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Impact of the COVID-19 pandemic on human papillomavirus–based testing services to support cervical cancer screening

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I have no conflicts of interest to declare.

(I am head of laboratory that performs HPV and COVID-19 molecular testing)

Elimination definition and 2030 targets

Vision: a World without cervical cancer

Goal: cervical cancer incidence below 4 cases per 100,000 woman/years

2030 TARGETS

90%

of girls fully vaccinated with the HPV vaccine by the age of 15

70%

of women screened using a high-performance test by the age of 35, and again by the age of 45

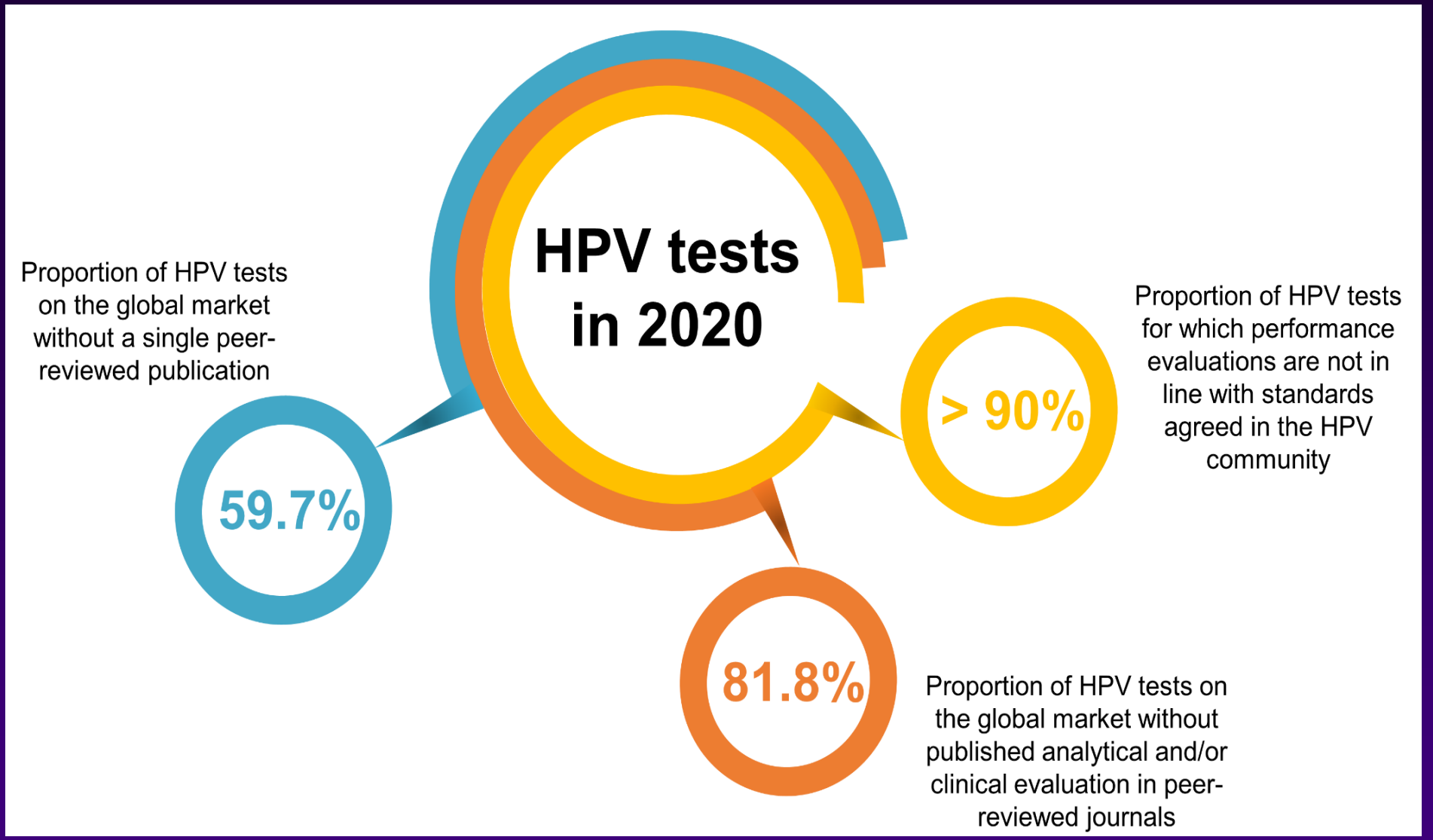
90%

of women identified with cervical disease receive treatment and care

2030 target: 30% reduction in mortality from cervical cancer

the global HPV test supply needed to reach the 70% screening coverage aspiration of the WHO is estimated to be in the range of 1.4 to 1.5 billion HPV tests over a time span of 5 years

(N. Broutet, personal communication)



Poljak M at al. Clin Microbiol Infect 2020; 26: 1144-50

to promote and facilitate access to safe, reliable, and appropriate in vitro diagnostic technologies, the WHO performs prequalification of in vitro diagnostics for high-burden diseases

currently, only 3 tests for HPV-based screening have been WHO prequalified

there is still a relatively small pool of HPV tests that fulfill the operational and performance characteristics required to meet the global screening challenge

COVID-19-related problems arising…..

- unprecedented health and economic impact of the COVID-19 pandemic
- extraordinary demand on a global scale for sampling devices, reagents, consumables, and diagnostic instruments needed for timely diagnosis of SARS-CoV-2 infection
- manufacturers' shift toward new niche market with unprecedented market growth opportunity
- serious COVID-19-related supply chain problems (reagents and consumables)
- preexisting microbiology lab employee shortage, then COVID-19 pandemic hit

Supply shortages impacting COVID-19 and non-COVID testing

Oct. 15, 2020 SHARE THIS

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117 CLIA-certified labs who have responded to the survey report running at an average of 41% testing capacity for COVID-19

73% of laboratories reported a shortage of commercial testing kits for SARS-CoV-2

70.8% of labs reported a shortage of supplies for molecular detection of sexually transmitted infections, including HPV

65% of labs reported a shortage of non-COVID-19 testing supplies for detection of routine bacteria and 50% for routine fungal testing

HPV Prevention and Control Board reaction…..

