TRANSLATION

REPORT #1 CA-COVID-19-OMC on diagnostic tests

THE NEED TO CLARIFY THE EFFICIENCY OF COVID-19 DIAGNOSTIC TESTS AND ORDER THEIR PURCHASE AND USE BY THE NHS

Report 4/05/2020 from the Advisory Commission to the CGCOM (Spanish General Medical Council)

Executive summary and key proposals:

COVID-19 diagnostic tests are essential for health care and for public health. There is concern about the validity of existing tests, confusion about their validity and validation, and about the need of transparency so that all healthcare services and experts can share their knowledge and information, so that actions are effective and consistent in the entire National Health System, and professionals are correctly informed, and information is updated based on the evaluation of knowledge and technique.

For this purpose, we propose the Ministry of Health to create a NHS Technical Commission to optimize the acquisition and use of COVID-19 diagnostic tests. This expert commission, with a broad regional representation, should make it possible to face the current multiple and uncoordinated NHS purchasing systems, and allow the systematic sharing of information and experiences. It would also be a vehicle to inform about the problems of brands and lots reported to be ineffective in certain places, to investigate whether it is true, and to make decisions about their purchase and use in general.

As long as the ability to perform diagnostic tests does not broadly cover all health and public health needs, high priority groups should be identified:

1- Workers in healthcare settings, socio-sanitary residences, control and disinfection tasks (police, Emergency Military Unit, firemen) and home help services in potential contact with patients.

2- Suspected cases and their contacts.

3- Patients in hospitals, and residents of nursing homes and other social and healthcare centres.

4- Mobility of people towards environments of high vulnerability and low prevalence (provinces, rural areas, or socio-healthcare institutions).

The COVID-19 Advisory Commission of the Spanish General Medical Council (CGCOM) is a panel of experts from various professions, fields and specializations, which was created on April 21, 2020 to advise CGCOM on scientific, technical and organizational aspects of the pandemic, to suggest actions, and to draft technical reports to support CGCOM's public positions.

The CGCOM Advisory Commission for COVID-19 discussed the diagnostic tests available and necessary for the epidemiological and clinical approach to this pandemic. It is considered a key issue, because only with an accurate diagnosis through validated analytical tests is conceivable a reliable clinical and public health strategy.

Doctors and other health professionals observe with great concern the confusion and lack of information about the existing tests, their validity, their usefulness and their use. Although the scientific difficulties underlying a new health problem are understood, the maximum transparency of the information that exists and that becomes available would be highly beneficial.

The contributions of the experts and the contributions received in the Advisory Commission's Work and Discussion Forum make it possible to forward this **Report # 1** on diagnostic tests to the CGCOM Board, in order to formulate scientific, technical and professional criteria on the subject, and its eventual use in future CGCOM positions.

a) The validity problems of the diagnostic tests.

In this strategic input, scientific-technical aspects are combined with those of purchase and distribution. It is not only a qualitative but a quantitative problem: knowing what types of diagnostic tests, for what situations and with what characteristics of sensitivity, specificity, predictive values and appropriate indications for their use.

The CE marking does not currently provide any guarantee on the clinical use characteristics of the tests, unless accompanied by a declaration of conformity of Directive 98/79/EC (in vitro diagnostics medical devices) by the manufacturer; for this reason, tests carried out before or after their purchase are essential to evaluate the real effectiveness of these diagnostic technologies.

> *Information on: Guidelines on COVID-19 in vitro diagnostic tests and their performance. COMMUNICATION FROM THE COMMISSION: here:* https://ec.europa.eu/info/sites/info/files/testing_kits_communication.pdf

Tests, both serological and PCR, are approved by a process called self-certification according to which the only obligation is to notify the AEMPS (Spanish Agency for Medicines and Health Products) that a product is placed on the market with "CE mark". If an inspection is made, the manufacturer will have to make the technical dossier available to the Agency, where all the trials done to develop and validate the test must be recorded. Therefore, this procedure (and CE marking) doesn't guarantee that the test has been validated.

