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Corowell is an easy to use, low-cost, and rapid medical device to screen for possible COVID-19 positive person

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Corowell: New simple App-combined smell test to screen patients for suspicion of COVID-19 infection

The WHO declared, on March 11, 2020, COVID-19 as a pandemic with the sustained risk of further global spread. Extensively studied for more than 1 year (around 93.500 papers), viral COVID-19 infection is first characterized by fever, cough, shortness of breathing, sore throat, unusual fatigue and myalgia[1]. COVID-19 has expanded rapidly since it was first identified and has been shown to have a wide spectrum of symptoms and severity. Incubation period is between 2 to 14 days with an average of 5.2 days[2], and contamination period, after appearance of the first symptoms, estimated to 8 days[3]. Some recent studies let suppose that patients, during the incubation period[4], are able to transmit the virus. Even more asymptomatic patients[5], estimated between 10-30% of cases[6], are potential transmitters of the disease. In other words, substantial undocumented infection facilitates the rapid dissemination of the virus which can be the source of up to 79% of the documented cases[7]. The only valid test to detect the presence of the virus is the reverse transcription-polymerase chain reaction (RT-PCR), even if its sensitivity varies with the specimen types[8]. Nevertheless, the main problem with RT-PCR is its expensive price. The second problem is its efficiency in mass testing with few positive results, most of the time under 10% of the tested persons. An urgent need exists to find a simpler and cheaper solution to diminish the number of RT-PCR in having a first line of selection of patients to avoid the practice of so many negative tests[9]. Cheaper and rapid antigen detection test became to be used as frontline testing for COVID-19 diagnosis, notably by symptomatic patients, but with lower performance (sensitivity) because it needs a higher viral load[10].

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After some anecdotal unpublished and published reports of anosmia related to COVID-19 emanating from different countries and otolaryngological societies, a new interest grew up with the specific study of olfactory dysfunction which conducted to the publication of around 690 specific papers (PubMed daily search, key words “Covid-19/coronavirus”, and “anosmia”, or “olfaction”. Anosmia has already been reported in the course of others coronavirus, but as a rare occurrence[11]. With COVID-19, the situation progressively became different. After some initial studies, the occurrence of olfaction dysfunction with COVID-19 is demonstrated to be frequent[12], respectively in various studies from 33%[13], 41%[14], 44.2%[15], 47%[16], 48.47%[17], 49.6%[18], 60.7%[19], 61%[20], 66.6%[21], 68%[22],70.1%[23], 70.2%[24], 72%[25], 74%[26], 74.9%[27], 79.2%[28], 79.7%[29], 83.9%[30], 85.6%[31], and 86%[32], of cases. Ethnicity also plays a role[33]: Caucasians seem to have three times

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higher prevalence than Asians[34], or Indians[35]. These ethnic differences render the interpretation of the results of some meta-analysis quite confuse[36]. Another problem is related to the combination of recent and older studies[37]. The most recent one gives a global result of 47.85%, increased to 72.1% if anosmia is objectively measured[38]. Another meta-analysis confirmed this number to be 77%[39]. Viral loads were poorly correlated with COVID-19 symptoms and outcome, excepted for dyspnea and anosmia, which were significantly associated with lower viral loads[40]. It is significantly more frequent amongst COVID-19 patients than influenza patients[41]. The sudden reduction of smell, especially if not associated with rhinitis symptoms and nasal obstruction, should be considered as highly suggestive of COVID-19 infection[42]. To notice, nasal obstruction could be frequent (49.5%[43] up to 67.8%[44]) in patients with a mild form of COVID-19 infection. The second step was the validation that olfactory dysfunction could be the initial symptom of the infection[45], which was documented between 26.6%[46], 33%[47] 38.3%[48], to 40%[49] of patients, notably by pauci-symptomatic ones[50], and in the young population[51], or sometimes the sole