- in August 2020, the board held a meeting to discuss challenges in the HPV-based cervical cancer screening landscape, which included a session on the impact of COVID-19 on screening programs
- the discussion prompted the board to hold an additional 2-day meeting in November 2020 fully devoted to the impact of COVID-19 on cervical cancer screening and treatment, and HPV vaccination. At this meeting, the board members noted that COVID-19 had not only impacted screening attendance, but the availability and supply of consumables, equipment, and staff required for HPV based screening
- given that observations were based on the experience of those in the board, either directly and/or through anecdotal exchange(s) with colleagues, it was agreed that this important issue may be better understood through the creation and wide dissemination of a brief survey

HPV Prevention and Control Board reaction…..

- The purpose of the survey was to acquire real-life insight into the impact of SARS-CoV-2 on potential shortages of tests, equipment, consumables, and staff required to effectively run HPV-specific laboratory procedures.

- The survey also served as an opportunity to determine common challenges and to identify potential opportunities that may support sustainable HPV-based cervical cancer screening in the future.

- We also contacted five major manufacturers of clinically validated HPV tests to gain an understanding of their plans to mitigate current and future pressures on the demand for molecular testing.

https://www.uantwerpen.be/en/projects/hpv-prevention-andcontrol-board/resources/

- online questionnaire developed using QualtricsXM (London, UK)
- 19 items, mostly multiple choice, but with room to provide additional free text comments
- tested for comprehensibility and clarity in a small pilot
- targeted laboratory managers with responses limited to one per laboratory
- circulated among:
  - International Papillomavirus Society (IPVS) members
  - labs participating in the Global HPV LabNet DNA Genotyping Proficiency Panels in 2018 and 2020
  - in the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) member newsletter
- available online between 21 December 2020 and 2 February 2021

To contextualize the responses of users with those from industry, a limited number of companies with a molecular portfolio that includes clinically validated HPV and SARS-CoV-2 test(s) were invited to provide a statement on:

- support for the emerging need by national and regional governments for high volumes of molecular COVID-19 testing
- recent investment in manufacturing capacity, diagnostic infrastructure, and the supply chain
- safeguards and commitment to manufacture other molecular diagnostic assays (including HPV tests)
- current and post-pandemic strategy for HPV tests

Abbott Laboratories, Chicago, IL, USA

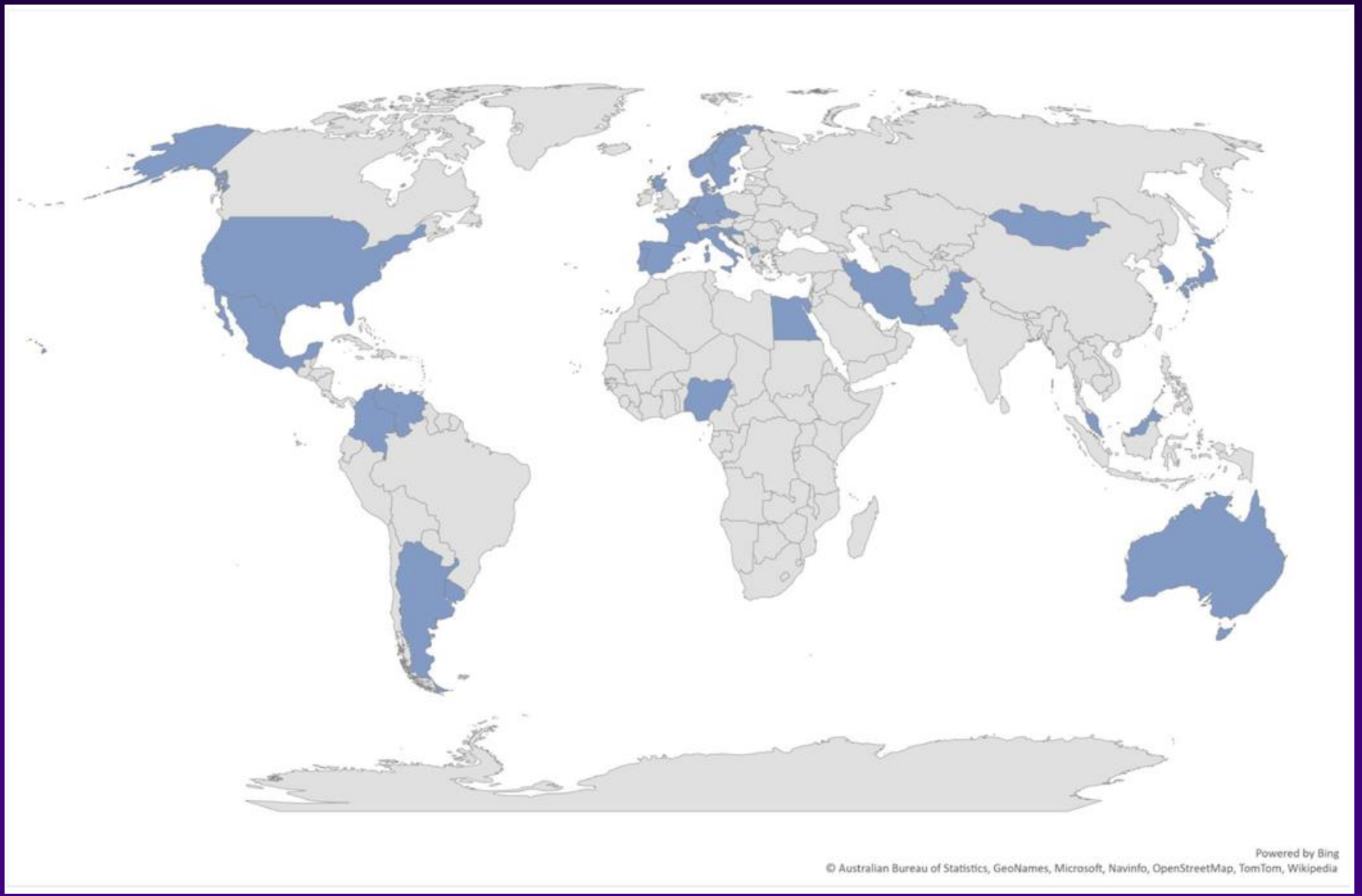
Becton Dickinson, Franklin Lakes, NJ, USA

