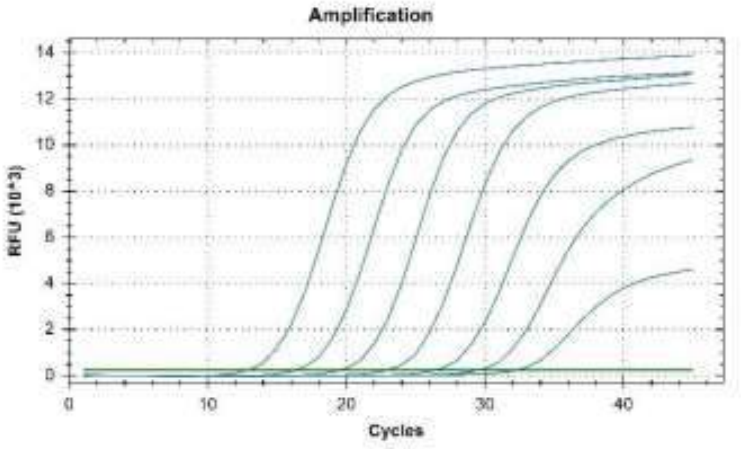
COVID-19 Technologies



Nucleic acid detection (RNA)

- RT-PCR (*Real Time-Polymerase Chain Reaction*)

  Allow the detection and quantification of small quantities of nucleic acids

- NGS (Next Generation Sequencing)

  Allow the detection, quantification and reading of the sequence of small nucleic acid fragment or the whole genome of the virus

NCBI·Reference·Sequence:·NC_045512.2¶

>NC_045512.2·Severe·acute·respiratory·syndrome·coronavirus·2·isolate·Wuhan-Hu-1,·complete·genome¶

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COVID-19 Technologies

Nucleic acid detection (RNA)

- Design
- RNA extraction

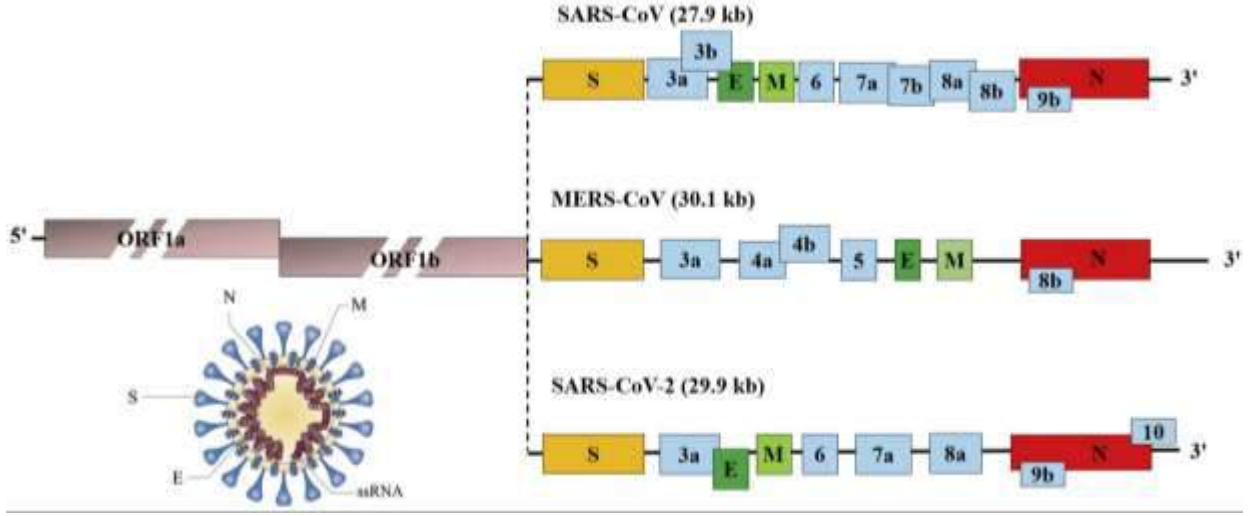
Common procedures to both technologies

Important impact on the sensitivity and specificity of the technologies

COVID-19 Technologies

Nucleic acid detection (RNA)

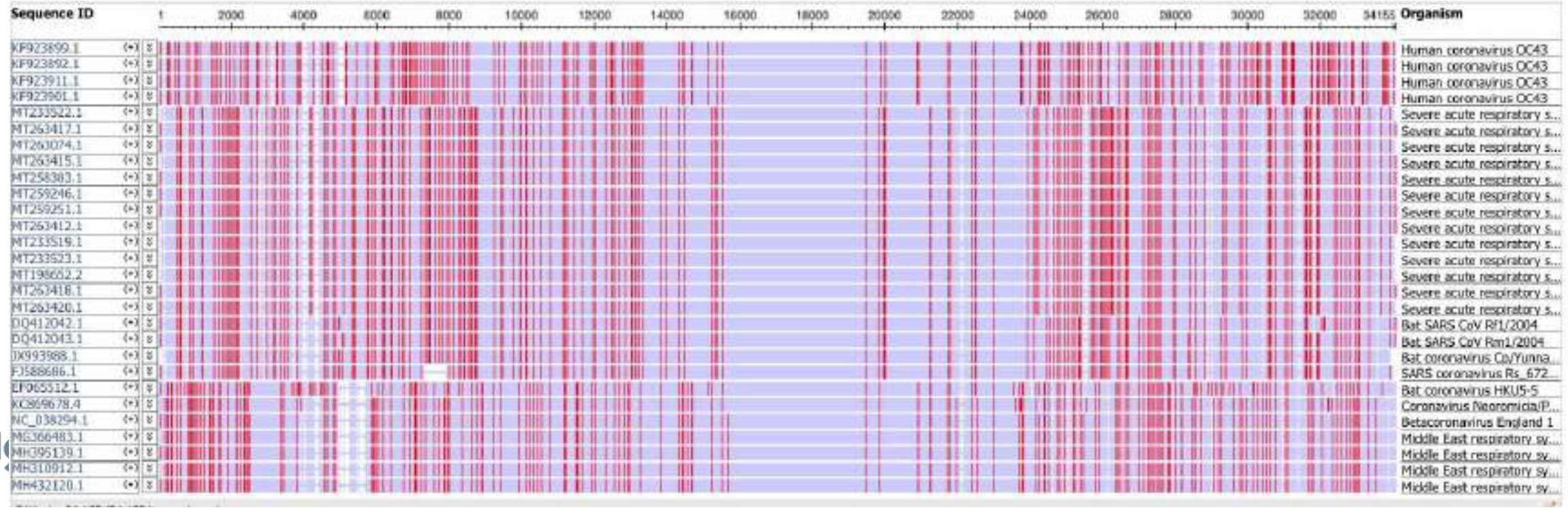
- **Design**



Li et al. *J Pharm Anal* 2020.

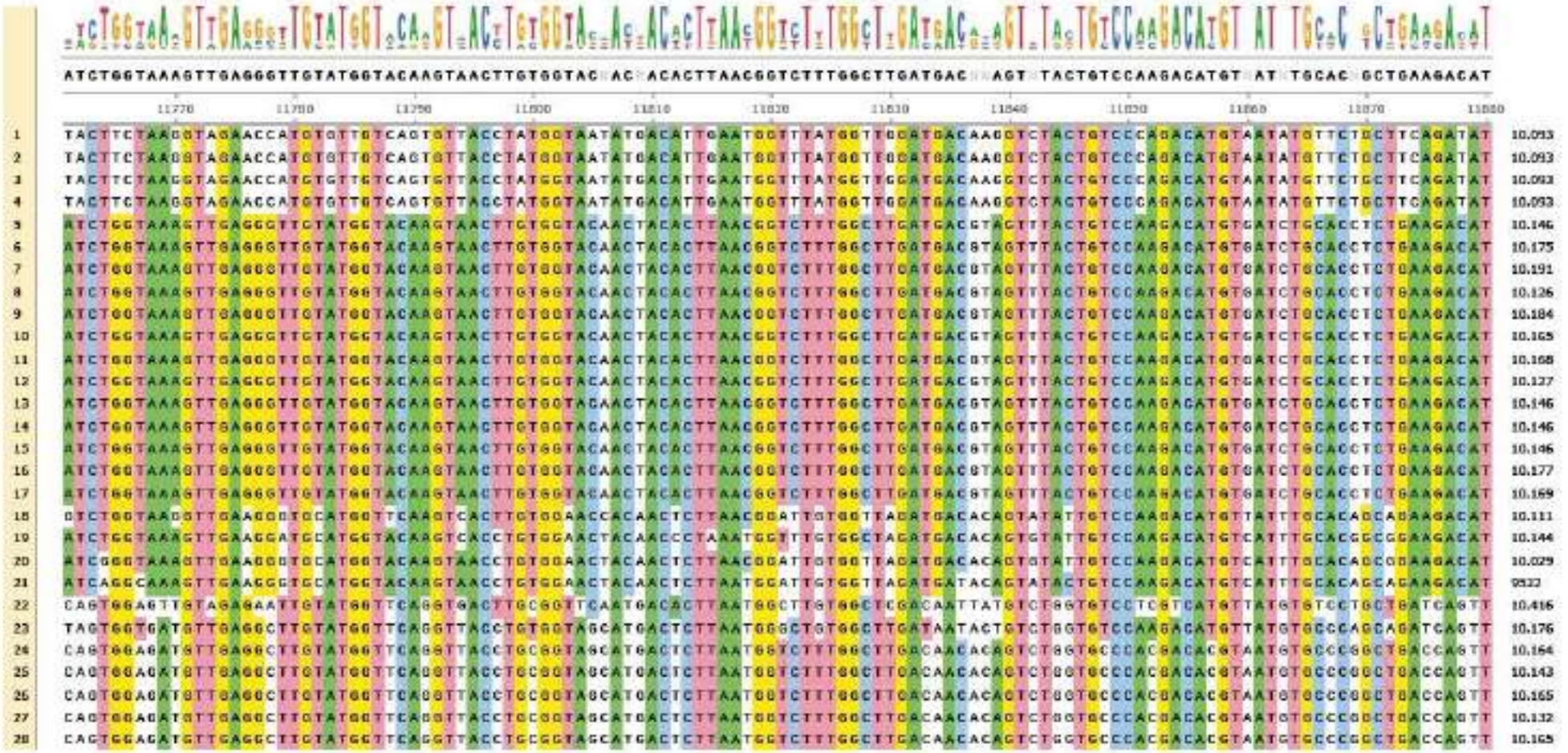
Specificity

There is no interference from other organisms that could be amplified by our primers



