INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

June 2021

Sports & Lifestyle
Online Training,
The New Trend

Comic Corner
Quit, don't quit?
Sweeteners, NO sweeteners?

Science Corner

Review of Current COVID-19 Diagnostics and Opportunities for Further Development (a paper summary)

NATIONAL INSTITUTE OF HEALTH RESEARCH AND DEVELOPMENT
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2021

INA-RESPOND newsletter

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FEATURES

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Newsletter

TRIPOD & PROACTIVE Study Updates

By: Eka Windari R., Lois E. Bang, Melinda Setiyaningrum, Retna Mustika Indah, Riza Danu Dewantara

STUDY UPDATES

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Per 6 May 2021, all the participants in the TRIPOD study have a study completed from 490 enrolled participants. Two hundred and fifty-four participants have completed the study, while 236 participants are terminated early (including death). From the uploaded CRFs, all participants from sites 520, 550, 560, 570, 580, 590, and 600 have completed the study.

The Source Document Worksheet upload from sites 520, 550, 560, 570, 580, 590, and 600 has been completed.

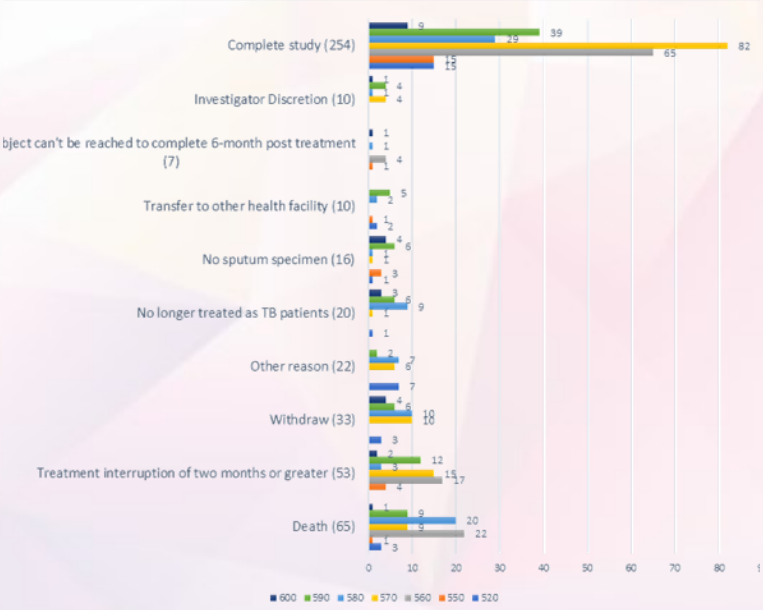
The database Quality assurance (except for TB Treatment pages) has been conducted for sites 520, 550, 560, 570, and 590. The Quality assurance of critical values for site 550 was conducted on 28-29 Apr 2021, and the quality assurance for subject random was conducted on 30 April - 23 May 2021.

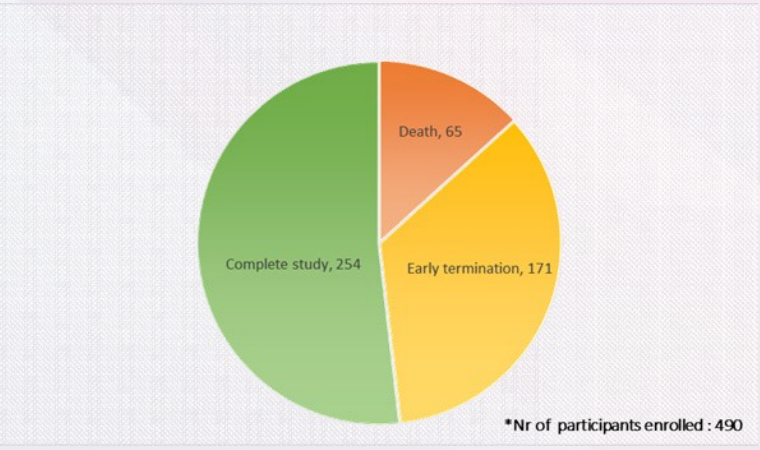
The Site Close-out Visit (SCV) has been conducted for site 520 on 30 November – 1 December 2020, site 570 on 15-16 December 2020, site 590 on 19-20 January 2021, and site 560 on 20-21 April 2021. All Site Close-out Visit (SCV) action items from sites 520, 570, 590, and 560 have already been resolved. The upcoming SCV will be conducted at site 550 on 22-23 June 2021, site 600 on 21-22 July 2021, and site 580 on 24-25 August 2021. All essential documents, CRF, SDW, and laboratory test results for all sites are available in the EDMS. In addition, the study documents from these sites will be archived in the IndoArsip for long-term archival at least five years after the study is closed.

The INA-RESPOND secretariat has announced an official letter and a final report on site closure to the hospital director and the local ethics commission. For sites 520, 570, 590, they were reported on 14-Apr 2021, and site 560's were reported on 18-May 2021. This procedure will be done for sites 550, 600, and 580 as soon as the SCV is completed at each site.

The TRIPOD isolate was sent to Central Laboratory in Padjajaran University Bandung on 12 April 2021 for subculture. The subculture will be prepared for several tests regarding TB, including TB strain examinations which is one of the TRIPOD secondary objectives.

Per protocol, there are 8 types of specimens collected on TRIPOD study for future used. Status for Repository specimens is provided in figure 4.





Site	Site Closed Out Visit	Current Status/Awaiting Items
520	Done,	Study documents has been sent to Indo Arsip
550 (n=25)	Planned, 22-23 June 2021	QA process has done, File Review has sent on 3 June 2021 by CRSS and Specimen Management Review by CRA
560 (n=108)	Done, 20-21 April 2021	Study documents has been sent to Indo Arsip DST result for 1 subject
570	Done,	Study documents has been sent to Indo Arsip
580 (n=83)	Planned, 24-25 Augusts 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA
590	Done,	Study documents has been sent to Indo Arsip
600 (n=25)	Planned, 21-22 July 2021	SCV preparation but not limited to QA Process by DM, File Review by CRSS and Specimen Management Review by CRA

Site	Specimen Type	Whole blood (EDTA) - DNA	Whole blood (Heparin) - PBMCs	Whole blood (Heparin) – Plasma	Whole blood (PAXgene) - RNA	Urine	Saliva	Sputum	MTB Isolate
520 (n=32)	BL (32)	90	22	91	27	125	62	19	36
	M1 (24)	NA	18	64	21	99	NA	16	12
	M2 (24)	NA	22	68	24	93	NA	11	0
	EOT (15)	NA	28	45	15	60	30	2	0
560 (n=108)	BL (108)	382	204	328	102	440	216	131	272
	M1 (95)	NA	188	285	94	381	NA	107	60
	M2 (87)	NA	172	261	86	348	NA	91	20
	EOT (73)	NA	142	219	73	292	146	75	19
570 (n=128)	BL (128)	438	177	380	121	519	254	119	192
	M1 (104)	NA	162	311	103	416	NA	43	92
	M2 (97)	NA	162	294	98	392	NA	22	38
	EOT (80)	NA	162	243	81	320	160	4	12
580 (n=83)	BL (83)	235	130	210	67	308	147	26	42
	M1 (44)	NA	70	102	38	156	NA	18	6
	M2 (38)	NA	54	81	36	148	NA	16	0
	EOT (29)	NA	50	71	27	124	61	8	0
590 (n=89)	BL (89)	340	170	255	84	344	147	78	55
	M1 (59)	NA	98	147	49	196	NA	17	8
	M2 (56)	NA	80	120	41	164	NA	8	0
	EOT (40)	NA	46	72	24	96	46	9	0
600 (n=25)	BL (25)	100	50	75	25	100	50	50	30
	M1 (13)	NA	26	39	13	52	NA	26	4
	M2 (11)	NA	22	33	11	44	NA	22	4
	EOT (9)	NA	20	30	10	40	20	20	0
550 (n=25)	BL (25)	95	48	72	24	100	51	10	27
	M1 (20)	NA	36	54	19	68	NA	7	7
	M2 (20)	NA	36	54	17	72	NA	6	4
	EOT (15)	NA	26	39	13	52	25	0	2

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Study follow up still ongoing at all Sites. Along with that, with respect to the subject's mobility, subject is given the flexibility to do follow-up visits at another Study Site if they move to the city that has a PROACTIVE Site. The study Team and Secretariat will process the transfer based on subject request and their approval through subject visit tracking card (*Kartu Pelacakan Kunjungan*). The principal investigator of the Transfer Site will complete the subject transfer form, and Secretariat will notify the Arrival Site. After that, the Data Manager will move the subject data assignment in Open Clinica from the Transfer Site to the Arrival Site. When the subject arrived at the Arrival Site, they will need to be reconsented as their agreement to continue the study at the new Site. As of 31 May 2021, from total 4,335 subject enrolled, 53 subjects have undergone Site transfer. Nevertheless, 12 subjects are not yet reconsented at the new Site because they usually visit the new Site along with their next follow-up visit. Therefore, it is very important for the study team of the Transfer Site and Arrival Site to close follow up this transfer subject before they arrive and reconsent at the new Site to maintain the subject retention.