Cepheid, Sunnyvale, CA, USA

Hologic, Marlborough, MA, USA

Roche Diagnostics, Indianapolis, IN, USA

responses received from 57 laboratories, from 30 countries across six continents, representing 19 high-income countries and 11 low- and middle-income countries



- 8 responses excluded from the analysis because of incomplete data
- 3 responses from laboratories that did not perform HPV tests

Table 1 | **Types of laboratories that participated in the survey.**

Type of laboratory	*n*	%
General molecular diagnostic laboratory	12	26
HPV reference laboratory	11	24
Other	9	20
General molecular diagnostic laboratory and other	4	9
HPV reference laboratory and general molecular diagnostic laboratory	8	17
HPV reference laboratory and other	2	4
Total	46	100

Table 2 | Shortage of specific consumables during COVID-19 pandemic reported by respondents.

Supply shortage	Number of times ticked
Collection and transport media	11
Plasticware: pipette tips, sample tubes, storage boxes, etc.	16
Extraction reagents	18
PCR reagents	12
Swabs	4
Molecular-grade fluids (ethanol), general disinfectants	8
Waste bins and waste collection services	5
Personal protective equipment	9
Bench/lab space due to reprioritization of services	9

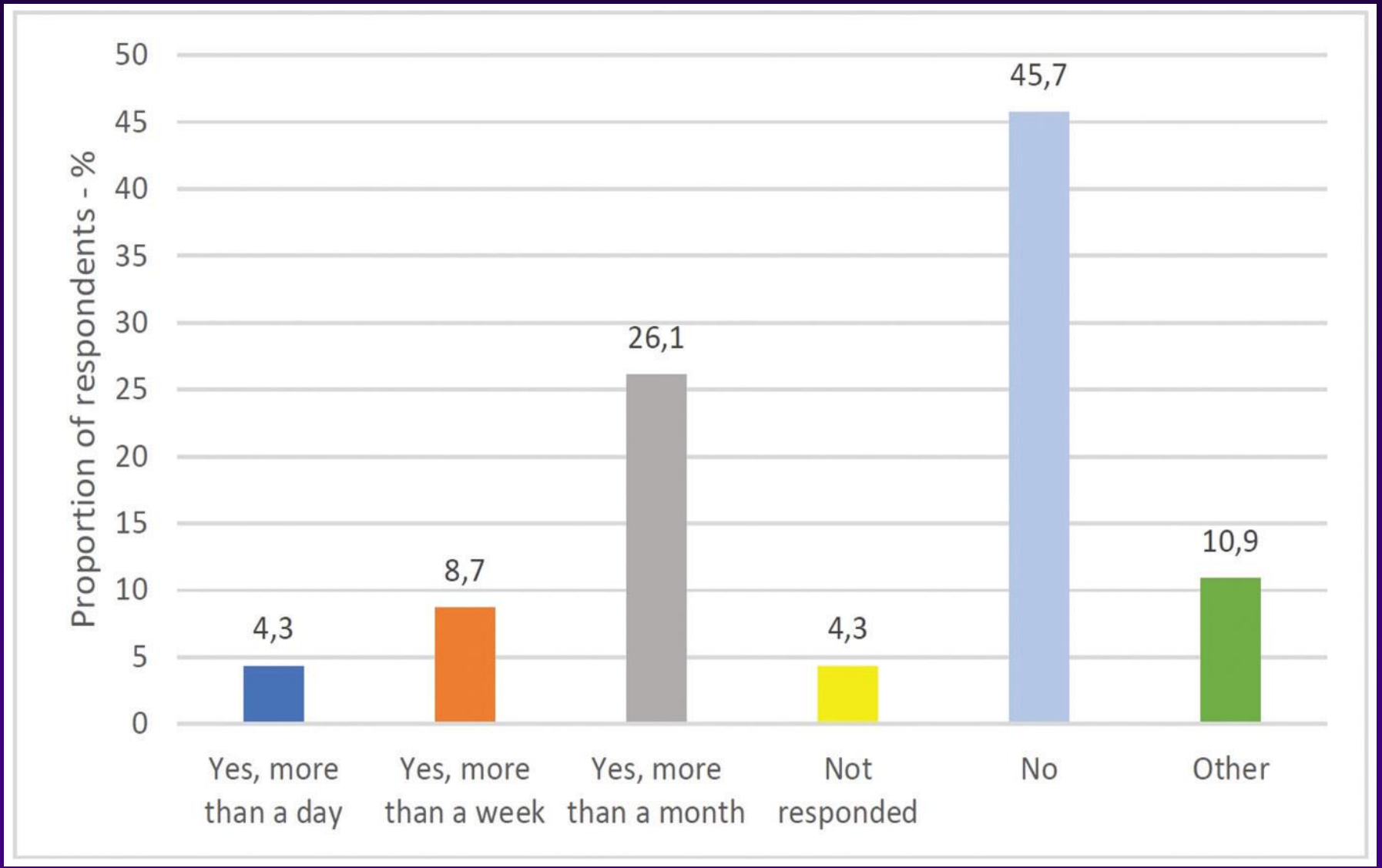
Respondents could choose multiple options for this question and tick multiple consumables.

Table 3 | Reasons for shortage of personnel in the laboratory during COVID-19 pandemic reported by respondents.