COVID-19 Technologies

Nucleic acid detection (RNA)



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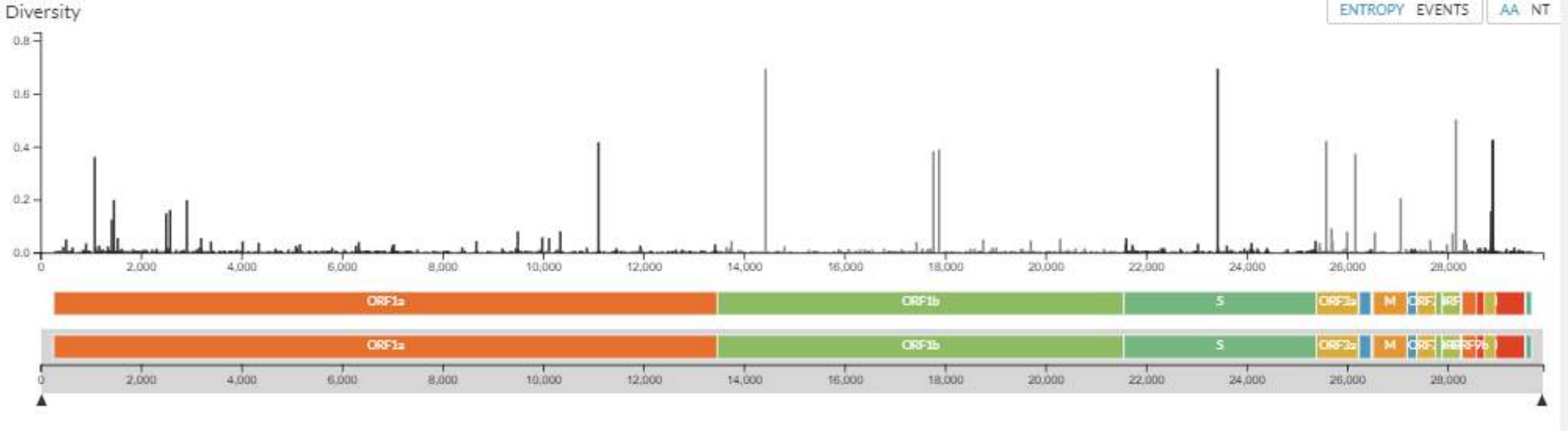
COVID-19 Technologies

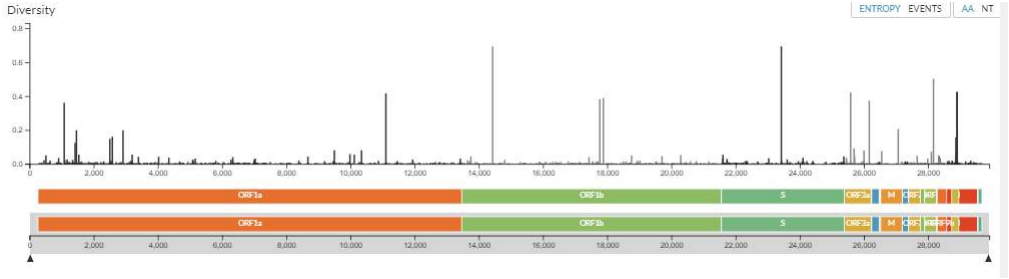
Nucleic acid detection (RNA)

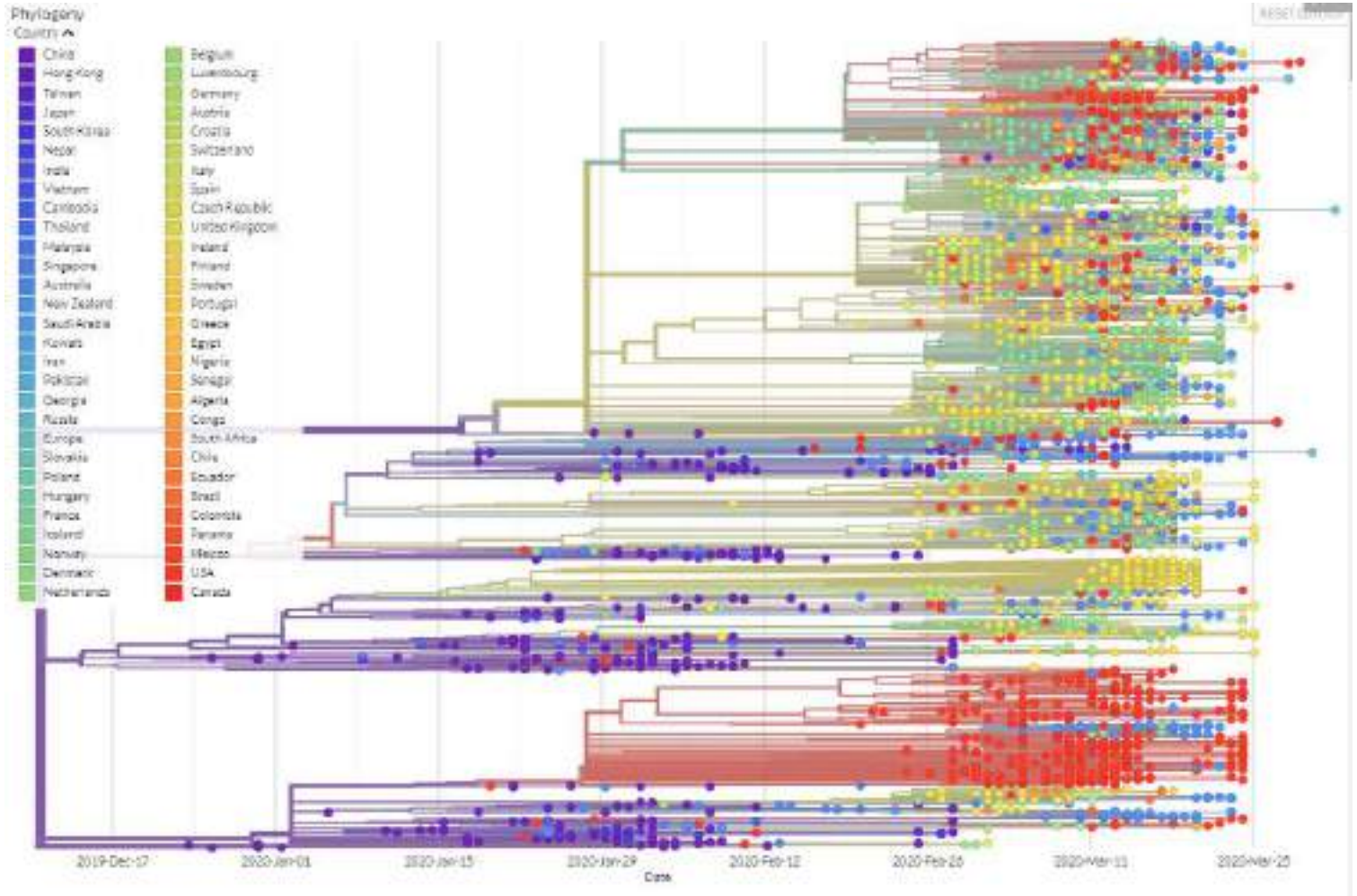
- **Design**
  Comparison of 185 complete SARS-CoV-2 genomes (GISAID database)
  Primer and probes sequences for SARS-CoV-2 ORF1ab, S gene, and N gene assays had 100% homology to all SARS-CoV-2 analyzed, except EPI_ISL_407084
  Sensitivity
  Test detects all known variants of SARS-CoV-2 (except EPI_ISL_407084)



COVID-19 Technologies

Nucleic acid detection (RNA)





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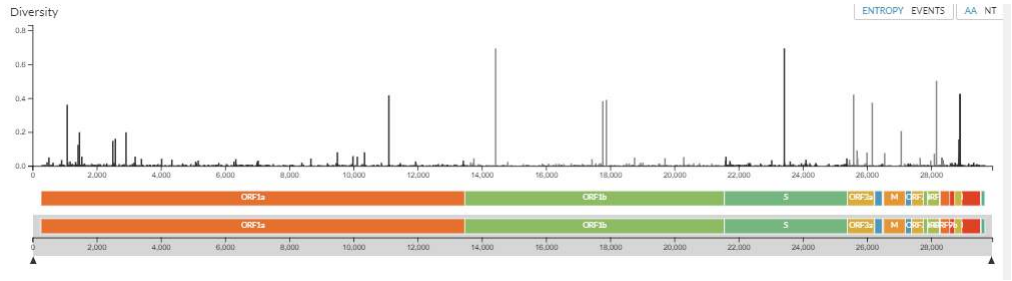
COVID-19 Technologies