Onsite monitoring visit was conducted to Site 690 Abepura Hospital on 8-10 June 2021, and it's also planned for Site 680 Soedarso Hospital on 22-24 June 2021.

No	**Site# / Name**	**Participants Transfer In**	**Participants Transfer Out**
1	510 – Hasan Sadikin	3	3
2	520 – Sanglah	3	2
3	530 – Cipto M.	7	3
4	540 – Sulianti Saroso	0	1
5	550 – Wahidin	1	0
6	560 – Kariadi	3	2
7	570 – Soetomo	4	4
8	580 – Sardjito	4	3
9	590 – Persahabatan	2	2
10	600 – Adam Malik	5	5
11	610 – Tangerang	1	1
12	630 – Ansari Saleh	1	7
13	640 – St. Carolus	9	3
14	650 – Budi Kemuliaan	3	5
15	660 – AW Sjahranie	2	6
16	670 – Zainoel Abidin	0	3
17	680 – Soedarso	2	0
18	690 – Abepura	2	2
19	700 – TC Hilers	1	1
	Total	53	53

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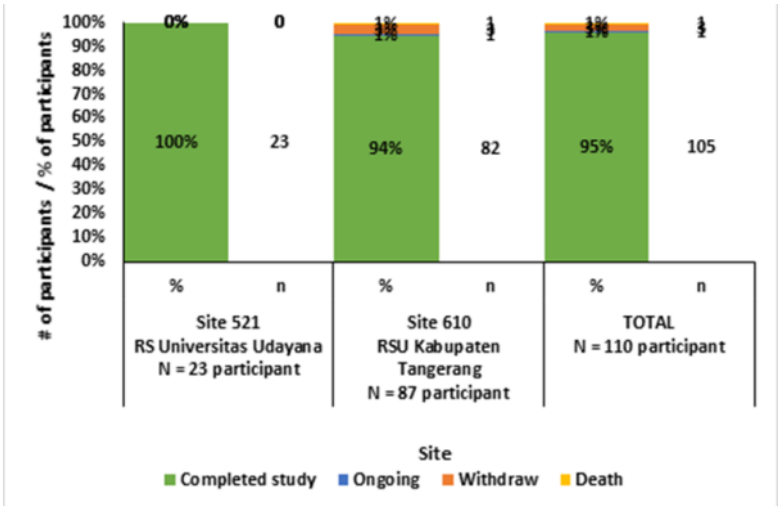
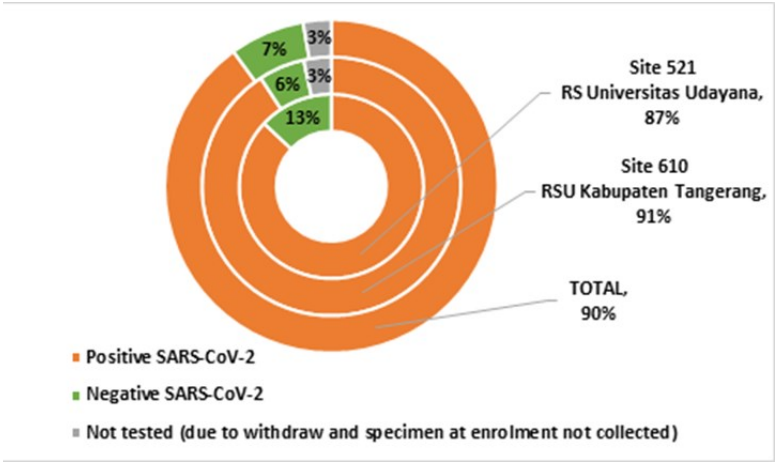
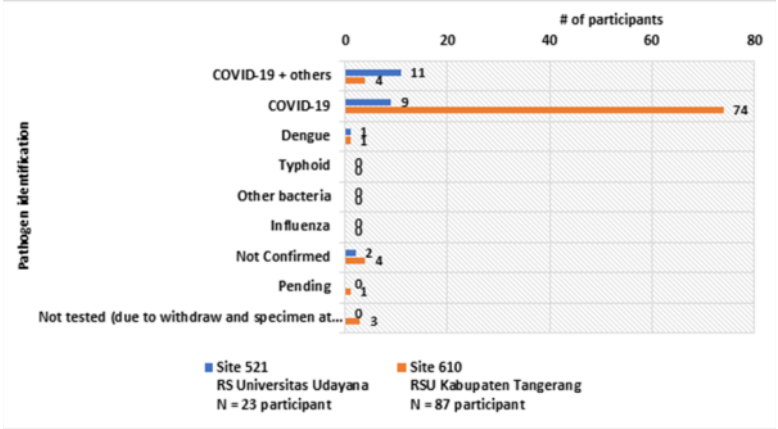
Based on uploaded CRFs as of 10 June 2021, 110 participants were enrolled in the ORCHID study, which consisted of 87 participants from site 610 (RSU Kabupaten Tangerang, Tangerang) and 23 participants from site 521 (RS Universitas Udayana, Denpasar). There were 105 participants (95%) who already completed this study, 1 participant passed away during the study, 1 participant still ongoing with the study, and 3 participants withdraw (figure 1).



Up to 10 June 2021, 99 participants (90%) were identified as positive SARS-CoV-2, 8 participants as negative SARS-CoV-2, and 3 participants not tested due to withdrawal. In site 610, the number of participants identified as positive SARS-CoV-2 was 79 participants (91%), 5 participants as negative SARS-CoV-2, and 3 participants not tested due to withdrawal. Meanwhile, in site 521, there were 20 participants (87%) identified as positive SARS-CoV-2 and 3 participants as negative SARS-CoV-2 (figure 2).



Based on pathogen identification data, at site 521, 11 participants (48%) pathogen were identified as COVID-19 with others and 9 participants (39%) as COVID-19 only. Meanwhile at site 610, 74 participants (85%) pathogen were identified as COVID-19 only, 4 participants (5%) as COVID-19 with others. Only one participant was identified as single Dengue infection at both sites. One participant was still pending due to waiting for other lab test results. Lab examination cannot be performed in 3 withdrawn participants (figure 3).



Considering the number of COVID-19 cases has exceeded 100 subjects, recalculation of sample size and/or changing laboratory examination plan towards COVID-19 are being discussed with NIAID. While waiting for the continuation of ethical clearance from NIHRD IRB, the Secretariat and NIAID team agreed to slow down enrolment until further study plan is finalized. In the meantime, UI Hospital preparation as the third site was stopped due to slow progress. The site was still at the stage of completing site assessment visit report. It was estimated that at least two more months is needed to complete the process. Several action items, such as site agreement, hospital permit, and site training were required for site opening. Hence, the Secretariat decided to discontinue study preparation and site's further participation to other studies will be confirmed later.

INA-RESPOND Newsletter

FLASHBACK MOMENT : COVID19 MASK FOR MAUMERE

By: INA104—Site 700 Team

Picture 1. The Mask Team for Sikka in the INARESPOND room at RSUD dr. TC Hillers Maumere (dr. Andre M.H as RA1 (two from left) and dr. Sandy

"One real deed, no matter how small, means more than a thousand beautiful words." Maybe that was the beginning of our long discussion in the small room of INA-RESPOND site 700 in this unfortunate situation. PI, co-PI, and two RA along with research documents and coffee flasks are the first reminders of that time.