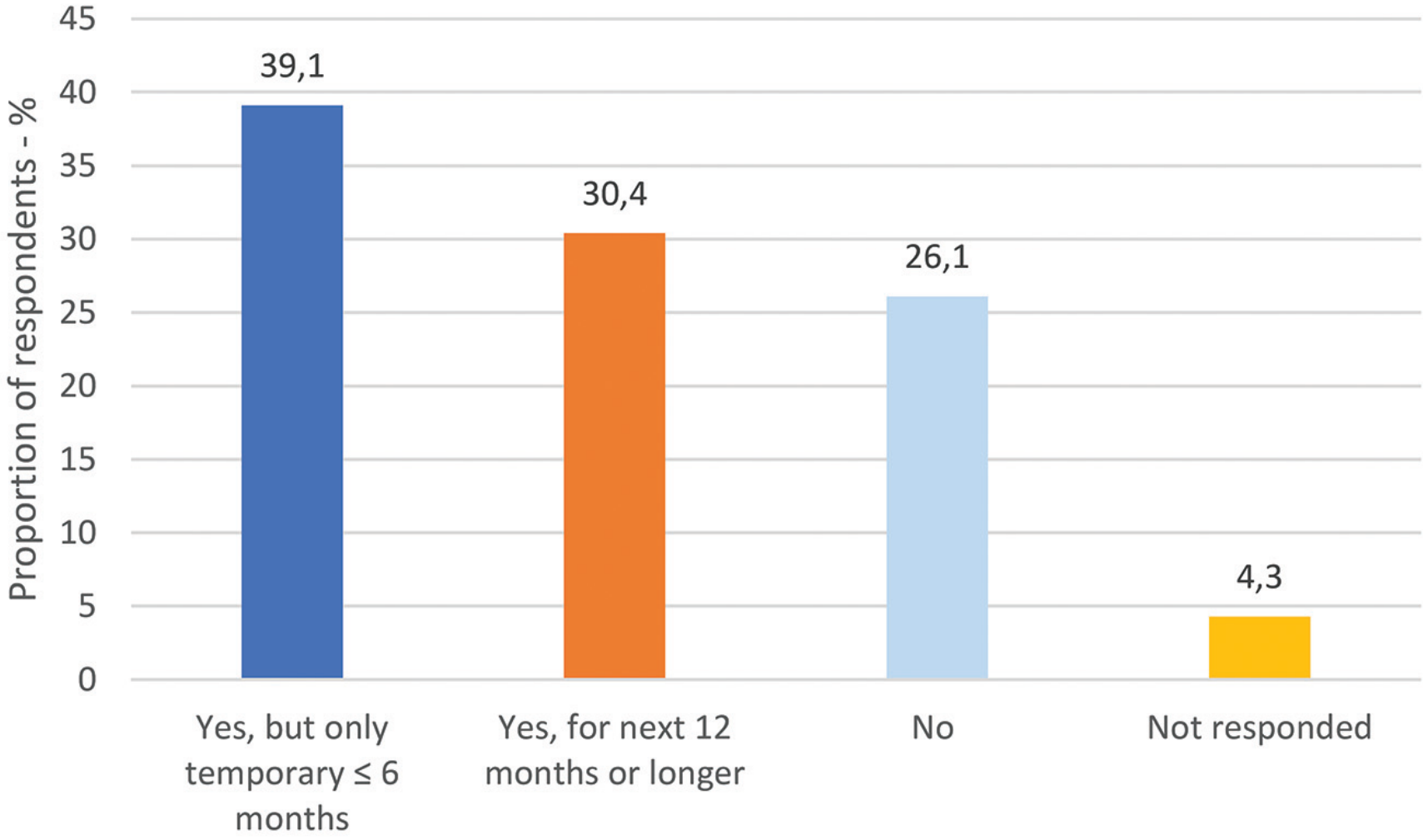
Reasons for shortage of personnel	Number of times ticked
Not all staff was allowed to work at the same time	12
Staff co-opted to support COVID-19 testing	12
Self-isolation	6
Other reasons	3
Not answered (no shortage)	22

Respondents could choose multiple options for this question and tick multiple reasons.

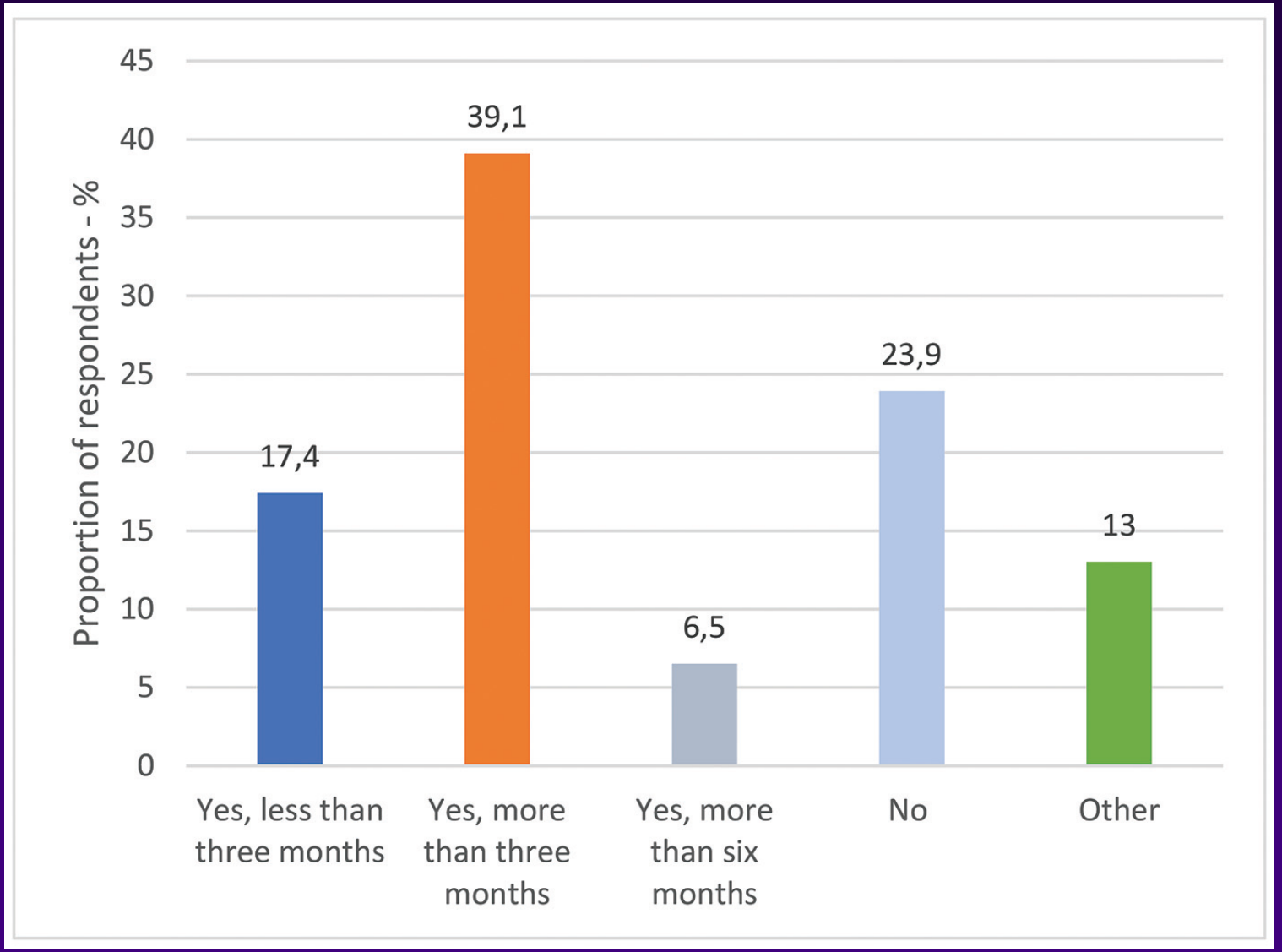
Was the time to receive HPV test results prolonged during the COVID-19 pandemic ?