Nucleic acid detection (RNA)



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COVID-19 Technologies

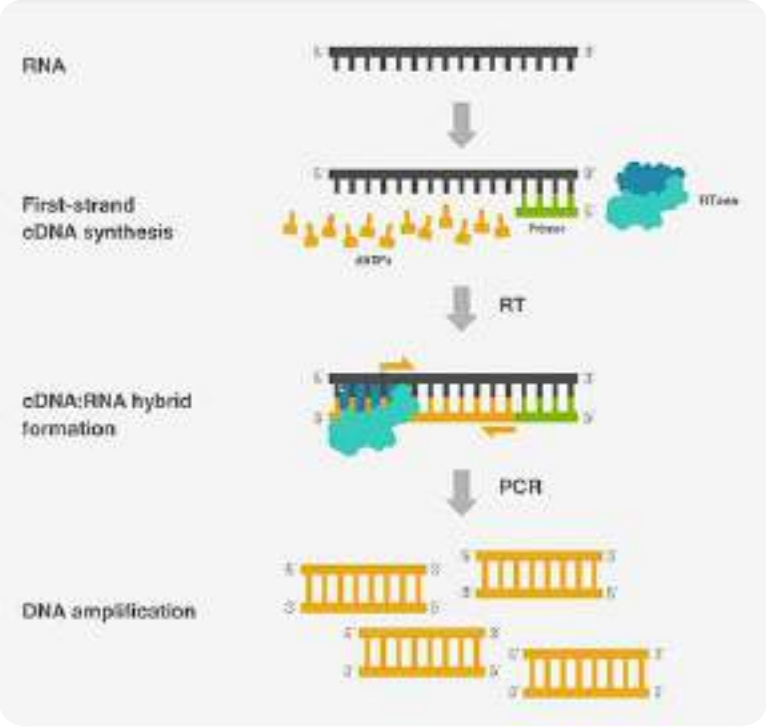
Nucleic acid detection (RNA)

- **Extraction**

  RNA (ribonucleic acid) is a very labile molecule and it degrades very easily

  We can transform single strand RNA (ss RNA) into double strand complementary DNA (ds cDNA) becoming more stable and easier to handle

  Prenalytics and preservation of the quality of sample significantly affects the sensitivity of the technique



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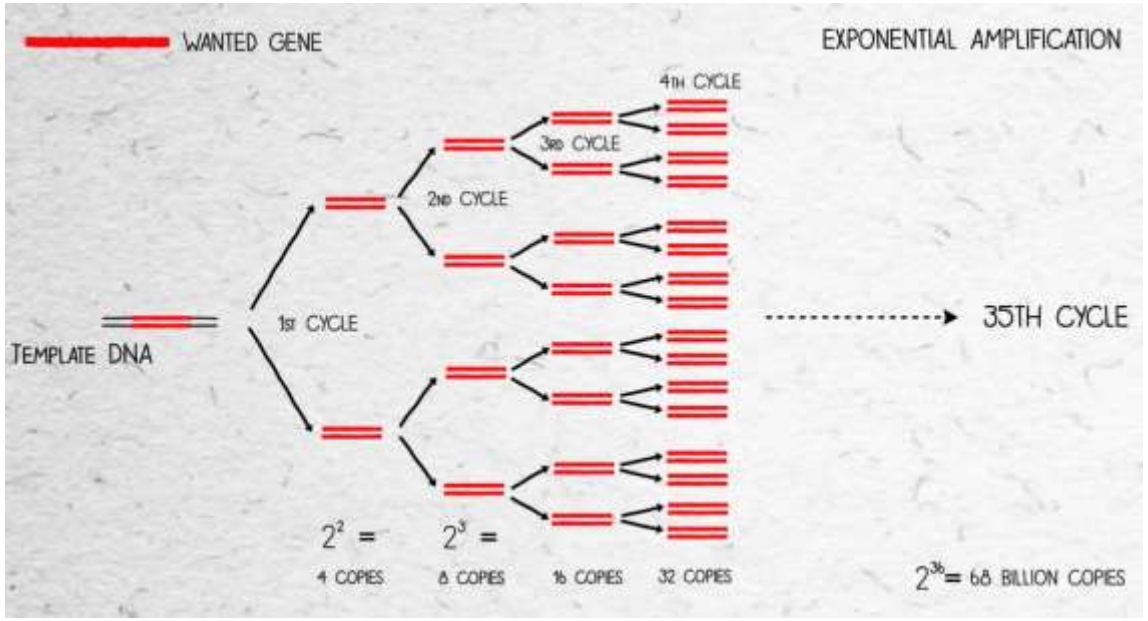
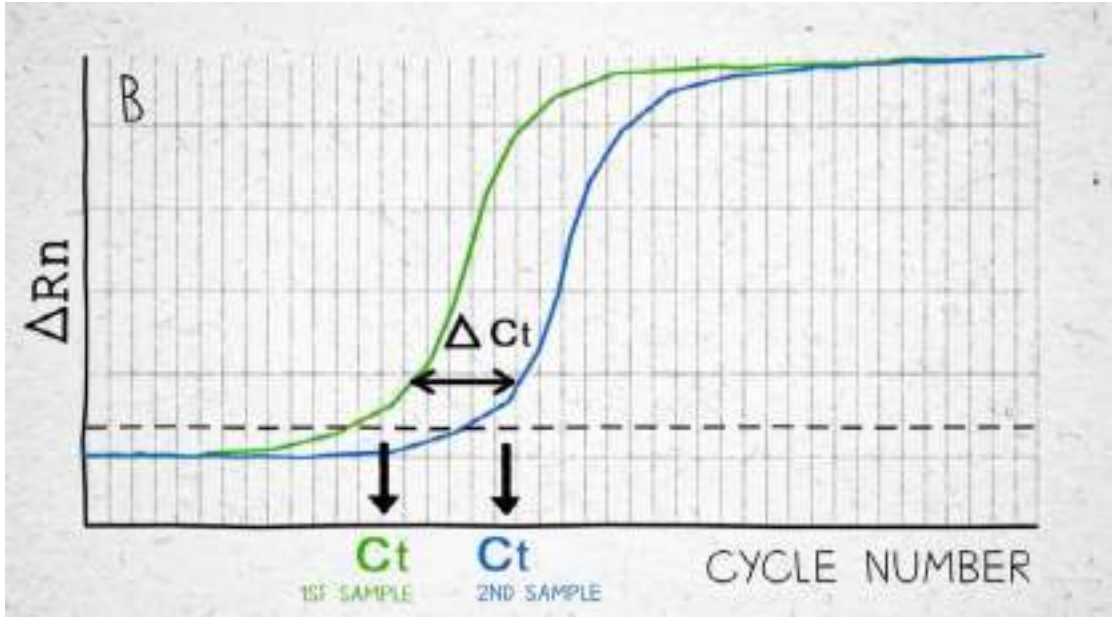
COVID-19 Technologies

Nucleic acid detection (RNA)

- RT-PCR (*Real Time-Polymerase Chain Reaction*)

  Allow the detection and quantification of small quantities of nucleic acids





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COVID-19 Technologies

Nucleic acid detection (RNA)

- RT-PCR (*Real Time-Polymerase Chain Reaction*)

  Allow the detection and quantification of small quantities of nucleic acids

Sample collection	Sample prep	Real-time PCR	Data analysis
Samples collected using BD™ Universal Viral Transport Collection Kits: • Bronchoalveolar lavage • Nasal aspirate • Nasopharyngeal swabs	Thermo Scientific™ KingFisher™ Flex Purification System with Applied Biosystems™ MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit	Applied Biosystems™ QuantStudio™ 5 Real-Time PCR System or Applied Biosystems™ 7500 Real-Time PCR System	Amplification curves generated using Applied Biosystems 7500 or QuantStudio 5 Real-Time PCR System software