Unfortunately, the EU Regulation 2017/746 on *in vitro* diagnostic medical devices, with which the EU wanted to solve this problem of validating the product before selling it, is not yet mandatory (moratorium period until 2021). It will be mandatory in 2021.

> *Information about CE Marking here: https://europa.eu/youreurope/business/product-requirements/labels-markings/ce-marking/index_es.htm*

However, the use of this mark should be considered as an additional criterion in the selection of equipment and tests. The information about the sensitivity and specificity of the tests in the case of serologies should be provided weekly from the beginning of the infection instead of globally.

It is important, due to this lack of information, that the National Centre for Microbiology of the Carlos III Health Institute validates PCR tests before placing them on the market. In addition, acquisitions should be made with a technical report from laboratory specialists.

b) Problems related to the use of diagnostic tests.

Proper use of a test requires a good clinical and public health judgment. The test request must include the patient's situation, the date of onset of symptoms and the purpose of this request. For example, in the case of a healthy person, a negative PCR is enough. In the case of a patient with symptoms, a negative

PCR is not excluding, and it would be necessary to carry out a second determination accompanied by serology from one week after the onset of symptoms.

PCR tests have problems inherent to technique, which can alter their potential validity.

- Sample collection: through a swab of oropharyngeal mucosa. This collection procedure is often wrong and there is not enough genetic material in it. Training staff for sample collection is essential.
- Extraction of genetic material: the RNA extraction procedure is not simple, it is not usually automated (in addition, there is now a shortage of extraction kits on the market, which is why it is starting to be done manually). If, in addition, the sample collection process has not been ideal, we may have nothing to amplify in the PCR process. Standardization and verification of these procedures is a necessary measure.
- Time in which the sample is collected: it is not the same to carry out a PCR with a sample taken on day 1 of the infection than on day 8. The viral load is different. If there is little viral load, the PCR may be inconclusive. Collecting the date of the symptom's onset would be very important, both in these tests and in the serological tests.

Immunological tests are of several types: those performed in a laboratory (ELISA or chemiluminescence) are much more sensitive and specific than the so-called rapid tests (Point of Care Test), by immunochromatography, which would have the advantage of being done in 15 minutes and out of the laboratory. WHO does not recommend them for clinical decisions.

A SEIMC report clearly supports PCR tests, recommending antibody tests as a complement to the former and for special uses (selection of plasma donors).

> *Spanish Society of Infectious Diseases and Clinical Microbiology, April 27, 2020. https://seimc.org/contenidos/documentoscientificos/recomendaciones/seimc-rc-2020-Recomendaciones_uso_de_las_pruebas_de_deteccion_de_anticuerpos.pdf*

Quick tests have other problems (in addition to their lack of validation):

- It appears that some rapid tests are being done with proteins not specific enough for SARS-CoV-2, so they can be positive when IgG or IgM of other similar viruses are detected. There are also problems of low sensitivity (in some cases 40%), and about the time of the disease or convalescence in which they are done. Another problem occurs when the test has been validated for serum or whole blood, and is used in capillary blood.
- On the other hand, the number of tests that are coming onto the market both with CE marking (self-certification) and with the approval of the FDA (Food and Drug Administration of the United States) for "health emergency" is enormous.

To get an idea of the magnitude of the market for COVID-19 diagnostic tests, this site collects 139 products from among the most reliable on the market (with their approval information from regulatory bodies when it exists): https://www.360dx.com/coronavirus-test-tracker-launched-covid-19-tests

c) The need for intelligence and organization in the NHS to handle the challenge of diagnostic tests; The need for a NHS Technical Commission.