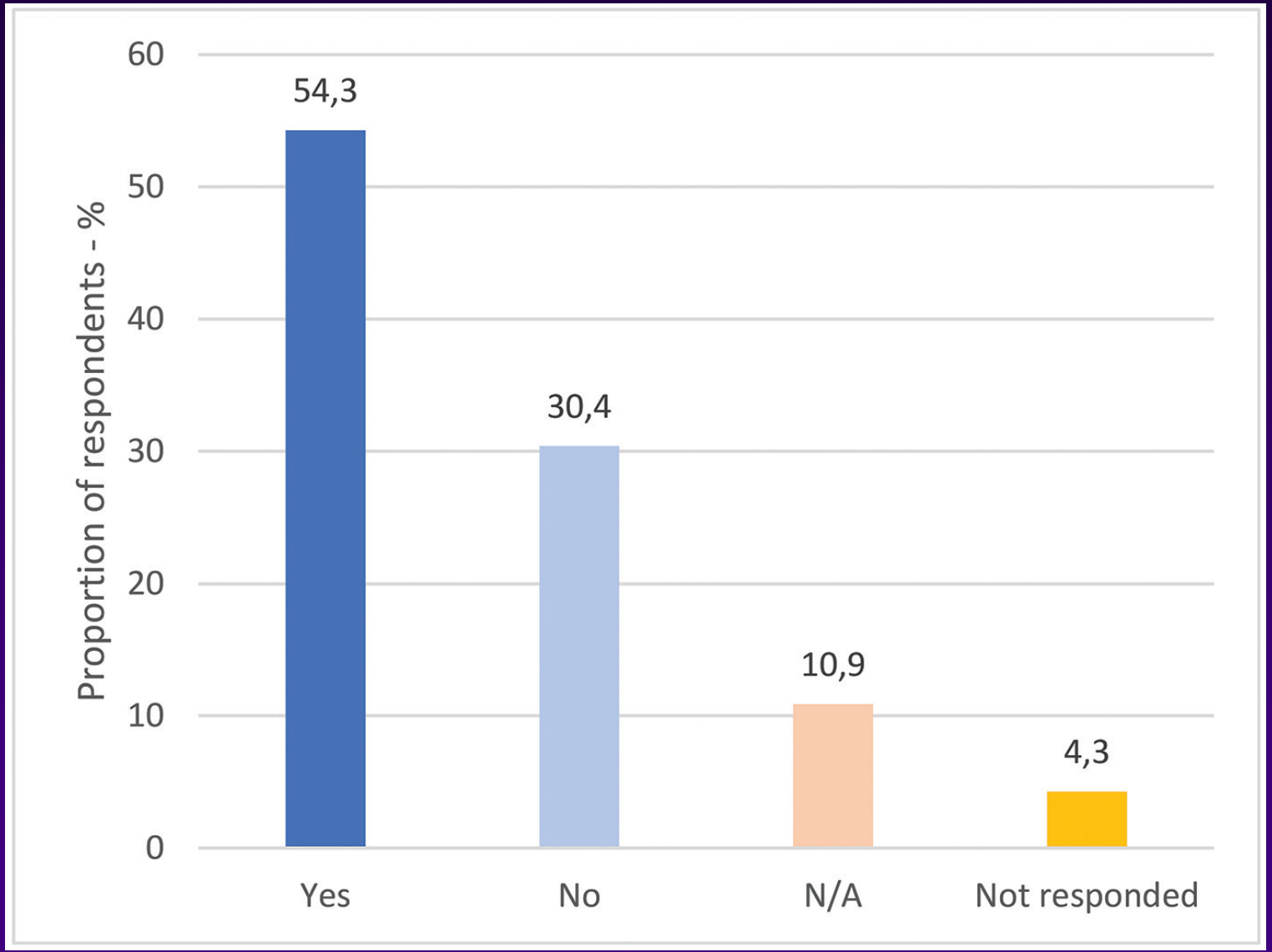
Impact of COVID-19 on HPV testing



Suspension of routine cervical cancer screening program due to COVID-19



Impact of COVID-19 on research and development capacity and activity of the laboratory