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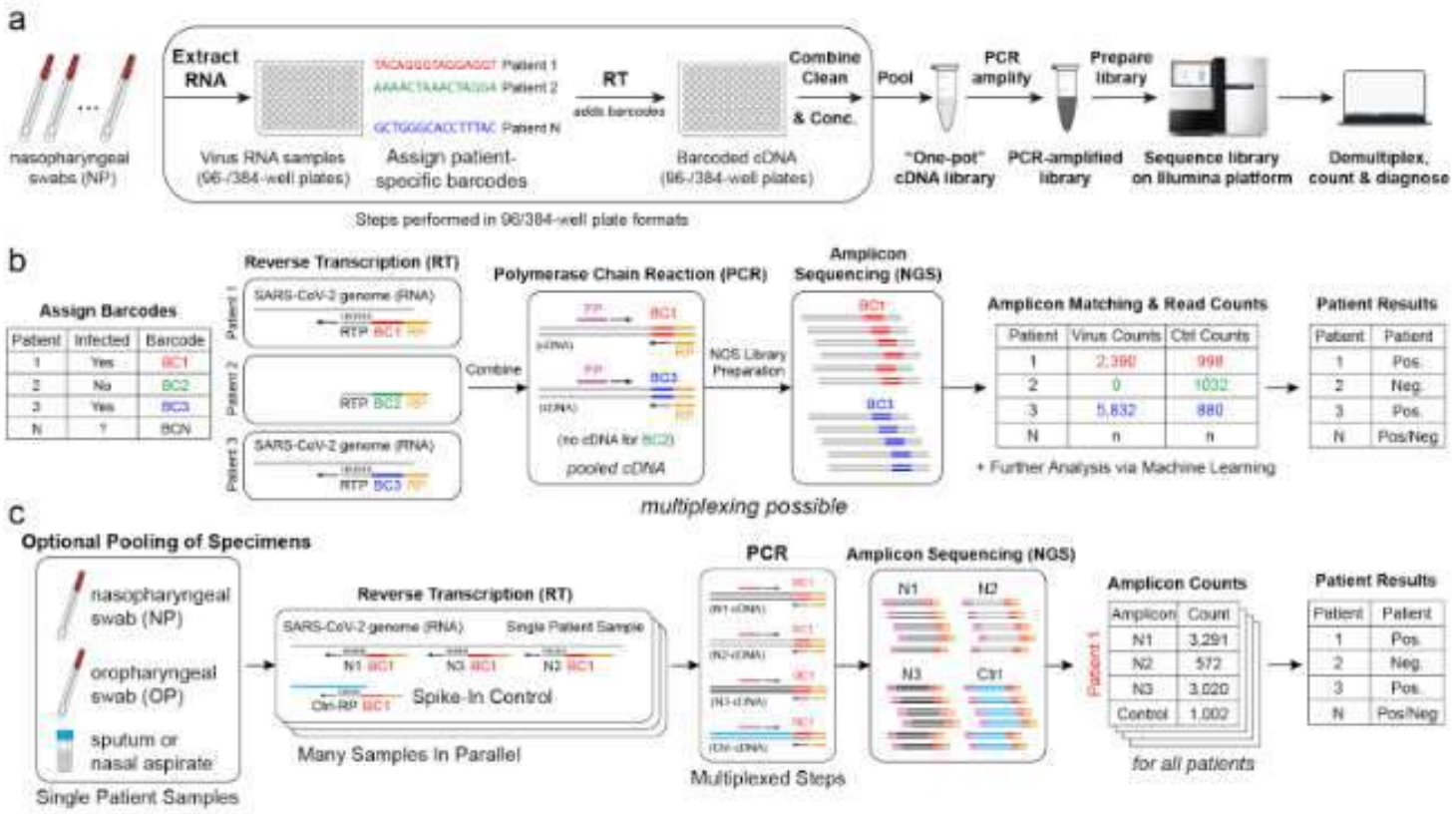
COVID-19 Technologies

Nucleic acid detection (RNA)

- NGS (Next Generation Sequencing)

  Allow the detection, quantification and reading of the sequence of small nucleic acid fragment or the whole genome of the virus



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COVID-19 Technologies

Nucleic acid detection (RNA)

- NGS (Next Generation Sequencing)

  Allow the detection, quantification and reading of the sequence of small nucleic acid fragment or the whole genome of the virus

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COVID-19 Technologies

Validation

All test must be validated before clinical uses

- **Analytic Validity**
  - **Limits of detection (LoD)**

    Limits of detection of the technique must be measured and documented
    LoD is the lower SARS-CoV-2 viral load or Genomic Copy Equivalents (GCE) that can be detected in, at least, 95% samples analyzed
    Our LoD for RT-PCR is 250 copies/ml of nasopharingeal fluid
    10 GCE por reaction
  - **Technology Robustness**

    Technology replicates around the limits of detection
- **Clinical Validity**

  Results correlate in a more than 100 clinical samples

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COVID-19 Technologies

Validation

All test must be validated before clinical uses

- **Clinical Validity**

Table 9 NP Clinical Evaluation Study

Final RNA Concentration in Sample	Number of Positives	Mean Ct S gene	Mean Ct ORF1ab	Mean Ct N gene
2X LoD	20/20[b]	30.9	30.6	29.3
3X LoD	5/5	30.0	30.1	28.8
5X LoD	5/5	28.7	29.0	27.9

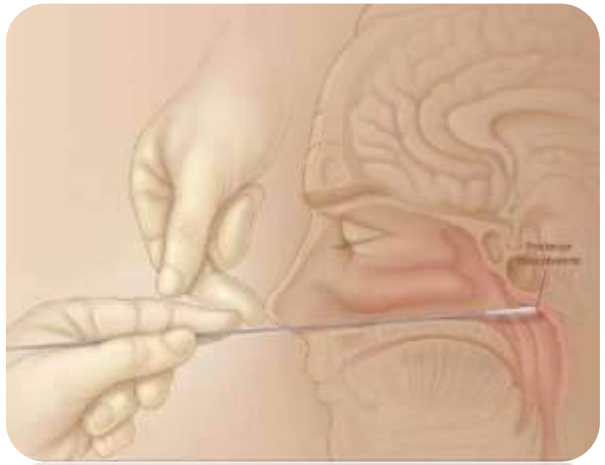
[a] Two samples gave inconclusive results and were not re-tested due to unavailability of the testing material.

[b] One sample initially gave an inconclusive result and was retested. The result was positive after the retest. Mean Cts are calculated including retest result.

Validación del test

- La NY Department of Health concluye que el mejor abordaje se realiza obteniendo la muestra mediante hisopo nasofaríngeo por su capacidad para concentra mayor cantidad del virus.
- En ausencia de nasofaríngeo, la FDA valida la utilización de orofaríngeo+nasal.

+JAMA Published online March 11, 2020



NEW YORK STATE OF OPPORTUNITY. Department of Health

ANDREW M. CUOMO
Governor

HOWARD A. ZUCKER, M.D., J.D.
Commissioner

SALLY DRESLIN, M.S., R.N.
Executive Deputy Commissioner

March 25, 2020

TO: Healthcare Providers, Healthcare Facilities, Clinical Laboratories, and Local Health Departments

FROM: New York State Department of Health (NYSDOH)
Bureau of Communicable Disease Control (BCDC)

HEALTH ADVISORY: NOVEL CORONAVIRUS DISEASE (COVID-19)
UPDATE ON SPECIMEN COLLECTION AND HANDLING
TO INCLUDE NASAL SWAB AND OROPHARYNGEAL SWAB SPECIMEN ALTERNATIVE

SUMMARY

- COVID-19 community transmission has been detected in New York State.
- COVID-19 testing is available at the NYSDOH Wadsworth Center and select clinical laboratories.
- For any suspected COVID-19 cases, ensure appropriate infection control precautions and immediately notify the infection control lead at your facility and the local health department (LHD).
- Review local testing options for those who do not require clinical outpatient/inpatient medical care.

SITUATION UPDATE

- As of March 24, 2020, there have been 48,289 COVID-19 cases with 590 deaths in the United States.
- As of March 24, 2020, New York had 25,665 reported cases of COVID-19 with 14,904 in NYC and 10,1761 in the rest of state with 210 deaths.

COVID-19 SPECIMEN COLLECTION AND HANDLING

- Collect a **nasopharyngeal (NP) swab** for initial diagnostic testing for COVID-19, placed in a vial containing Viral Transport Media (VTM) or Molecular Transport Media (MTM).
  - Oropharyngeal swab and sputum are no longer recommended for initial testing.
  - Sputum or lower respiratory specimens, such as bronchoalveolar lavage (BAL) or tracheal aspirate testing, may be considered, as clinically appropriate, and can be sent to a commercial or clinical laboratory. Collection of sputum should only be done for those patients with a productive cough. Induction of sputum is not recommended.