We have been grappling with a pandemic for more than a year. All aspects of our lives, health, economic, social fields are suffocating. Teaching and learning activities, communication with relatives, and even the work environment must be forced to be several miles apart. The series of discordant voices blaming each other between elements are also added to the commotion. The question is always in tune, "when will this pandemic end and life will return to normal?"

This disaster started in March 2020, or maybe someone put the starting line earlier in December 2019. One by one, countries fell; they locked down and closed their borders. Protocols were born to contain the spread of the infections: keep your distance, wear your protection, postpone your gatherings. The infections started from the island of Java and spread to all corners. Big cities fell victim one by one, and what about the fate of this small town?

Concerned by the limited infrastructure, IDI Sikka initiated a movement of its own. With the motto 'IDI Sikka Peduli,' the Sikka doctor association started community empowerment to meet the needs of personal protective equipment for COVID19 to prevent the spread of the virus in the community.

IDI Sikka chaired by dr. Mario B. Nara, Sp.A (also the co-PI of

INA104 at site700) empowers local communities to meet the needs of cloth masks for the Sikka community. "Killing two birds with one stone, people can also get income while meeting the needs of masks in the pandemic era," said dr. Asep Purnama, Sp.PD, FINASIM, the initiator and main motor of the IDI Sikka Peduli movement, also the PI of INA104 at site700.

The 'Masks for Sikka' began with collecting donations used to purchase materials, sewing, and distribution costs. Mask materials are then given to local people who have received sewing training. The amateur tailors receive a fee as wages for sewing the masks they produce. Then the cloth masks enter the packaging process which is carried out by the doctors in the INA-RESPOND room. These doctors also carried out the distribution process to each village. The farthest distance the team has ever traveled is four hours away (without traffic jams and still in one district).

Distribution of cloth masks to all regions, education, seminars, presentations of COVID-19, and how to deal with COVID-19 were done/given via radio, YouTube videos, newspapers, and limited meetings; they became a routine agenda for seven months. We also produced a jingle song, 'Let's Wear a Mask,' that opened all activity events. Two INA-RESPOND research assistants were part of the fast-moving team every day in this series of activities from the start.

Ninety-seven million rupiahs were collected, seventeen local tailors were empowered, and thirty-five thousand eight hundred cloth masks were distributed. For five months IDI Sikka and the INA-RESPOND team carried out fund-raising, fund management, empowerment, and remuneration of tailors, recording the production of mask distribution, and going into the field for every activity.

The movement has held twenty-three educational seminars, visited twenty-one sub-districts, met one hundred and forty village representatives and journalist associations in Sikka district. One high school and a church community also invited us as COVID-19 educators. Nine radio broadcasts, seven YouTube videos, and local newspaper reports also contribute to the reverberation of the movement to all levels.

Starting from an idea in March and bearing fruit until August 2020. News of COVID19, which was originally only in Java, has now spread to the villages of the city of Maumere. The village heads discuss health protocol, and almost all Sikka people now have at least one cloth mask. The pandemic has not stopped, but this movement may give us the means to survive.

From top to bottom:

dr. Mario B. Nara, Sp.A as chairman of IDI Sikka is giving cloth masks to representatives of sub-districts in Sikka

dr. Asep Purnama, Sp.PD, FINASIM is giving a presentation and education in one of the sub-districts

Banner of IDI Sikka Peduli Movement' Masks for Sikka' installed at Alok Market, Sikka Regency, Flores, NT

INA-RESPOND Newsletter

IMPORTANCE, OUTCOMES, AND CHALLENGES OF MD/PHD TRAINING IN THE UNITED STATES

By: Kyle Landers

Over the past 100 years, discoveries in biomedical research have significantly decreased mortality rates throughout the world. Such triumphs include the discovery of antibiotics, chemotherapeutics, and precision medicine techniques—all of which were only possible due to physicians and scientists tirelessly pursuing their observations in the hospital and the lab. These monumental discoveries have led to the development of several biological fields, requiring both more scientists and physicians to explore and answer necessary questions of our biological world to improve human health. Unfortunately, this exponential expansion has generated a significant gap in implementing discoveries from "the bench to the bedside." To address this increasing concern, academic biomedical research institutions and the National Institute of Health established funding mechanisms and a formal education pathway in the mid-1960s to develop cross-trained physician-scientists1.

Physician-scientists are rigorously trained in both realms of science and medicine, with the goal of "bridging the gap" between benchtop research and clinical application. This middle ground between worlds has been coined "translational research." At the end of their time in these formal training pathways, trainees will obtain both a full PhD and a full medical degree (in the US this can be an MD or DO). As of 2021, there are 125 MD/PhD and 5 DO/PhD programs in the United States, with approximately 10,500 alumni2,3,4. In total, the physician scientist workforce composes no more than 2% of all practicing physicians in the US.

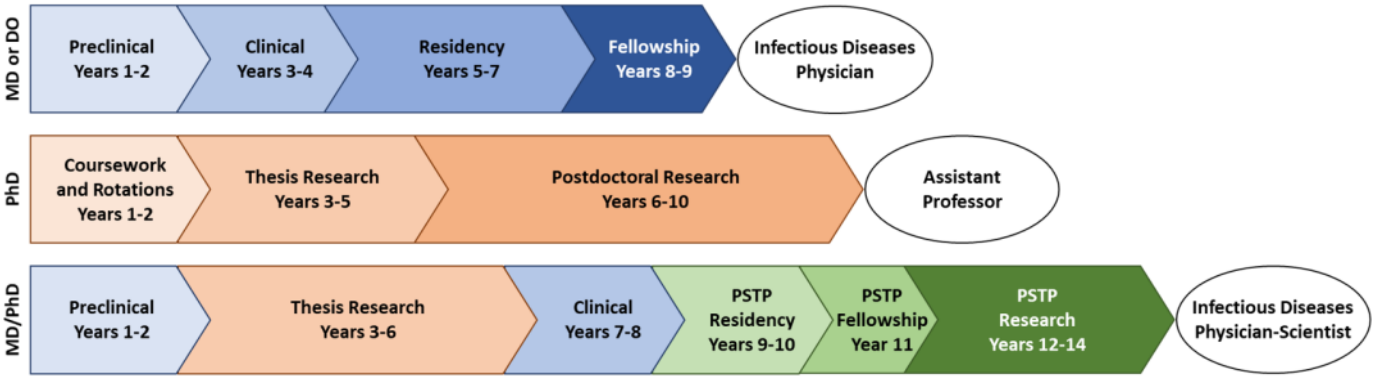
To better understand this unique training pathway, we can compare MD/PhD training programs to separate MD/DO and PhD training programs, as well as examine the opportunities each provide in the United States. All three pathways are post-graduate training programs, so a four-year university undergraduate degree is necessary first. The current medical education for MD and DO programs is four years, with the standard curriculum being split into two distinct sections: preclinical years and clinical years. The preclinical years compose the first two years of a future physician's training and focus heavily on basic science and textbook material. After these two years, medical students enter the clinical years, where time is spent in teaching hospitals and clinics to hone their communication skills and apply the material learned during the first two years. This education pathway is extremely structured and encompasses a broad knowledge base, which differs from biomedical PhD training, which can vary widely in length between 4-7 years6. Moreover, biomedical PhD training focuses on a specific topic and hones the candidate's scientific reasoning and hypothesis generating skills. Though medical training and doctoral training are very distinct, both have been integrated in medical scientist training programs (MSTP).

MSTPs, of which there are 50, are accredited programs supported by the National Institute of General Medical Sciences (NIGMS). The most common structure utilized by these MD/PhD and DO/PhD programs is a 2-4-2 format, where approximately four years of PhD training is placed in-between the preclinical and clinical years of medical training. To further integrate and bridge the bench and bedside, candidates will commonly conduct research during the summer breaks of their first two years of medical training, and they will continue obtaining clinical experience during their doctoral research years. Programs may also require the PhD research and thesis to include how the research can be applied in the clinic and may require a physician on the research committee, further weaving and strengthening science and medicine.

Once a candidate has completed an MD/DO, PhD, or MD/PhD training pathway, further specialization and/or experience is needed before reaching the typical goalds of practicing medicine independently, conducting research independently, or a mixture of both, respectively. The specialization training for physicians is termed "residency" and can vary in length depending on the field (i.e. three years for internal medicine and seven years for neurosurgery). After some residencies, further specialization is necessary in the form of a "fellowship," which can add an additional one to three years of training7. Individuals completing a PhD

Kyle Landers, future physician-scientist

Kyle has spent the past year working with CCRB. He will leave NIAID at the end of May to enter the highly competitive Medical Scientist Training Program at the University of Alabama at Birmingham, where he will study to earn MD and PhD degrees to pursue a clinical research career in immunology and infectious diseases.