HPV diagnostic companies response (i)

four companies provided a statement in response to a question about mitigation and plans to support and develop molecular microbiology testing during and after the COVID-19 era

all companies clearly expressed a commitment to being on the "front line" to support the emergency across the world for high volumes of COVID-19 testing

all companies described substantial growth in diagnostics activity and business; two companies described tremendous growth in sales of around 100%, mainly driven by a continued unprecedented global demand for their portfolio of lab-based COVID-19 tests

all companies described sizable increases in manufacturing capacity (including of emerging products) and investment in new supply chains and molecular and core laboratory solutions

HPV diagnostic companies response (ii)

one company reported that pre-pandemic they launched, on average, five microbiology assays per year, whereas in 2021 they anticipate a launch of 17 assays, including molecular, antigen, and serology assays; doubling of PCR capacity reported in early 2021 and anticipated tripling of PCR capacity by the end of 2021

one company described a significant increase in manufacturing capacity - adding 60 new manufacturing lines for consumables, with 17 new locations, and 20 new manufacturing lines for reagents, along with four major facility expansions as well as one new manufacturing space for instruments

statement that the increase in manufacturing capacity dispersed across the world should help create a regionally responsive supply of core reagents and consumables

HPV diagnostic companies response (iii)

there was an acknowledgment that recent scale up and developments (and the structural "shifts" within the companies required to deliver these) are likely to have positive consequences for molecular diagnostics in general terms

two companies specifically referred to opportunities for the use of platforms installed a priori for COVID-19 testing to support HPV testing in time

two companies stated that with multimillion euro investment in manufacturing facilities they will safeguard the European supply not only for SARS-CoV-2 assays; this will also safeguard the manufacture of their other molecular diagnostic assays, including HPV assays

Caveats and limitations to the survey and approach

although the number of responses was somewhat limited, they represented a global sample, covering all continents

it is also possible that we received a disproportionate response from laboratories that had experienced issues or challenges, whereas laboratories that were unaffected may have felt less of an impulse to respond

given the nature of the dissemination, we accept that the analysis is largely descriptive, but we nevertheless hope that it highlights and facilitates further discussion on what is an important issue

due to the study design, it was not possible to identify differences between the first and second pandemic waves concerning the impact of the COVID-19 pandemic on HPV-based testing


In the midst of every crisis,
lies great opportunity.

First opportunity

we need accurate and rapid low-cost portable instruments and tests using low-complex, low-cost chemistry

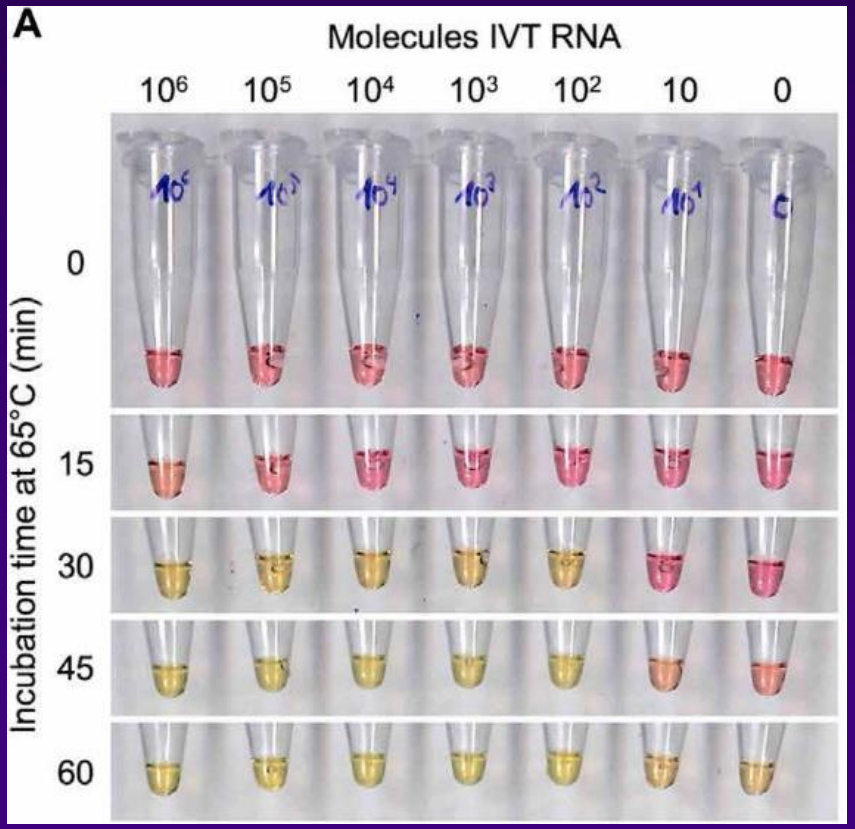
target is to have tests for price less of 1 EUR for HPV screening