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symptom[52], or even unnoticed[53]. In a case report of a reinfection, it is mentioned as the unique symptom[54]. The next step was the establishment that anosmia could be the initial indicator of the infection, including otherwise asymptomatic patients[55]. Even more, it became considered as a possible predictor for COVID-19 infection, with a better sensibility and specificity than fever[56]. Finally, smell testing might help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine[57]. Even more, because of its highly specificity as COVID-19 symptom[58], olfactory dysfunction has been shown to be the strongest predictor of COVID-19 positivity when compared to other symptoms in logistic regression analysis[59]. It could also be used as an indicator of the COVID-19 pandemic[60]. In another study, anosmia is considered, with fever and myalgia, as the strongest independent predictors of positive assays[61], even anosmia alone as the most discriminative symptom between seropositive (53%) and seronegative persons (4%)[62]. To notice, anosmia is more frequent in non-hospitalized COVID-19 patients than in hospitalized ones[63], letting suppose a milder form of disease[64].

With this new paradigm, smell tests began to be proposed and used in such patients. Three classical types of tests exist: questionnaires, quantitative tests, and olfactometry. The simplest and cheapest solutions are questionnaires which can be online, notably on the form of self-reported smartphone app[65]. One limitation is that self-reporting is not confirmed with objective testing[66], notably because of the low affective response and attention to odors[67], showing the importance to have an objective test[68]. The smell loss as a screening symptom was found to show

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Landersdorfer CB et al. Smell and test dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc* 2020;95(8):1621-1631.

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a high specificity and moderate sensitivity for the detection of COVID-19 infection[69]. In another study, data stress the necessity for an awareness of loss of smell as a cardinal symptom[70]. The development of the ODoR-19, a 1-10 scale to screen for recent smell loss, supports this affirmation[71]. In conclusion and as demonstrated in the greatest part of the most recent studies[72], smell testing is justified as a screening tool for COVID-19, and might be valuable for early diagnosis[73], notably when rapid screening is needed[74]. A recent study demonstrated a negative predictive value of 89.01%[75]; and three others that in case of recent anosmia, 91.18%[76], 93%[77], and 95%[78] of cases were COVID-19 positive. A Swedish study demonstrates a high odds ratio of 28.4 by seropositive COVID-19 persons[79]. Unfortunately, no simple and cheap solution to test smell function was proposed until now[80]. Some are in development in various places. Nevertheless, as time is progressing, many publications highlight the importance of such a test[81] and its cost efficiency, such as: "screening for olfactory dysfunction could be a high impact and cost-effective method for broad COVID-19 screening and surveillance."[82] Even more, it could reduce the reproduction number of 55%, thus better than most of the lockdown techniques[83]

We have developed Corowell, a simple and low-cost consumer qualitative smell testing system in association with an App-Questionnaire composed of six specific questions, usable in about one

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minute to screen a possible COVID-19 infected person. The test is presented on the form of a double paper credit card-size holder on which a code bare is printed. With the smartphone, the person scans the code which open the Corowell App, with first the smell test and eventually the six questions.

The first part of the test is a qualitative smell test, where the person needs to recognize a specific scent delivered by scratching on the respectively marked zone of the consumer. Actually, twelve random scent specimens are presented: orange, peppermint, coffee, vanilla, cinnamon, apple, pine, rose, lavender, cherry, chocolate and cloves. The person must select the right answer on the list presented in the App. If the response is inaccurate, the test is considered "failed".

The second part of the test is a questionnaire, proposed only if the first part is valid (accurate response).
Question 1 is related to the transmission time of COVID-19 which is accepted to be less than 8 days after the onset of the first symptoms: *"Have you been tested "positive" for COVID-19 in the last 10 days?"*
Question 2 is focused on the possible recent (non-protected) contact with infected persons and based on the fact that incubation period is limited to a maximum of 14 days: *"Have you been in contact with a suspected or infected person in the last two weeks?"*
Question 3 is associated with the possible presence of typical COVID-19 symptoms: *"Do you suffer from fever, cough, shortness of breath, sore throat, unusual fatigue, headache, or muscular pain?"*
Question 4 searches for the presence of an olfactory dysfunction: *"Did you have a recent smell disorder?"*
Question 5 corresponds to the ODoR-19 newly proposed scale olfactory test[84]: *"Rate your recent ability to smell on the following scale, 0 being no smell and 10 excellent smell."*

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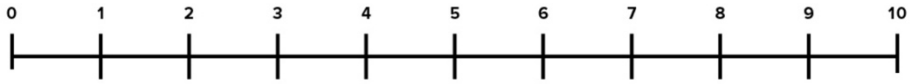

Question 6 corresponds to the confidence of the test: *"I have truthfully answered all questions."*

The App lists the possible answers. Except for question five with the scale between 0 to 10, all other questions have two possibilities of answer: yes or no. If one question is inaccurate (yes for questions 1 to 4, and no for question 6), or if the result of question 5 is below 4, the test is considered invalid. The complete test needs around 1 minute to be practiced.