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When

...must we use them

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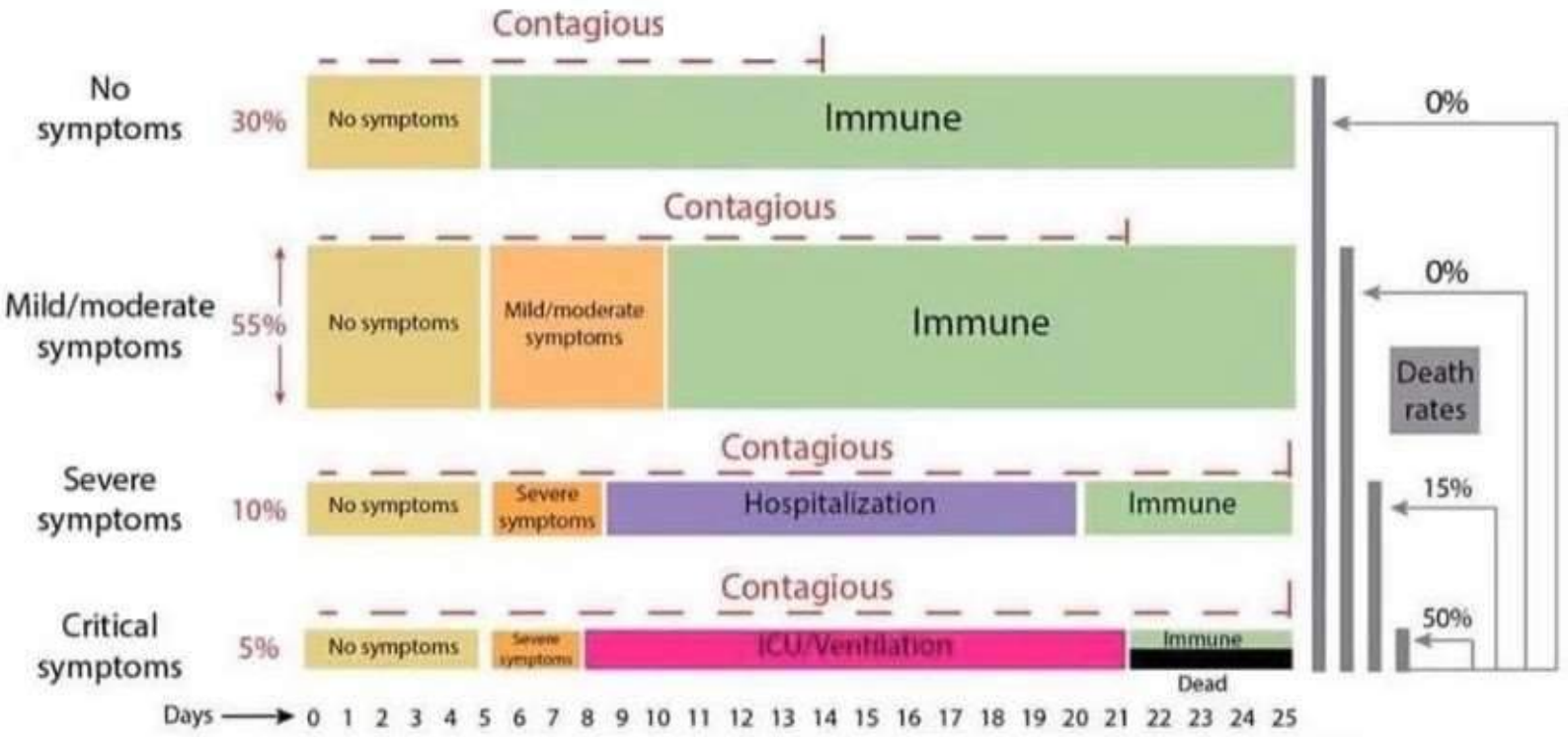
COVID-19 Pathophysiology



References:
1. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Lauer SA et al. Ann Intern Med. 2020 Mar 10.
2. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand. Neil M Ferguson et al. Imperial College COVID-19 Response Team. 16 March 2020.
3. Viral dynamics in mild and severe cases of Covid-19. Yang Liu et al. The Lancet, March 19, 2020.

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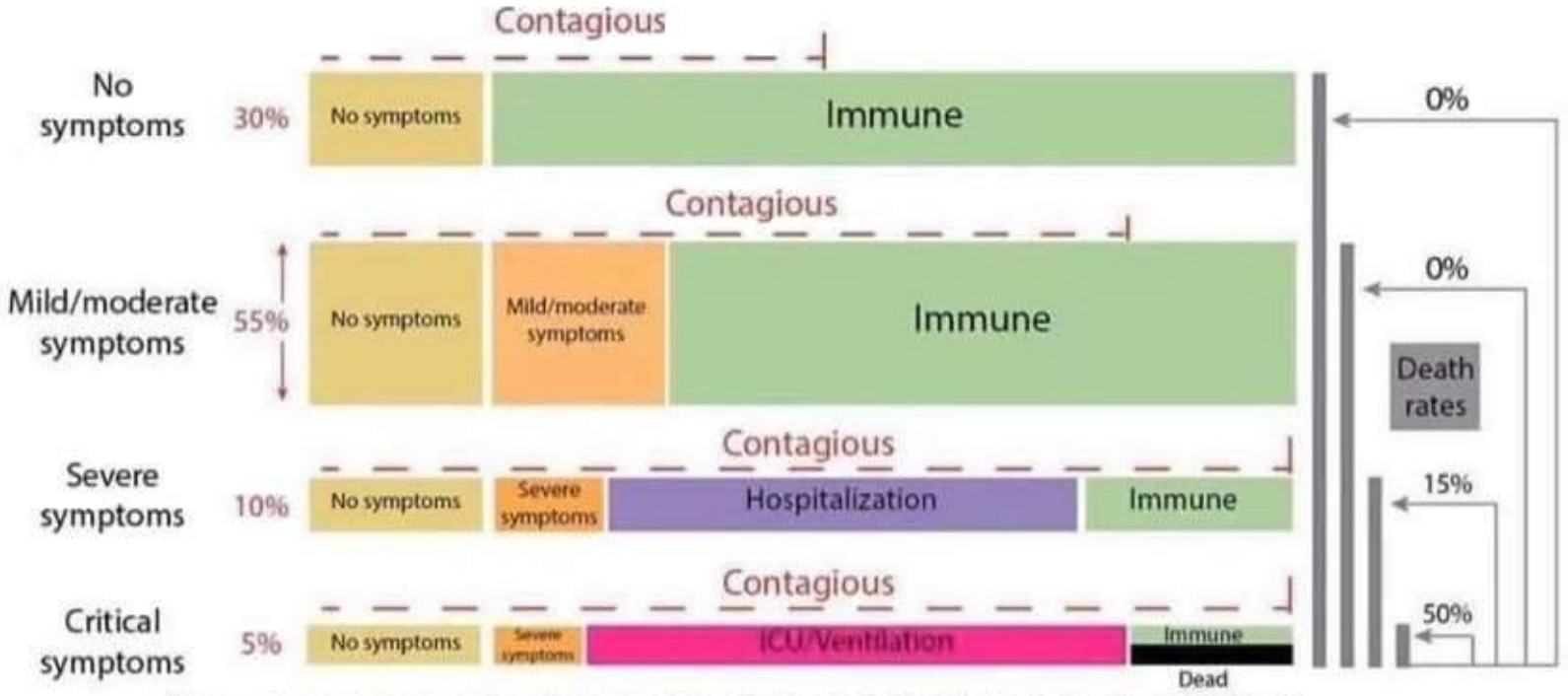
COVID-19 Pathophysiology



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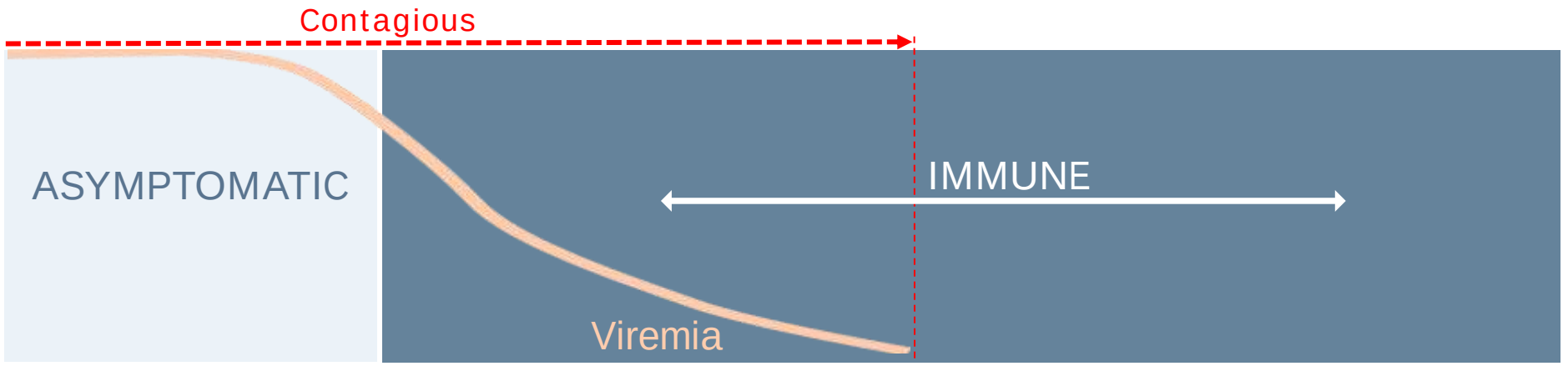
COVID-19 DETECTION

30% of people will be asymptomatic and finnally imune, as long as viremia is present these people will be contagious



RT-PCR	✓ COVID-19 diagnostic test: Gold standard ✓ High sensitivity and specificity
NGS	✓ COVID-19 diagnostic test ✓ High sensitivity and specificity

Immunoglobulines TEST

- ✓ Only detects antibodies after Immune Response
- ✓ One patient can be both infected and immune. And contagious. In this case, RT-PCR will be necessary to confirm or discard