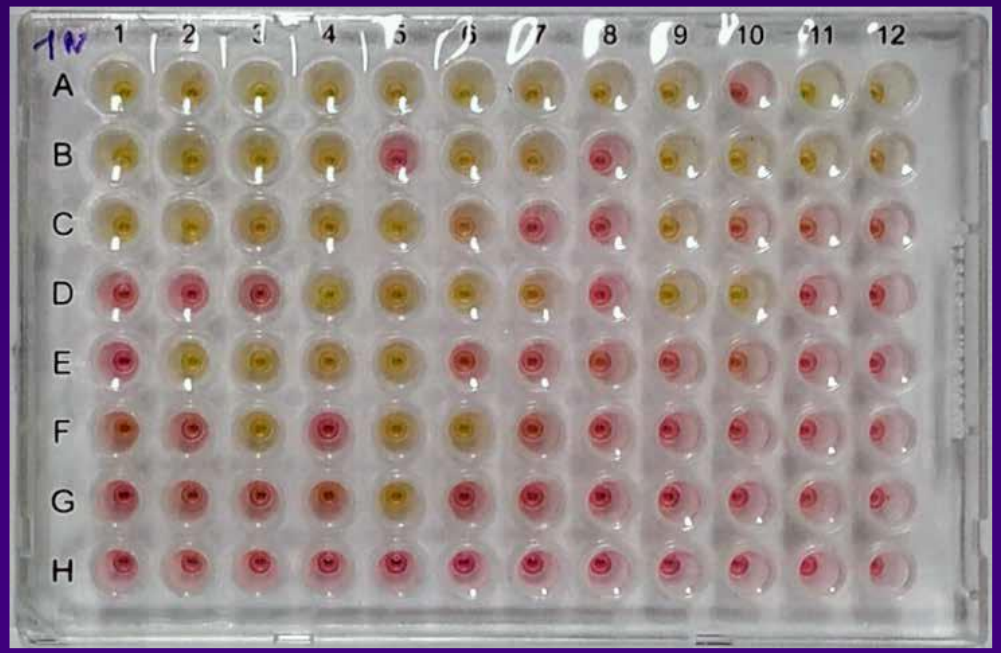
general innovation around molecular COVID-19 testing tools and recycling of neglected technologies e.g. microfluidic devices, different isothermal amplification technologies, CRISPR-based technology may be converted in the near future to affordable low-cost assays for HPV, with potential applicability in point-of-care and field settings in low income countries, but these require coordinated efforts of governmental agencies and manufacturers

A colorimetric RT-LAMP assay and LAMP-sequencing for detecting SARS-CoV-2 RNA in clinical samples

Viet Loan Dao Thi[1,2]*, Konrad Herbst[3†], Kathleen Boerner[2,4†], Matthias Meurer[3†], Lukas PM Kremer[3,5,6], Daniel Kirrmaier[3,5], Andrew Freistaedter[1,2], Dimitrios Papagiannidis[3], Carla Galmozzi[3,6], Megan L. Stanifer[2], Steeve Boulant[2,5], Steffen Klein[1,2], Petr Chlanda[1,2], Dina Khalid[2], Isabel Barreto Miranda[2], Paul Schnitzler[2], Hans-Georg Kräusslich[2,4], Michael Knop[3,5,6]*, Simon Anders[3]*

Sci Transl Med 2020;12:eabc7075





CRISPR-Cas – based diagnostic assays

The Nobel Prize in Chemistry 2020

© Nobel Media. Ill. Niklas Elmehed.

Emmanuelle Charpentier

Prize share: 1/2

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Jennifer A. Doudna

Prize share: 1/2

The Nobel Prize in Chemistry 2020 was awarded jointly to Emmanuelle Charpentier and Jennifer A. Doudna "for the development of a method for genome editing."

Electric field-driven microfluidics for rapid CRISPR-based diagnostics and its application to detection of SARS-CoV-2

www.pnas.org/cgi/doi/10.1073/pnas.2010254117

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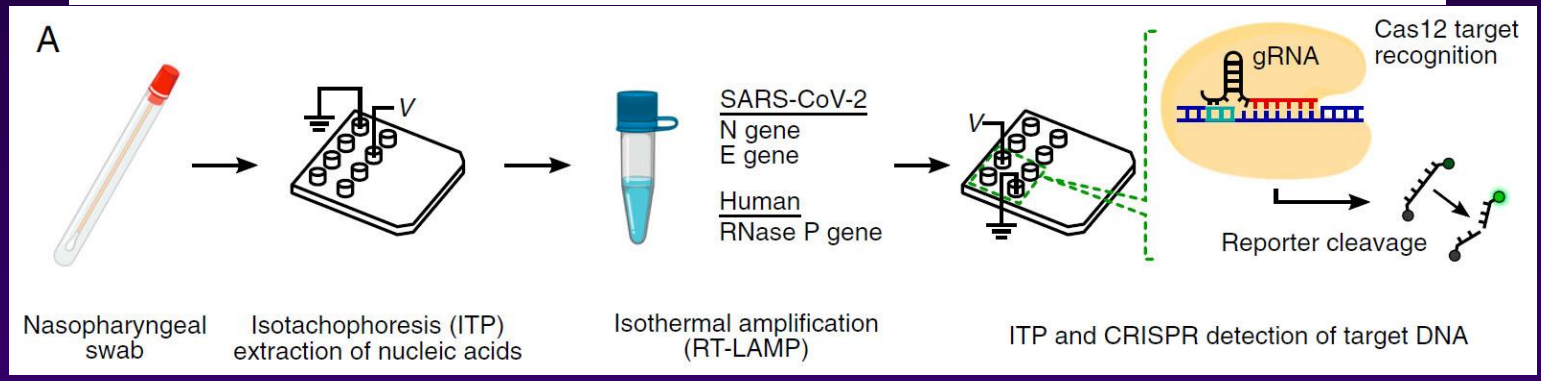
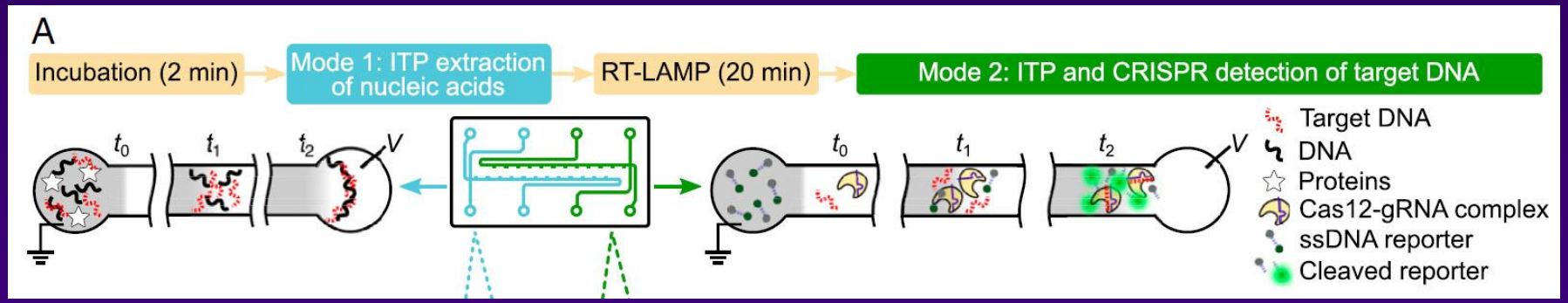
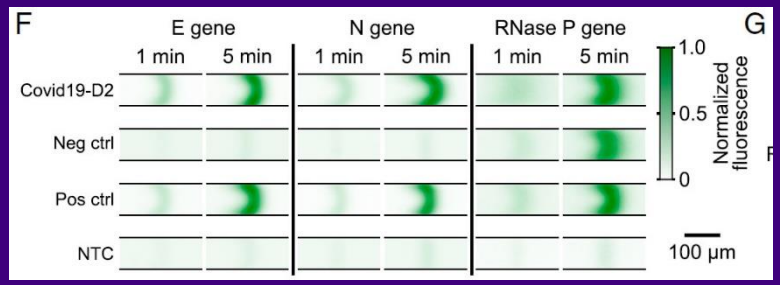