Typical timelines for U.S. MD/DO, PhD, and MD/PhD training programs.

program have several career options including industry, government, and academia. For those pursuing an academic tenure-track faculty position in biomedical research, one or more post-doctoral fellowships are required, which average 4.5 years per fellowship8. Unfortunately, a post-doc of any length does not guarantee a tenure position, and more experience or specialized training may be required. MD/PhD graduates can follow either a traditional residency program, a post-doctoral fellowship, or a Physician Scientist Training Program (PSTP). Similar to MSTPs, a PSTP incorporates a residency, fellowship, and post-doctoral training into one seamless program. This provide physician scientists with protected lab time during the clinical training years that potentially increases their chances of academic faculty positions. Of the 20 recognized residency specialties in the US, 15 specialties offer this training format9. It is important to note that PSTPs are also opportunities for MD/DO trainees to enter and develop biomedical research skills despite not having a PhD degree.

Once formal training is complete, most physician scientists stay in academia to conduct independent translational research. Results from a 2018 survey showed that 80% of all MD/PhD alumni continued to conduct research, and nearly two-thirds were independently funded10. This is unsurprising given their extensive training and ability to cut across clinical, basic, and translational research. In comparison to physicians and PhD scientists, MD/PhD alumni also had higher rates of obtaining competitive research grants. This is significant given that NIH funding has been stagnant for nearly twenty years despite the supply of PhD scientists continuing to increase, making funding sparse and highly competitive10. The increase in funding translates to MD/PhD graduates being three times more likely to obtain a faculty position compared to PhD-only graduates1. Additionally, the physician-scientist's training provides them with perspectives that a physician may not think of in the clinic or a scientist in the lab, allowing them to translate observations and discoveries more efficiently and fluidly between both fields. In the case of scientists, taking discoveries in the lab and applying them in the clinic requires collaboration with a physician. It is also possible that a physician may notice an interesting observation in the clinic but not be able to properly construct a hypothesis or experiment that can be tested in the lab, which requires expensive equipment and time that is already dedicated to patient care.

Though Physician Scientists have more options and are extensively trained, there are challenges in successfully bridging the gap between the bench and bedside. The most prominent challenge is the time commitments to patient care and bench research. The standard division of time is described as 80/20— 80% of time in the lab and 20% in the clinic. However, the time split between clinic and lab varies drastically and is dependent on the institution, specialty, and individual. In some academic hospitals, there may be pressure on physician-scientists to spend more time in the clinic since this is more financially beneficial to the institution. In this case, physician-scientists are at a detriment to their PhD-only counterparts, as they cannot make the necessary discoveries in the lab to renew competitive grant funding11. This critical situation leads to the greatest number of physician-scientists abandoning research due to no other funding mechanisms being in place to aid them in establishing a research lab12. This challenge is recognized, as several publications claim that this paradigm will need to shift if more physician-scientists are to be retained in biomedical research in the coming years. Another challenge facing physician-scientists is the time it takes to complete MD/PhD training and become independent, which has substantially increased since the conception of the training pathway in the 1960s. MD/PhD graduates between the mid-1970s to 1980s took on average 6.69 years and held a full time position 3.98 years after their MD/PhD training program. In contrast, the most up-to-date survey information (2005-2014) revealed that alumni take on average 8.25 years to complete the program and 5.88 years to obtain a full-time faculty position4. It is projected that the average age in completing both the MD/PhD training and reaching a full-time faculty position will continue to increase, as it is becoming more common for matriculants to take time in-

between their undergraduate career and applying to an MSTP to gain more experience. Only in exceptionally rare cases, the varying time commitment to the lab and clinic make it difficult for physician-scientists to be outstanding in both medicine and science, a "master of none." However, as the reach of medicine and biomedical science becomes broader and potentially extends the distance between the dots that are necessary to connect for groundbreaking discoveries, further specialization and training is becoming ever more common. The physician-scientist, though an incredibly long and demanding career path, will continue to be essential in a scientific research world in need of a "jack of all trades."

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INA-RESPOND
Newsletter

REVIEW OF CURRENT COVID-19 DIAGNOSTICS AND OPPORTUNITIES FOR FURTHER DEVELOPMENT (A PAPER SUMMARY)

By: Yan Mardian

Diagnostic testing plays a critical role in addressing the coronavirus disease 2019 (COVID-19) pandemic. Rapid and accurate diagnostic tests are imperative for identifying and managing infected individuals, contact tracing, epidemiologic characterization, and public health decision making. Diagnostic approaches to COVID-19 can be divided into two broad categories: Clinical diagnostics and in vitro diagnostics.

CLINICAL DIAGNOSTICS

Clinical diagnostics for COVID-19 include the initial assessment of possible COVID-19 related symptoms and exposure history. These should be considered in the context of the SARS-CoV-2 incubation period, which is estimated to be up to 14 days from exposure, with a median of 4-5 days. Eleven common symptoms of COVID-19 are noted by the U.S. CDC: fever or chills, cough, dyspnea, fatigue, muscle pain, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea. A recent report by a UK study mentioned that the newest Variant of Concern (delta variant) might have different symptoms with "classical" COVID-19, with headache, sore throat and runny nose are the most common symptoms reported. Radiography may also support clinical suspicion of COVID-19, and chest CT scanning has been used as a complementary approach for early diagnosis and evaluation of disease progression. CT scan findings are variable and can include multiple bilateral ground-glass opacities in the peripheral lower lung zones. Common laboratory findings amongst COVID-19 patients include leukopenia, lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase (LDH) levels, and elevated inflammatory markers (e.g., ferritin, C -reactive protein, and erythrocyte sedimentation rate)