* Ver anexos

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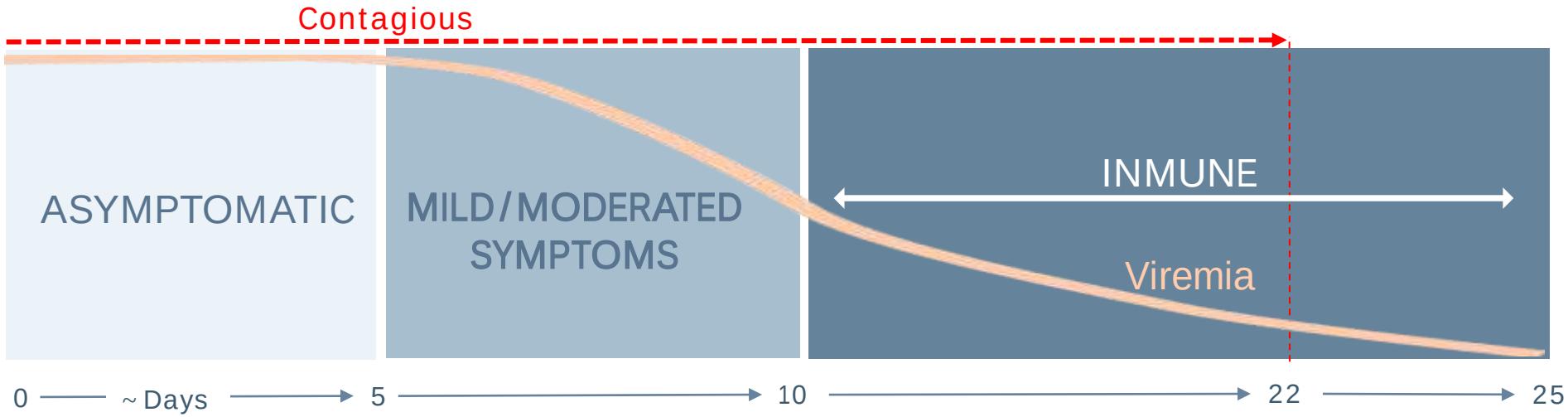
COVID-19 DETECTION

55% of population will develop mild/moderate symptoms. In these cases, a combination of technologies provides the higher fiability and accuracy



RT-PCR

- ✓ COVID-19 diagnostic test: Gold standard
- ✓ High sensitivity and specificity.

NGS

- ✓ COVID-19 diagnostic test
- ✓ High sensitivity and specificity

Immunoglobulines TEST

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* Ver anexos

COVID-19 Technologies

	FASt tests Antigen specific	ELISA IMMUNOGLOBULINES	RT-PCR	NGS
Main indication	Screening **test** **High viral load** **apparent symptoms**	**COVID-19 Late stages** immunization **status**	Diagnostic test **for** **COVID-19 complete stage** Asymptomatic	**COVID-19 complete stage** Asymptomatic
Target	M and N protein Antigens	IgM and IgG Antibodies **immune response**	Virus RNA	Virus RNA
Validation	**Test recientes sin publicaciones científicas**	Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica · seimc	FDA U.S. FOOD & DRUG ADMINISTRATION · Instituto de Salud Carlos III	**In-house validation**
Sample	**Nasopharyngeal and orophanryngeal fluid**	**Blood/serum**	**Nasopharyngeal and orophanryngeal fluid**	**Nasopharyngeal and orophanryngeal fluid**
False Negatives	**HIGH %**	**LOW %**	**LOW %**	**LOW %**
Fiability	**Low/Average**	**High**	**High** **Gold standard**	**High**
Throwput	**Low**	**Medium/high**	**High**	**Medium/High**

Take Home Messages

- Testing is crucial for:
  - A(pre)symptomatic individuals in early stages (tracing and isolation)
  - Accurate diagnostic of patients and monitorization of immunization
- Several types of tests
  - SARS-CoV-2 RNA (its genome) — RT-PCR/NGS
  - Immuno response of the patient (Antibodies and antigens) — ELISA
- Detect different physiological phases of infection
  - SARS-CoV-2 presence RNA (viral load) — RT-PCR/NGS
  - Immuno response and immunization status — ELISA
- Combined use of both approaches should be the standard
- Testing requires
  - Experienced professionals and high expertise in the use of technologies
  - Validation (in house) of technologies
  - Pre-analytical process is crucial

Igenomix® foundation FORWARD THINKING

Lessons and recommendations

...for the day after

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“Our key message is: **test, test, test**”

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WHO head: 'Our key message is: test, test, test'

World Health Organisation head Tedros Adhanom Ghebreyesus says there has not been an urgent enough escalation in testing, isolation and contact tracing, which should be the "backbone" of the global response.

He said it is not possible to "fight a fire blindfolded", and social distancing measures and handwashing will not alone extinguish the epidemic.

16 Mar 2020

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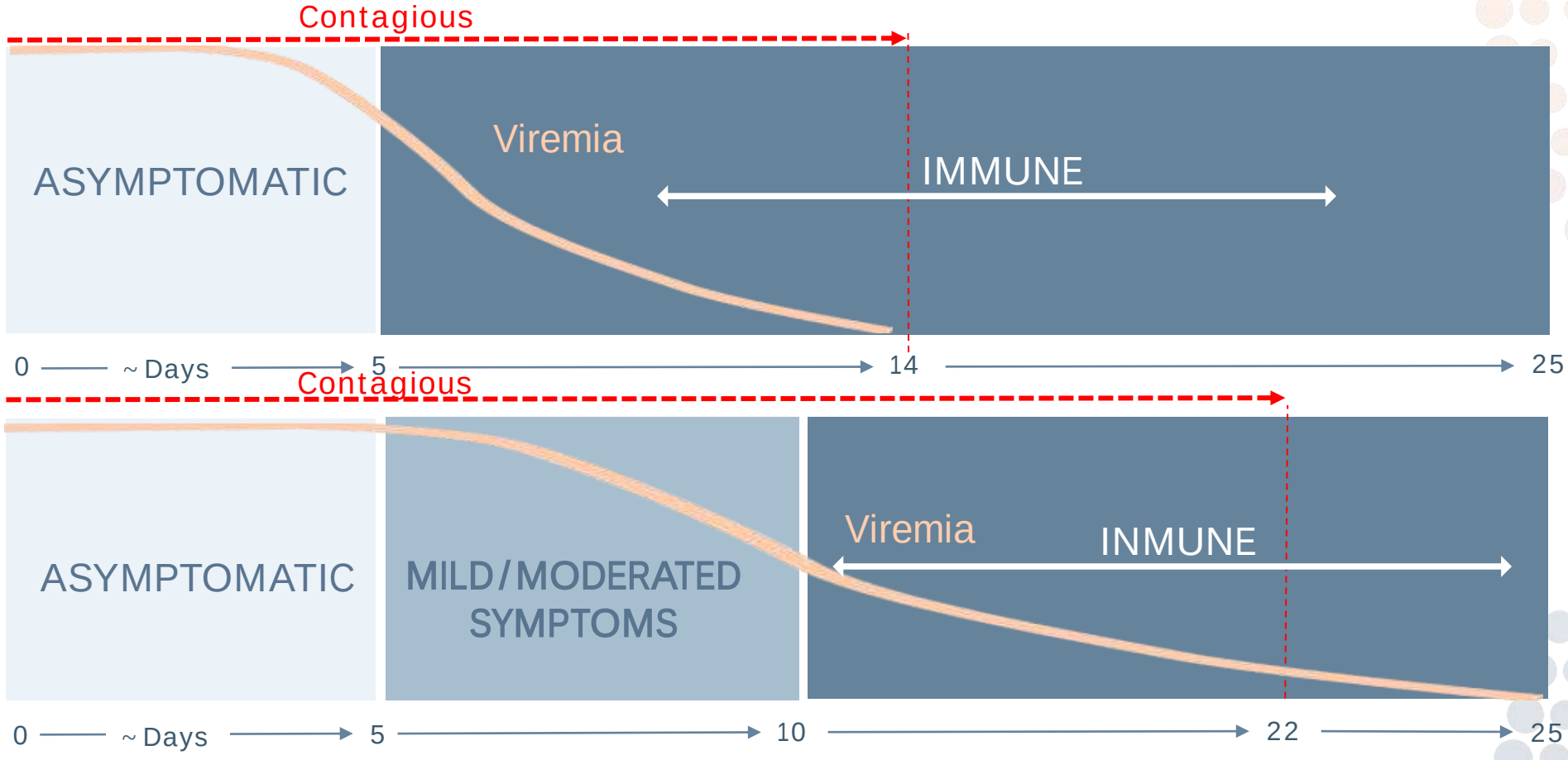
COVID-FREE Clinics and Facilities



RT-PCR

- ✓ COVID-19 diagnostic test: Gold standard
- ✓ High sensitivity and specificity.

Igenomix® foundation FORWARD THINKING

Immunoglobulines TEST

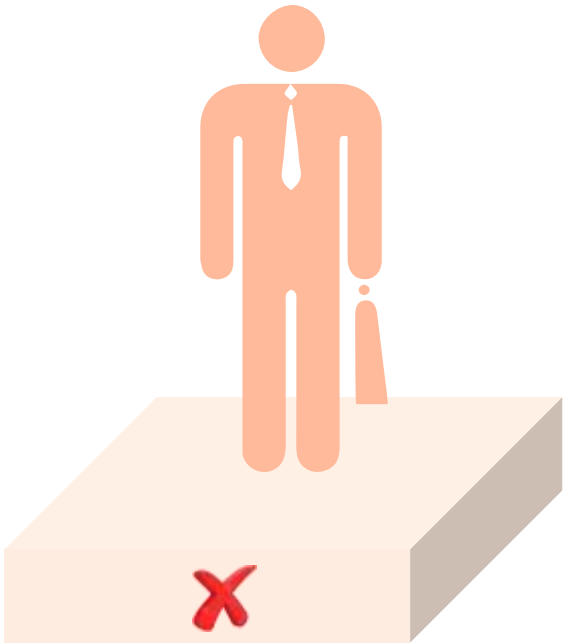
- ✓ Only detects antibodies after Immune Response
- ✓ One patient can be both infected and immune.