As there is a NHS multiple and uncoordinated purchasing function, different institutions and entities are acting without systematically sharing information and experiences. It is particularly important that information about ineffective brands and lots that may arise in certain places is circulated among all the NHS institutions, to investigate if it is true, and to make decisions about their acquisition and use

in general. This would facilitate the use of purchasing systems for the NHS for a series of validated commercial reagents with a maximum price, which would simplify contracting, would improve prices and guarantee qualities.

From a National Health System point of view, there should be some kind of authority (a **commission of experts with a broad regional base**) that actively shares all the information available on the diagnostic tests they know and have experienced.

These aspects are particularly important:

a) evidence discarded due to clear low quality;

b) clinical accuracy of tests in use;

c) preliminary results available in antibody tests in healthcare professionals that have not had symptoms since the beginning of the epidemic;

d) update on new tests and their quality.

The technical information generated would be transferred to the central and autonomous health authorities.

It should be noted that there is a report of April 24 on the interpretation of COVID-19 diagnostic tests, which can provide a reference to their indication, use and interpretation.

https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/INTERPRETACION_DE_LAS_PRUEBAS.pdf

d) Prevention of misuse in diagnostic resources for COVID-19.

In a public health crisis, the population vision and the general interest must prevail. Scarce resources, in this case diagnostic equipments, must be at the service of priority actions to identify and treat patients, and prevent the spread of the epidemic.

We suggest four groups of high priority when using these scarce diagnostic resources:

1- Workers in health centres, socio-sanitary residences, control and disinfection tasks (police, UME, firemen), and home help services that may be in contact with patients affected by COVID-19.

Argument: In addition to a predominance criterion of work safety, there would be another one of public utility: if a significant part of the spread of COVID-19 has occurred in contact with services and workers (nosocomial socio-sanitary infection), focus intervention at this node can be, in addition to fair, very effective.

2- Suspicious cases and their contacts.

Argument: Controlling the outbreak and preventing the re-outbreak will depend largely on effectively managing the use of the tests, so that the diagnostic effort is guided by clinical interaction.

3- In-patients (particularly long-stay ones), and residents of senior centres and other social and healthcare centres.

Argument: Research is directed towards the repositories of the most vulnerable people, and when cases may have more serious effects and spread more quickly.

4- Mobility of people towards environments of high vulnerability and low prevalence: between provinces or areas with different confinement transition phases, between urban and rural areas, or when visiting nursing homes.

Argument: It is about encapsulating the most vulnerable groups with intensified diagnostic measures.

Quite the opposite, and as long as the shortage prevails, the private use of diagnostic tests is not ethically or socially convenient, regardless of whether individuals or entities can finance it privately.

Their use in the workplace must be approached with due caution. Those responsible for companies and occupational risk prevention services must clearly prioritize adaptation measures for jobs, hygiene and disinfection. And they must know the current insufficiency and inability of the tests - particularly the serological that are sold to be used with a drop of blood such as POCT (Point of Care Test) - to ensure that a person with IGG+ antibodies is effectively immunized. This insufficiency should encourage employers to prioritize and take extreme measures of environmental hygiene and early identification of workers with symptoms, to implement specific control of suspected cases and their contacts.

Likewise, the durability of the immunity acquired by the convalescent is doubtful, and only the observation of the dynamics of the pandemic will be able to provide us with accurate information.

These technological restrictions nullify the usefulness of the so-called "immunological passports", regardless of the ethical and implementation debates that may arise.

It must be stressed that companies must prioritize the effective actions to avoid infection: promote personal hygiene, increase hygiene in workplaces, assess the specific risks of the activities, introduce changes in the organization and facilities, facilitate appropriate personal protection equipments and measures, identify particularly sensitive workers and actively collaborate in the study and management of their contacts.

There is a report on the website of the Ministry of Health of April 8, 2020, which can be particularly useful for the Occupational Risk Prevention Services. https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/PrevencionRRLL_COVID-19.pdf

And this other report with action criteria and the indication of diagnostic measures in companies may also be interesting. https://www.mscbs.gob.es/en/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/instruccionesPruebasDiagnosticasEmpresas.pdf