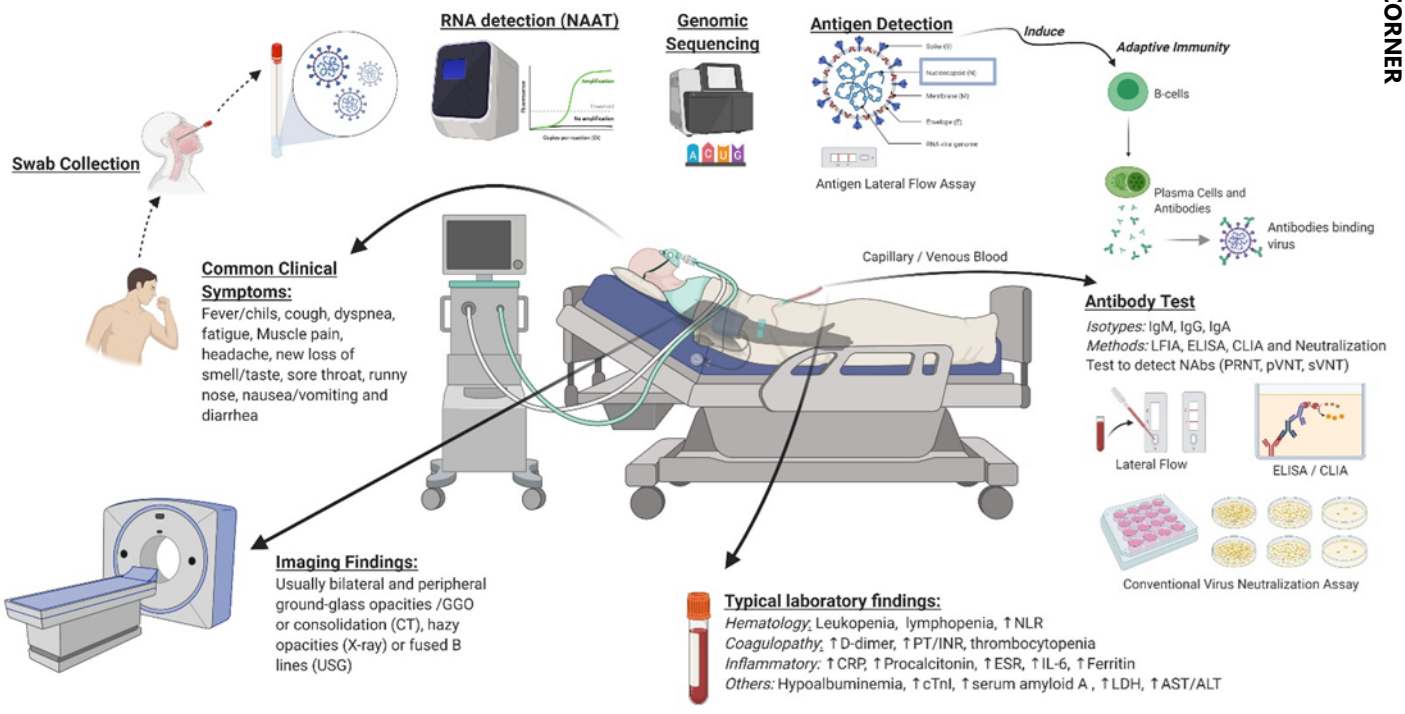

Figure 1. Clinical and in vitro diagnostics for COVID-19. Clinical diagnostics consist of common clinical symptoms, imaging findings, and laboratory markers. In vitro diagnostics include molecular testing, antibody tests, and viral antigen detection. NAAT: nucleic acid amplification tests; PoC: point of care; CRISPR: clustered regularly interspaced short palindromic repeats; NAbs: neutralizing antibodies; PRNT: plaque reduction neutralization test; pVNT: pseudovirus-based virus neutralization test; sVNT: surrogate virus neutralization test; LFIA: lateral flow immunoassay; ELISA: enzyme-linked immunosorbent assay; CLIA: chemiluminescent immunoassay; NLR: neutrophil-lymphocyte ratio; PT/INR: prothrombin time and international normalized ratio; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-6: interleukin 6; cTnI: cardiac troponin I; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CT: computed tomography; USG: ultrasound sonography. Image was created in Biorender.com

IN-VITRO DIAGNOSTICS: MOLECULAR TESTING

SARS-CoV-2 infection is confirmed by detection of SARS-CoV-2 RNA using nucleic acid amplification tests (NAATs). For detecting RNA viruses like SARS-CoV-2, Reverse Transcription quantitative PCR (RT-PCR) is recommended as the most sensitive NAAT method. Conventional NAAT begins with RNA extraction from respiratory specimens, followed by RT-PCR, in which the purified total RNA (viral RNA and the host RNA) is reverse transcribed into complementary DNA (cDNA) first by reverse transcriptase, followed by cDNA aliquots undergoing qPCR to exponentially amplify the target gene of interest. This two-step assay usually takes 3.5-4.0 hours and requires three reagent kits: one for the RNA extraction, one for cDNA synthesis, and another for the amplification and detection of the target nucleic acid, as well as specialized lab equipment. Systems that automate nucleic acid extraction, purification, amplification and detection are also available. These provide rapid, high-throughput results with minimal hands-on time (HoT) and less contamination.

Like all diagnostic tests, false-negative results can occur with RT -PCR. False negatives have been reported to occur in ~30% (range 10-40%) of patients with COVID-19. Contributing factors may include (a) collecting the sample when the viral load is low (e.g. early after exposure and before the peak associated with symptom onset, or late in disease course), (b) sample collection technique resulting in reduced quality or quantity, (c) inadequate preservation of the unstable RNA virus, as specimens may degrade without appropriate transport medium or storage, and (d) technical limitations of the RT-PCR test. Test sensitivity may also be impacted by natural mutations in the primer region, which could result in false-negatives. Though this does not necessarily mean that a primer would fail to bind, it reveals variability of the target region. Report showed deletion in S-gene positions 69 and 70 in the VOC B.1.1.7, or Alpha variant, causes S-gene target failure (SGTF) in at least one RT-PCR–based diagnostic assay, the ThermoFisher-TaqPath COVID-19 assay, and may serve as a means of identifying infection with this variant.

COVID-19 cases are typically confirmed by centralized RT-PCR testing in certified labs, which requires expertise, specialized equipment, and well-developed specimen management infrastructure. Due to the burden of large-scale testing suddenly placed on most labs, results may take a week or longer to be returned. This has spurred significant interest in reliable PoC molecular tests that produce rapid results (<1 h), as they facilitate timely patient management decisions. Other methods of viral detection has also been developed. Loop-mediated isothermal amplification (LAMP) combined with reverse transcription (RT-LAMP) has been developed as an alternative. RT-LAMP isothermally (60–65°C) amplifies DNA fragments of interest, thus does not require expensive thermal-cyclers or real-time PCR. Detection is based on photometric measurement of turbidity resulting from magnesium pyrophosphate precipitation that occurs as a by-product of amplification. This method enables real-time monitoring of results using colorimetric or fluorescent dyes. Along with isothermal amplification, another category of nucleic acid tests that could be used for SARS-CoV-2 is the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) based method. CRISPR belongs to a family of palindromic nucleic acid repeats found in bacteria, which are recognized and cut by a unique set of effector enzymes known as the CRISPR-associated (Cas) proteins. The Cas enzymes are exceptionally sensitive and specific as they can be programmed to identify and cut SARS-CoV-2 RNA sequences. Another approach, droplet digital PCR (ddPCR), has been developed to detect SARS-CoV-2 and measure viral load, which facilitates surveillance of inter and intra-case variability. ddPCR is based on partitioning the sample into thousands of micro-reactions of defined volume.

Genomic sequencing does not play a part in routine SARS-CoV-2 laboratory diagnosis; however, this technique is essential for phyloepidemiological evaluation of changes in the viral genome over time and to trace transmission patterns. Sequencing protocols based on Sanger and next-generation sequencing (NGS) (e.g., Illumina and MinION / Nanopore) are being applied to rapidly generate genome sequences, with the promise that data will inform diagnostic development, epidemiologic investigations, host-virus interactions, viral evolution, pathogenesis, and prevention and treatment targets. As of June 2021, several Variants of Concern have been identified as more transmissible (e.g. Variant B.1.1.7 or Alpha Variant and B.1.617.2 or Delta Variant), increasingly resistant to neutralization by monoclonal antibodies, and less susceptible to vaccine induced immunity (e.g. Variant B.1.351 or Beta Variant and P.1 lineage or Gamma Variant). Given the SARS-CoV-2 genome's evolving nature, genomic surveillance should be conducted at levels that allow early temporospatial identification of new variants.

Over 300 tests for SARS-CoV-2 NAAT/molecular testing are currently described in FIND (Foundation for Innovative New Diagnostics), a diagnostics resource center established in collaboration with WHO to accelerate development and access to diagnostics as part of the global response to COVID-19. Results are available online at: https://www.finddx.org/covid-19/sarscov2-eval-molecular/. Many molecular and serological PoC tests have also been granted EUAs from the U.S. FDA. Information on these assays can be found at: https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-