COVID-FREE Clinics and Facilities

Three main groups of asymptomatics:

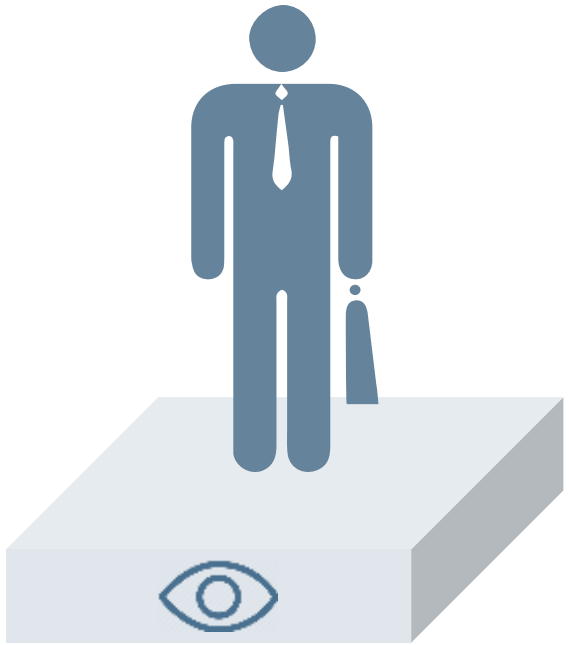
INFECTED

PCR positive



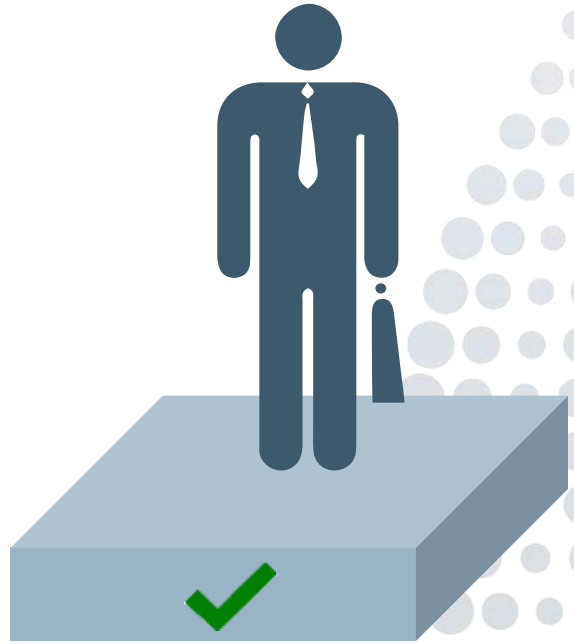
AT RISK

PCR negative
+
Antibody negative



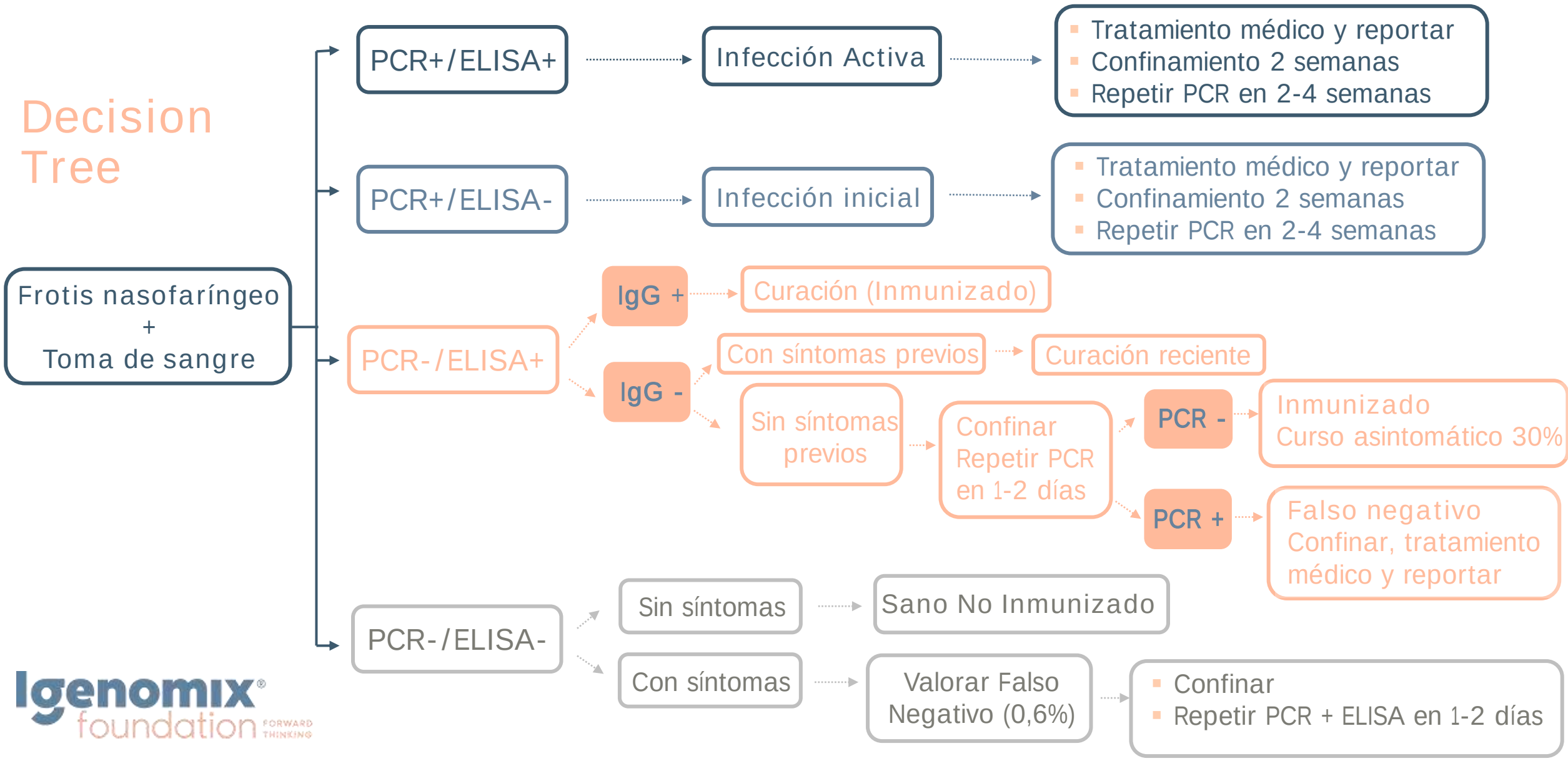
APT - IMMUNIZED

PCR negative
+
Antibody positive



COVID-FREE Clinics and Facilities

Decision Tree



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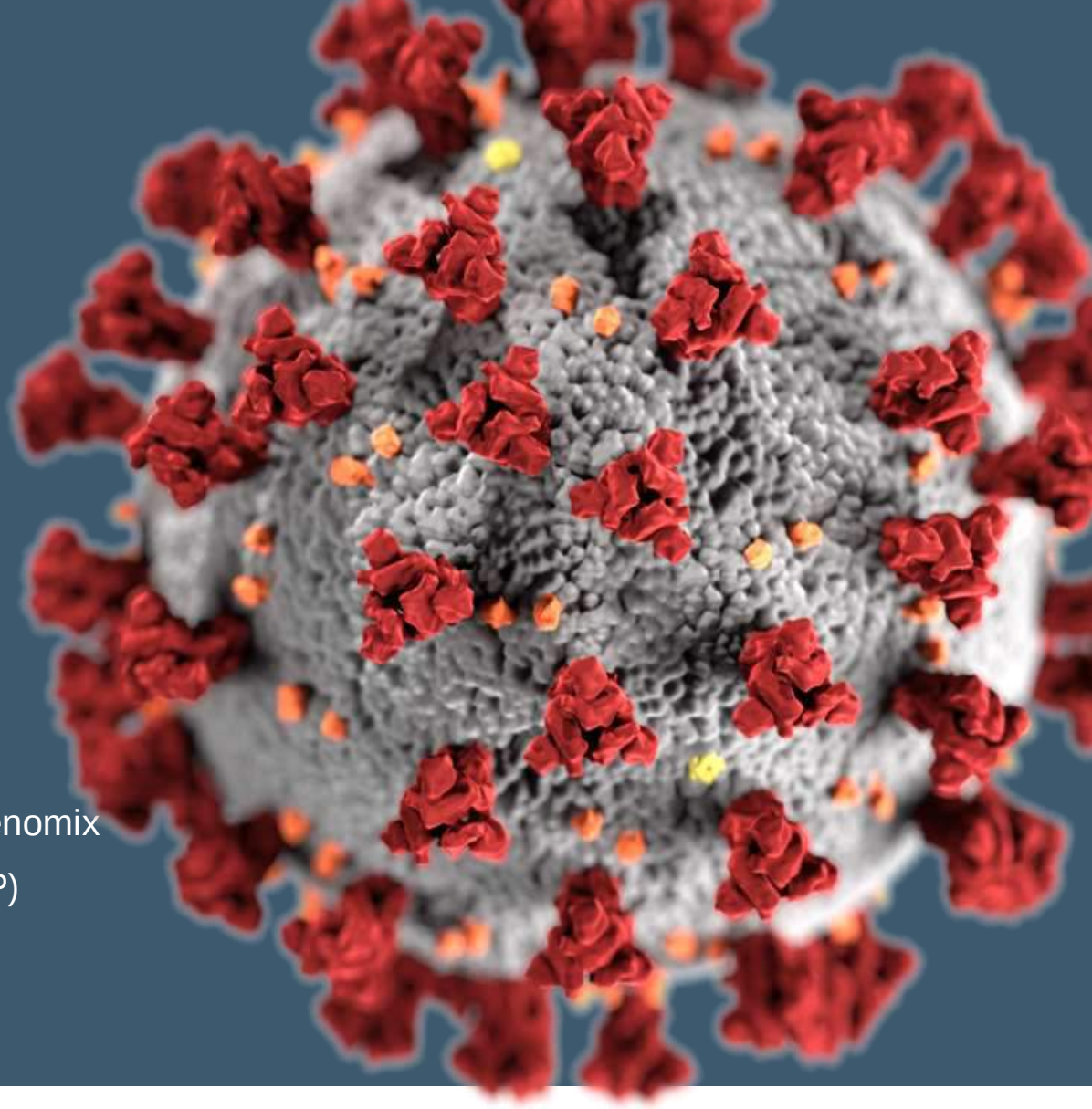
Técnicas para detectar COVID-19:

Cuáles, cómo y cuándo



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Clinical Development & Scientific Advisor Rare Diseases Director, Igenomix

Presidente de la Asociación Española de Diagnóstico Prenatal (AEDP)

European Molecular Genetics Quality Network (EMQN) Assessor

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¡¡Gracias por la atención!!

COVID-FREE CLINICS

El empleado visita la web y el contenido educativo

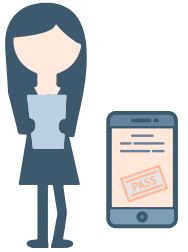
El servicio médico de la compañía firma el TRF y el empleado el consentimiento informado

Frotis nasofaríngeo + toma de sangre en punto de extracción o servicio médico de la empresa

Realización test en el laboratorio de Igenomix

Envío del informe del test**

Dashboard con datos agregados a nivel de compañía



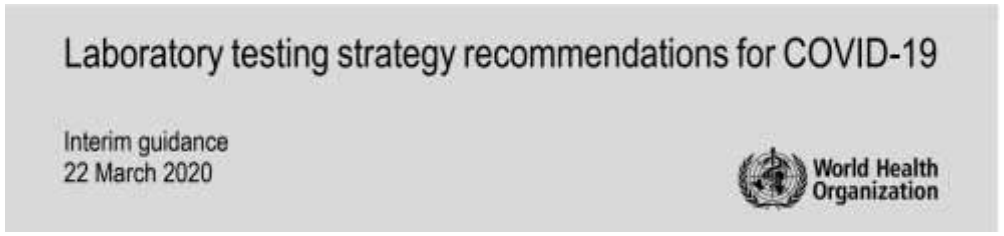
Envío al empleado de un "pasaporte digital"

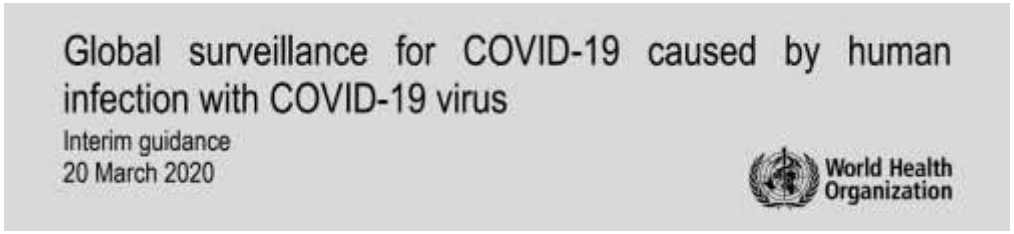
1 → 2 → 3 → 4 → 5 → 6 → 7

(**) En caso de PCR positivo y de acuerdo a regulación actual, Igenomix deberá notificar el resultado a las autoridades sanitarias.

Igenomix®

WHO testing recommendations





- All countries should increase their level of preparedness, alert, and response to identify, manage, and care for new cases of COVID-19; laboratory testing is an integral part of this strategy.
- Any persons meeting the criteria for testing should be tested for COVID-19 infection using available molecular tests.

Countries that have not yet reported cases
Countries dealing with sporadic cases
Considerations for countries dealing with clusters of cases

WHO recommends that all suspect cases be tested for COVID-19

Countries dealing with community transmission

Laboratories will need to be prepared for the significant increase in the number of specimens that need to be tested for COVID-19. Testing constraints should be anticipated, and prioritization will be required.

https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov)
https://apps.who.int/iris/bitstream/handle/10665/331509/WHO-COVID-19-lab_testing-2020.1-eng.pdf

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Coronavirus Covid-19: ESHRE Statement on Pregnancy and Conception: March 14th, 2020

"There is no strong evidence of any negative effects of Covid-19 infection on pregnancies, especially those at early stages, as indicated by the latest updates from the Centers for Disease Control and Prevention (CDC) in the USA and others in Europe."

PATIENT'S MANAGEMENT

As a precautionary measure - and in line with the position of other scientific societies in reproductive medicine - we advise that:

1. **All fertility patients** considering or planning treatment, **even if they do not meet the diagnostic criteria for Covid-19 infection**, should avoid becoming pregnant at this time.

2. For those **patients already having treatment**, we suggest considering deferred pregnancy with oocyte or embryo freezing for later embryo transfer.

3. **Patients who are pregnant or** those (men and women) **planning or undergoing fertility treatment** should avoid travel to known areas of infection and contact with potentially infected individuals.

https://www.cdc.gov/coronavirus/2019-ncov/prepare/pregnancy-breastfeeding.html?CDC_AA_refVal=https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/pregnancy-faq.html
https://www.rcog.org.uk/globalassets/documents/guidelines/coronavirus-covid-19-infection-in-pregnancy-v2-20-03-13.pdf

Igenomix foundation

ASRM Patient Management and Clinical Recommendations during the Coronavirus (COVID-19) Pandemic: March 17th, 2020

"*Given the information we do have, while it would be wise for individuals with confirmed or presumed COVID-19 infection to avoid pregnancy, there appears to be no cause for alarm for those already pregnant.*"

PATIENT'S MANAGEMENT

1. **Suspend initiation of new treatment cycles**, including ovulation induction, intrauterine inseminations (IUIs), in vitro fertilization (IVF) including retrievals and frozen embryo transfers, as well as non-urgent gamete cryopreservation.

2. Strongly consider **cancellation of all embryo transfers** whether fresh or frozen.

3. Continue to care for patients who are currently "in-cycle" or who require urgent stimulation and cryopreservation.

4. Suspend elective surgeries and non-urgent diagnostic procedures.

5. Minimize in-person interactions and increase utilization of telehealth.

6. **Patients with active COVID-19 should not undergo fertility treatment**, unless they require urgent fertility preservation.

https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covidtaskforce.pdf

Reactions to the ASRM Patient Management and Clinical Recommendations

FERTILITY PROVIDERS ALLIANCE

The Fertility Providers Alliance (FPA) that represents over **400 fertility specialists**, requested ASRM to revisit and reshape it's recommendations to the reproductive endocrinology community, based in 3 reasons:

1. The actual public health burden created by the continuation of fertility care

The vast majority of fertility centers across USA are free-standing medical facilities that operate without hospital affiliation.

2. The classification of infertility treatment as 'non-urgent' or elective

The reproductive health community has fought diligently to recognize infertility for what it is: a disease state that includes many diverse medical conditions.

3. The harmful consequences of an indeterminate delay in access to care

For these patients, "revisiting guidelines periodically as the pandemic evolves" creates an anguishing and indeterminate state of reproductive limbo.

Source: FPA Communicate

Validación del test

✓ EVALUACIÓN CLÍNICA

- El test de Igenomix ha sido validado en nuestras instalaciones siguiendo las recomendaciones oficiales de los organismos oficiales y la FDA.

- Comprueba que distintas concentraciones de límite de detección más grandes, siempre detectan el 100% de los casos:

Tabla 9 NP Estudio de evaluación clínica

RNA Final- Concentración por muestra	Nº de positivos	Ct Promedio gen S	Ct Promedio gen ORF1ab	Ct Promedio gen N
2XLoD	20/20b	30,9	30,6	29,3
3XLoD	5/5b	30	30,1	28,8
5XLoD	5/5	28,7	29	27,9

a Dos de las muestras dieron resultados no concluyentes y no fueron reanalizadas debido a la no viabilidad de la r
b Una de las muestras dio inicialmente un resultado no concluyente y fue reanalizada. El resultado fue positivo tras el reanálisis. Los Cts promedio se han calculado inluyendo los resultados del reanálisis

Take Home Messages

- Testing is crucial for:
  - A(pre)symptomatic individuals in early stages (tracing and isolation)
  - Accurate diagnostic of patients and monitorization of immunization
- Several types of tests
  - SARS-CoV-2 RNA (its genome) — RT-PCR/NGS
  - Immuno response of the patient (Antibodies and antigens) — ELISA
- Detect different physiological phases of infection
  - SARS-CoV-2 presence RNA (viral load) — RT-PCR/NGS
  - Immuno response and immunization status — ELISA
- Combined use of both approaches should be the standard
- Testing requires
  - Experienced professionals and high expertise in the use of technologies
  - Validation (in house) of technologies
  - Pre-analytical process is crucial

Igenomix® foundation FORWARD THINKING