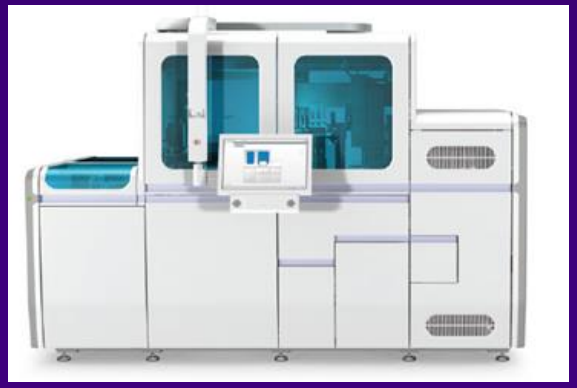
Total assay time: 35 min

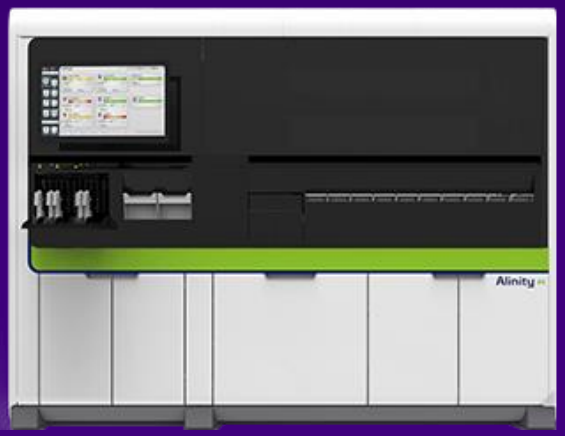
Plastic chips could be produced through the injection molding process for about $4 each.

Second opportunity

fully integrated, high-throughput, automated sample-to-result molecular analyzers installed initially for COVID-19 testing are likely to experience redundancy in the future; one that could be successfully occupied by large scale HPV testing needed to cope with cervical cancer elimination efforts

some diagnostic companies referred specifically to opportunities for the use of platforms installed a-priori for COVID-19 testing to support HPV testing in time





Third opportunity

while the laboratory workforce may currently be a limiting factor due to unprecedented COVID-19 testing requirements, the speed of recruitment and/or cross training of staff to support the organization and delivery of COVID-19 testing will ensure a future, larger cohort of trained laboratory personnel in virtually all countries in the world (of various grades of seniority and experience) who will have skills that are highly transferable to general molecular systems, including HPV

Conclusion remarks

COVID-19 pandemic is likely to lead to a temporary delay in reaching the cervical cancer elimination targets, with the potential to catch up through repurposing of equipment, infrastructure, and human resources from COVID-19 testing

it is our shared responsibility to make sure that the targets are eventually reached, to remain alert to the new opportunities that have arisen from the COVID-19 pandemic, and to ensure they are smoothly implemented into the cervical cancer elimination strategy as well as in other fields of medicine

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Abstract

Introduction: The World Health Organization elimination goal for cervical cancer relies on screening 70% of women at ages 35 and 45, preferentially through molecular HPV testing. The SARS-CoV-2 pandemic has led to an unprecedented demand for molecular tests and platforms. Our objective was to gain insight into the impact of SARS-CoV-2 on the actual or anticipated shortage of tests, equipment, consumables, and staff required to deliver molecular HPV laboratory services and to consider the implications for the sustainability and development of cervical screening programs.

Methods: A 19-item online questionnaire was created and made available online between December 2020 and February 2021. Five companies with clinically validated HPV and SARS-CoV-2 tests in their portfolios were invited to provide a statement on the volumes of molecular COVID-19 tests produced, relevant changes to manufacturing capacity, and their current and post-pandemic strategy for HPV tests.

Results: We received responses from 57 laboratories representing 30 countries and six continents. Among these, 74% reported experiencing a supply shortage, 54% reported a shortage of personnel, and 33% reported delays in ordering equipment. Three companies described expansion of manufacturing lines, investment in diagnostic infrastructure, and scale-up of manufacturing capacity. Two companies specifically referred to opportunities for the use of platforms for COVID-19 testing to support HPV testing in time.

Conclusions: The demand for SARS-CoV-2 testing is competing with HPV testing, compounded by a shortage of staff. This represents a challenge for existing laboratory services and for settings keen to implement HPV-based screening. However, supply challenges may be addressed in time, given the significant investment in manufacturing capacity. In addition, innovation around molecular COVID-19 testing systems may result in solutions that address the shortage of rapid low-cost HPV testing systems for low-resource settings. Finally, because the demand for COVID-19 testing is likely to decrease, this may release both workforce and platform capacity for high-throughput HPV testing. The global health community should be alert to the opportunities around innovation and capacity if cervical cancer elimination goals are to be reached.

Keywords: molecular testing, COVID-19, human papillomavirus, HPV, cervical cancer screening

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