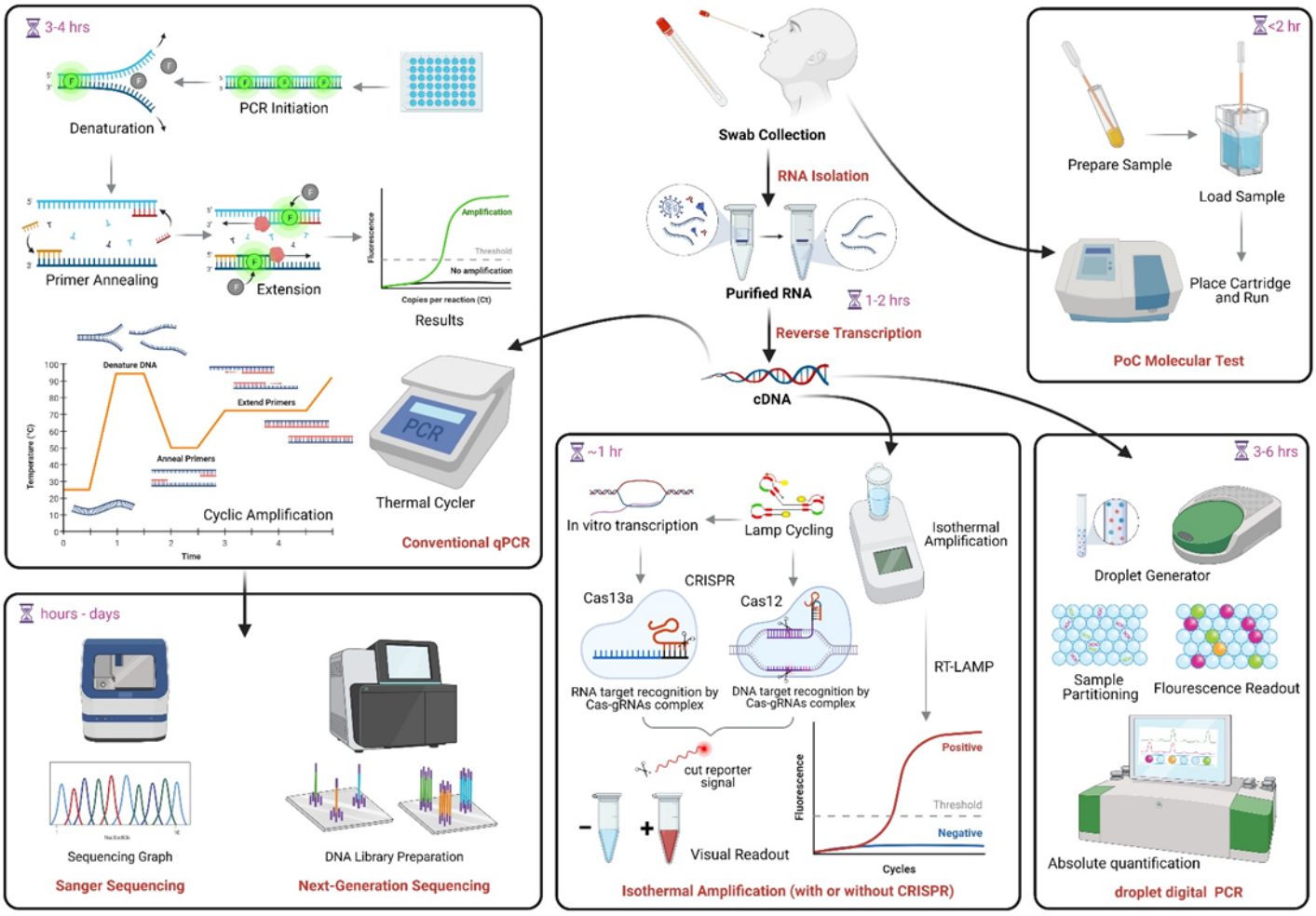

Figure 2. COVID-19 molecular testing. NAAT begins with RNA extraction followed by reverse transcription into complementary DNA (cDNA). The same cDNA can be used for conventional qPCR, RT-LAMP, which can also be coupled with CRISPR technology, and droplet digital PCR. PoC assays (uppermost right) use direct specimen and cartridge-based tests to produce rapid results. The PCR amplification product may be used to generate viral genome sequences (lowermost left). NAAT: nucleic acid amplification tests; qPCR: quantitative polymerase chain reaction; PoC: point of care; LAMP: Loop-mediated isothermal amplification; CRISPR: clustered regularly interspaced short palindromic repeats. Image created in Biorender.com

emergency-use-authorizations-medical-devices/vitro-diagnostics-euas. Fig. 2 shows a conceptual overview of COVID -19 molecular testing approaches.

IN-VITRO DIAGNOSTICS: ANTIBODY ASSAYS

Serologic measurement of specific antibodies can be used to assess prior exposure to SARS-CoV-2 and infer potential immunity to the virus. As a diagnostic tool, antibody serology is particularly useful for patients with delayed clinical presentation, typically at least two weeks after illness onset, who may be missed by NAAT. Serological data is particularly useful for epidemiologic purposes, such as estimation of the attack rate, R0, and case fatality rate, and to evaluate the impact of control measures (lockdowns, broad testing, and other policies). Antibody evaluation can also facilitate identification of plasma donors and assessment of vaccine immunogenicity, especially in elderly or otherwise immunocompromised people. However, in a pandemic context where early diagnosis is essential for patient management and outbreak control, antibody assays are suboptimal due to delayed seroconversion and performance variability, therefore are not the preferred frontline test.

IN-VITRO DIAGNOSTICS: ANTIGEN TESTING

SARS-CoV-2 antigen testing is another type of serologic assay that is attractive as a potential PoC diagnostic. Antigen-based diagnostics detect protein fragments on or within the virus, rather than viral nucleic acids, in specimens collected from NP swabs or nasal cavity. This type of testing can detect active infections within 15 min compared to hours with RT-PCR. Therefore, a highly sensitive method that directly detects viral antigens in clinical samples would be a great asset in in the containment of transmission during early infection.

TABLE 1 | *In vitro* diagnostics for COVID-19 and potential areas for development.

In vitro diagnostic	Currently available assays	Brief description	Development areas
Molecular testing, NAAT	RT-PCR assays (conventional or automated). Alternative terminologies include rRT-PCR or RT-qPCR.	• NAAT detects the presence of viral RNA (62) • Purified RNA from clinical specimens is reverse transcribed into complementary DNA (cDNA), then added to a master mix containing target primers and a fluorophore-quencher probe. The RT-PCR process is carried out in a thermal cycler. The fluorophore-quencher probe is cleaved, generating a fluorescent signal that corresponds to the amplified product (63, 114) • While conventional NAAT begins from manual RNA preparation, followed by rRT-PCR; automated systems integrate RNA extraction, purification, amplification, and detection, resulting in rapid, high-throughput results and less contamination (70–72, 74)	• Pre-heating specimens to skip RNA extraction (66–69) • Accuracy with alternative, less invasive specimens (e.g., Saliva) in comparison with standard NP specimens (87–89, 91) • Lower respiratory specimens may provide benefit later in the disease course (94), while non-respiratory specimens may correlate with local symptoms (e.g., stool) or clinical severity (e.g., blood) (99, 103, 133) • Swab pooling to increase testing capacity (93) • Different PCR target regions may affect sensitivity (116, 122–124) • Monitoring effect of SARS-CoV-2 genome mutations on RT-PCR performance (118, 136) • One-step (consolidated RT and PCR) vs. two-step (separate RT and PCR) assays, and uniplex vs. multiplex RT-PCR (63, 65, 114) • Subgenomic RNA and/or Ct value as the surrogate for infectious/live virus (139)
	PoC–Xpert® Xpress SARS-CoV-2	It targets the E and N2 SARS-CoV-2 genes, performed on an automated GeneXpert instrument. LOD 8.26 copies/mL and TAT is 45 min (146)	Further development of Xpert® to detect important SARS-CoV-2 mutations may be needed, as is done for TB (148)
	PoC–CovidNudge	It is based on a fully-automated multiplex RT-PCR targeting seven SARS-CoV-2 gene targets (RdRp1, RdRp2, E-gene, N-gene, N1, N2, and N3). LOD 250 copies/mL and TAT is 90 min (155, 156)	• CovidNudge has low throughput compared with RT-PCR (1 sample per run), multiple instruments may be needed depending on the clinical setting (157) • Studies have only assessed performance with NP/OP swabs (156). Further validation is warranted, and other sample types should be examined
	PoC–TrueNat	This chip-based portable PoC targets SARS-CoV-2 E and RdRP genes. LOD 486 copies/mL and TAT is <1 h (160, 161)	Despite affordability and portability, this technology is low throughput and further external validation studies are warranted (63)
	PoC–ID Now COVID-19	It is based on the Nicking Enzyme-Assisted Reaction (NEAR), which targets the SARS-CoV-2 RdRP gene. LOD 125 genome equivalents/mL and TAT is 5–13 min (149, 150)	Suitability of ID Now as a confirmatory test is uncertain due to a study suggesting low PPA, despite using freshly collected specimens as now recommended by the manufacturers (151, 152)
	PoC–BioFire® Respiratory Panel 2.1 (RP2.1)	It was created by adding primers targeting M and S genes of SARS-CoV-2 to the existing multiplexed BioFire® Respiratory Panel 2 (RP2), which can detect multiple pathogens in a single swab. LoD 500 copies/mL and TAT is 45 min (162, 163)	As RP2.1 detects spike genes, a hotspot for mutation, utility of this PoC test for detection of variants should be routinely assessed.
	PoC–cobas® Liat®	It identifies and differentiates SARS-CoV-2 (targeting ORF1a/b and N genes), influenza A and B virus via multiplex RT-PCR. LoD 12 copies/mL and TAT is 20 min (164)	Since it simultaneously tests for influenza and SARS-CoV-2, thus allowing differentiation between both viruses that may co-circulate in the annual flu season (165). Validation with other multiplexed assays is desired
	PoC–GenMark ePlex	It targets the N gene of SARS-CoV-2 and uses electrowetting and GenMark's eSensor technology based on competitive DNA hybridization and electrochemical detection. LoD 750 copies/mL and TAT is <2 h (155, 171)	The multiplex version (ePlex RP2 Panel) should be further validated with another multiplexed assay (e.g., BioFire® RP2.1 and Cobas® Liat) since NAAT methods differ between those assays
	PoC–Diasorin Simplexa™	It targets SARS-CoV-2 ORF1ab and S genes, can run 8 samples per disc; LoD 500 copies/mL and TAT ~90 min (155, 173, 174)	As it detects the spike gene, a mutation hotspot, utility for detection of variants should be routinely assessed
	RT-LAMP	It detects multiple SARS-CoV-2 genes, including ORF1ab, S, E, and/or N gene, using isothermal amplification, thus does not require thermal cycling (175–178). Real-time results are monitored with colorimetric or fluorescent dyes (43, 180)	• False positives may occur due to presence of multiple pair primers (183), while false-negatives may occur with low viral RNA (175, 183); indicates evaluation should be performed across a range of SARS-CoV-2 viral loads • Smartphone integration and combination with nanopore sequencing and CRISPR-based detection platforms may improve performance (183, 184, 313)

(Continued)

Although more evidence is needed, data suggest Ag-RDTs are likely to perform well (91–100% sensitivity) in patients with high viral loads (Ct values ≤25 or >106 genomic virus copies/mL), which usually appear in the pre-symptomatic (1-3 days before symptom onset) and early symptomatic phases of the illness (within the first 5-7 days of illness). In its September 11th, 2020, interim guidance, WHO recommends use of SARS-CoV-2 Ag-RDTs that meet the minimum performance requirements of ≥80% sensitivity and ≥97% specificity compared to a NAAT reference assay. Testing should be conducted by trained staff in strict accordance with the manufacturer's instructions and within the first 5-7 days following onset of symptoms. Patients who present more than 5-7 days after symptom onset are more likely to have lower viral loads and false-negative results with Ag-RDTs.

FUTURE DIRECTION

Availability of diagnostic assays is rapidly expanding, as demonstrated by the ever-increasing list of assays granted EUA status by the U.S. FDA. Well-designed validation studies should be conducted to identify products with the best performance and to obtain the data necessary to support licensure. As early diagnosis is essential for patient management and outbreak control, development of rapid, scalable, and high-accuracy PoC assays should be prioritized. Highest priority should be assigned to cost-effective multiplexed PoC tests that identify multiple pathogens. Access to scalable diagnostic tools and continued technologic advances, including machine learning and smartphone integration, will facilitate control of the current pandemic as well as preparedness for the next one. Basic principles of in vitro diagnostics, exploring their pros and cons as well as appropriate indications and potential areas for development, are listed in Table 1.

TABLE 1 | Continued

In vitro diagnostic	Currently available assays	Brief description	Development areas
	CRISPR	The guide RNA (gRNA) targets SARS-CoV-2 RNA sequences, which can be recognized by CRISPR-associated (Cas) proteins, result in collateral cleavage of the reporter probes and the appearance of a positive band on the paper strip (178, 187–189)	• Advantages in comparison to RT-PCR include rapid TAT and reduced equipment and reagent requirements (194) • Emerging CRISPR-based methods require validation and additional field testing (195)
	ddPCR	In this digital PCR, the sample is fractionated into thousands of droplets, and the PCR amplification of the template molecules occurs in each droplet, thus allowing for absolute quantification of genomic material (197)	ddPCR assays enable nucleic acid measurement and pathogen diagnosis with limited sample processing, therefore may have a role in monitoring viral load during the disease course and convalescence (199)
	NGS	Sequencing is used to determine the order of the bases within the genome. NGS has three general steps: DNA library preparation, clonal amplification of the library, and DNA sequencing by detecting emitted optical or chemical signals (67, 200)	• Cost is currently high • Potential high utility in genomic surveillance to monitor variants with increased transmissibility and/or virulence, ability to evade detection by current diagnostics, and ability to escape antiviral treatment or immunity (203)
Antibody assays	Serology Assay: • ELISA • CLIA • LFIA	• Antibody serology assays detect antibodies against SARS-CoV-2 (15) • ELISA uses plates pre-coated with viral antigens, such as Spike or Nucleocapsid protein (226, 227), and CLIA uses magnetic, protein-coated microparticles to detect antibodies (228). If the serum contains SARS-CoV-2 antibodies, antibody-protein complexes form and are bound with anti-human antibodies tagged with the enzyme to produce a light-based, luminescent readout (229, 230) • LFIA employs a similar method with sandwich ELISA, but the immunological reaction is carried out on the chromatographic paper by capillary action, results in the appearance of a colored line on the strip (225)	• Serological data is most useful for epidemiologic purposes and may facilitate identification of potential convalescent plasma donors and assessment of vaccine immunogenicity (214, 216, 217), although protective titer is not yet well-defined • Poor sensitivity of LFIA compared with ELISA/CLIA may be associated with use of capillary blood for PoC-LFIA test vs. serum/plasma use on ELISA/CLIA (223) • Possible cross-reactivity with other pathogens and/or rheumatoid factor (248, 264) • Unclear whether Spike Protein-based Assay vs. Nucleocapsid Protein-based Assay has better sensitivity (226, 248) • Seroconversion timing between antibody class varies across studies (276, 281) • Dynamic antibody profiling data between severity stages and the duration of antibody response are not well-established (278, 285) • Theoretical possibility that mutations will affect assay performance (259) • Variable accuracy of results amongst different commercially available kits (236)
	Neutralization Assay: • PRNT • pVNT • sVNT	• NAbs are specific for viral epitopes that mediate entry of the virus into a host cell; thus their presences indicate protective immunity (255) • Conventionally, NAbs were measured by PRNT, in which serial dilutions are incubated on a host cell monolayer for several days to determine final dilution titer at which virus plaque formation is inhibited (97) • pVNT has a similar method but uses other viruses pseudotyped with SARS-COV-2 Spike to mimic the infectious virus (256) • sVNT detects NAbs without the need for live viruses or cells. Using purified RBD from the S protein and the host cell receptor ACE2, this test mimics the virus-host interaction in an ELISA plate well (252)	• PRNT is labor-intensive, requires BSL-3 facility, and takes 2–4 days to complete; it is thus impractical for large scale applications (252). Pseudovirus is safer to handle in a BSL-2 laboratory, but still requires culture methodology (256) • Studies did not clearly define sVNT cut-off value in relation to conventional PRNT titer. Validation with different clades or emerging variants is needed to ensure its robustness (252) • Some studies showed positive correlation between the SARS-CoV-2 viral NAbs titer and the S-RBD–specific IgG, with a NAb titer of 1:80 approximately equivalent to a titer of 1:1,280 for S-RBD-specific IgG (253), or NAb titers 1:160 corresponds to anti-RBD titer ≥ 1:1,350 (254). Studies differ in specific assay used, so titers between studies may not be equivalent. NAb protective titer is not yet well-defined
Antigen assays	ICT and FIA assay	• Antigen-based diagnostics detect protein fragments on or within the virus (178). They mostly target the C-terminus of N gene/protein via a diagnostic sandwich assay using monoclonal Abs (259) • ICT uses colloid gold conjugated antibodies, resulting in visible colored bands, while FIA is usually read by the automated immunofluorescence reader (290)	• As antigen tests perform best in samples with high viral loads and during the first 5–7 days of symptoms (302), they may be useful for early diagnosis and interruption of transmission (307) • Validation studies needed for fresh vs. frozen swab samples (300), viscous vs. non-viscous specimens (298), NP vs. saliva samples (297) • Performance of antigen assay might be impacted by virus mutations (259)

NAAT, nucleic acid amplification tests; RT-PCR, real-time quantitative reverse transcriptase polymerase chain reaction; dsDNA, double-stranded DNA; NP, nasopharyngeal; PoC, point of care; LOD, limit of detection; TAT, turnaround time; LAMP, Loop-mediated isothermal amplification; CRISPR, clustered regularly interspaced short palindromic repeats; ddPCR, droplet digital PCR; NGS, next-generation sequencing; ELISA, enzyme-linked immunosorbent assays; CLIA, chemiluminescent immunoassays; LFIA, lateral flow immunoassays; Nabs, neutralizing antibodies; PRNT, plaque reduction neutralization test; pVNT, pseudovirus-based virus neutralization test; sVNT, surrogate virus neutralization test; RBD, receptor binding domain; BSL, biosafety level; ICT, immunochromatographic; FIA, fluorescence immunochromatographic assay.

Source: Mardian Y, Kosasih H, Karyana M, Neal A, Lau CY. Review of Current COVID-19 Diagnostics and Opportunities for Further Development. Front Med (Lausanne). 2021 May 7;8:615099. doi: 10.3389/fmed.2021.615099. PMID: 34026773; PMCID: PMC8138031.

INA-RESPOND Newsletter

ONLINE TRAINING, THE NEW TREND

By: Marco Ariono

COVID-19 pandemic has been going on for more than a year and has affected many aspects of our life. Working from home, school from home, online meetings, etc., have become common in our daily life. Avoiding a big crowd or public space has been a choice for many people. Working from home situations also impact our physical and mental well-being.1

These routines have become a problem because people tend to move less. Sedentary activities like sitting or lying are increasing. In a long time, this behavior will give us other issues like increasing chronic diseases such as hypertension, diabetes mellitus, heart disease, and other non-communicable chronic diseases.2

Going to a gym may still be a difficult or highly risky choice for some people. Of course, the dumbbells and machines that have been used together become a higher risk of spreading infection. The tight spaces between the treadmill or ergo cycle are another problem. The other problem is the ventilation. Most gyms are indoor, and there's concern about airborne COVID-19 transmission. People still worry about going to the gym nowadays.3

Outdoor Exercise

Outdoor exercise has become more popular. Walking or running is a common activity that people do on the weekend, especially before the pandemic. The Governor of Jakarta has created bicycle tracks, including on the main road. Moreover, the city has designed special routes for faster road bikes.4 This good idea aims to invite people to exercise, and if this becomes a daily routine, we hope air pollution can reduce.

However, some people do not have much time to go outside because of their work or busyness. Others are still afraid to go outside where there is a higher chance of getting infected by COVID-19 from others, so they prefer to stay at home.3

Online Training

American College of Sports Medicine (ACSM) did a survey about fitness trends for 2021. Over 4,300 health and fitness professionals participated in the survey. No surprise, the survey shows online training has become the most popular fitness trend dur-

ing this pandemic era beating wearable technology and bodyweight training.5

Online training usually uses digital streaming technology to deliver exercise programs. The training can be done anytime because we do it at home in a live or from a prerecorded class. The digital platform that people usually use is YouTube. There's a lot of online training available. However, if we want something more personal, we can use applications such as Mirror, Zwift, Nordic Track, and iFit. Each application has a different function and pricing. These applications usually encourage the user to be active and generate personalized user data. The data can be obtained from wearable technology such as Garmin, Fitbit or Apple watches to track the wearer's activities and heart rate.6

Many exercise options don't need equipment, such as walking, dancing with video, yoga, or bodyweight training. We can also use alternate tolls like a bottle as a dumbbell, a towel in resistance training, and stairs for step-up exercise.6

Benefits

Following the physical activity guidelines (150 minutes per week moderate to high intensity and two times a week strength training) is greatly associated with reduced risk for severe COVID-19 outcomes7. Regular physical activity and taking other precautions are considered effective in dealing with the health outcomes of the COVID-19 pandemic.8 Spaulding et al. suggest that regular exercise may reduce the risk of acute respiratory distress syndrome, which becomes a main cause of death in COVID-19 patients.9

Online media becomes an important source, especially for exercise during the COVID-19 pandemic. Mutz et al. find that a fifth of the German population (19%) is engaged in digital fitness exercises at home during the lockdown. Thus, online training helps people to stay active and healthy despite the restriction of COVID -19 mitigation.

Usually, people use online training when there's a limitation to go outside, and the COVID-19 case still high enough. But when the restriction was suspended, many people switched back to their usual sports activities such as running, biking, hiking, etc.10

In their systematic review, Ballin et al. found that digital exercise interventions in obese adults may reduce waist circumference.11 Virtual exercise also can be done by healthy pregnant women. A study by Silva-Jose et al. found that a virtual exercise program throughout pregnancy during COVID-19 confinement can help to control systolic blood pressure before and immediately after delivery in healthy pregnant women. The virtual exercise was supervised with three weekly sessions of about 60 minutes activities.12

Weakness

One of the weaknesses of online exercise is that not all people have proper tools to exercise, such as dumbbells, resistance bands, etc. We must know what kind of tools and facilities we have to find a suitable exercise regiment. Another weakness is that if something bad happens to us when we exercise alone, no one will help immediately. So, it is better if there are other people around us to help.

Conclusion

Online training has become popular during the COVID-19 pandemic. The digital platform that we use to do exercise may give us the benefit of staying active. Although we don't have proper exercise tools at home, we can still do bodyweight exercise. We can also use other tools as an alternative, such as bottles as dumbbells and towels as resistance bands. Training regularly will give us a lot of benefits, especially during the COVID-19 pandemic. So stay active. Let's get moving!

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INA-RESPOND Newsletter

QUIT, DON'T QUIT? SWEETENERS, NO SWEETENERS?

By: Aly Diana

A wise man says sugar/sweetener makes everything better. However, too much sweetness can make your life miserable. And… nobody wants a miserable life. Consequently, growing concerns about health and quality of life have encouraged people to adapt healthy lifestyles and avoid consuming food rich in sugars or calories to prevent obesity and other non-communicable diseases. With increased consumer interest in reducing energy intake, food products containing non-sugar sweeteners (NSSs) rather than simple sugars (monosaccharides and disaccharides) have become increasingly popular.

A sugar substitute (artificial sweetener or high-intensity sweetener) is a food additive that duplicates the effect of sugar in

taste but usually has less food energy. Consumers often select foods composed of low-calorie sweeteners because they want the taste of sweetness without the added calories. To date, six high-intensity sweeteners are FDA-approved as food additives in the United States: saccharin, aspartame, acesulfame potassium (Ace-K), sucralose, neotame, and advantame. In addition, generally recognized as safe (GRAS) notices have been submitted to FDA for two types of high-intensity sweeteners (certain steviol glycosides obtained from the leaves of the stevia plant (Stevia rebaudiana) and extracts obtained from Siraitia grosvenorii (swingle fruit), also known as Luo Han Guo or monk fruit).

Replacement of sugars with NSSs bears the promise of health benefits primarily by reducing the contribution of sugars to daily calorie intake and thus reducing the risk of unhealthy weight. However, evidence for health effects due to the use of NSSs is conflicting. While some studies report an association between NSS use and reduced risk of type 2 diabetes mellitus (T2DM), overweight, and obesity (thus suggesting a benefit for general health and the management of diabetes), other studies indicate that NSS use could increase the risk of overweight, diabetes, and cancer.

In addition, recent studies have suggested that NNS consumption can induce gut microbiota dysbiosis and promote glucose intolerance in healthy individuals that may result in the development of T2DM. This sequence of events may change the gut microbiota composition through microRNA (miRNA)-mediated changes. The mechanism(s) by which miRNAs alter gene expression of different bacterial species provides a link between NNS consumption and the development of metabolic changes. Another potential mechanism that connects NNS to metabolic changes is the molecular crosstalk between the insulin receptor (IR) and G protein-coupled receptors (GPCRs).

All in all, the majority of clinical studies performed in humans thus far report no significant risks or beneficial effects of artificial sweeteners on health outcomes. Still, it should be emphasized that the study duration of most studies was limited. Clearly, further well-controlled, long-term human studies investigating the effects of different artificial sweeteners and their impact on gut microbiota, body weight regulation, and glucose homeostasis, as well as the underlying mechanisms, are warranted.

For now, before we know for sure about the real long-term effects of NSS, consuming sugar at recommended amount probably will be the best bet. Taken together, scientific studies currently indicate that public health will be improved by reducing intake of all sweeteners, both caloric and non-caloric. Currently, recommended daily intake of sugar for adults is around 50 grams (12 teaspoons or 4 tablespoons). Enough sweetness keeps our life happy and healthy!

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