A final validation, is given by the App, saying "PASS" (valid) or "FAIL" (invalid) test. If the answer is "FAIL", it means that the tested person has a supposed risk to be a COVID-19 holder, meaning a possible transmitter. This person must be further checked for the eventuality of the presence of Covid-19 infection. If the test is passed the index of suspicion is probably very low, and thus acceptable with the usual recommended protective measures (mask, cleaning and distancing). Corowell can be repeated as many times as necessary and used wherever a screening for COVID-19 is needed without any specific structure.

Of course, Corowell has some limitations and must be used with caution with already anosmic persons[85]. The incidence of olfactory dysfunction in the general population is a matter of discussion[86]. Most investigations identified increasing aging[87], and smoking habits in a dose-related manner[88], as important factors in terms of the occurrence of smell dysfunction. A difference exists between patients under 60 years of age, the incidence being around 5%[89], and over 60 years of age, incidence being more than 15%[90]. Some pathologies[91] can play a role, essentially in older age, especially Parkinson and Alzheimer[92], but also medications[93]. A recent study demonstrated a significant difference between the prevalence of anosmia among old black adults (22.3%) and old white adults (10.4%)[94]. Even more recent COVID-19 infected persons can have a persistent anosmia many weeks after the onset of the disease. In such kind of situation, other methods of screening need to be used (official medical certificate, recent negative PCR, etc.)

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A systematic and voluntary daily screening study of around 50 employees at the Clinique de Montchoisi (Swiss Medical Network), Lausanne, Switzerland, a surgical structure without COVID-19 patients, was initiated: 384 Corowell Tests were performed during 3 consecutive days (11-13 November) and again 5 consecutive days (16-20 November). All users were mostly tested every day, until "failing" the Corowell Test. 367 tests passed (95.3%). 17 tests failed (4.7%), of which 10 PCR were executed after discussion with the clinical supervisor, and three (3) of the ten (10) were found PCR-positive. All three positive PCR were identified by the Corowell Test based responses to the questionnaire, two because a recent contact and one because of symptoms related to COVID-19. All the three had at least one Corowell test before, which was initially "passed". The one who failed with onset of new symptoms, also did a Corowell test one day later, test which "failed", because the person then did not recognize the scent. One user suffering of chronic rhino-sinusitis directly presented with a recent medical certificate concerning her anosmia. Regardless, she was tested with Corowell, and as to be expected, "failed" the test, and the subsequent PCR was negative. Another user, who did not recognize the scent, subsequently PCR was negative. However, "passed" the Corowell Test on the following day (initial "fail" likely stress-related). During the above reported test days, three employees were absent: Two people had previously tested COVID-19 positive (PCR) within less than 10 days, and one had reported COVID-19 symptoms but did have a negative PCR. The Corowell Test would have failed all three, if they would have presented to take the test.

The identification of 3 infected users (6%) out of the group of around 50 random, but otherwise homogenous and not isolated from normal life, is highly encouraging. Another user who failed the objective "scent" test was identified with a positive PCR (on 30 November). It was demonstrated a high efficiency and complementarity of the two parts of the Corowell test, such as differently demonstrated in a recent proposed scoring predictive system[95]. In addition, the test and re-test repeatability of results, on a 24 h schedule, is also very pertinent. That bears an enormous potential for the Corowell Test in view of continued assessments, evolution, i.e. changes of results and fast response to a possible failing of a subsequent test, in order to break infection chains and perform targeted in-Vitro Testing, based on Corowell Screening results.

Interestingly, the clinical staff discussed, due to the Corowell study, an increased awareness regarding the pertinence of anosmia and its possible importance in COVID-19 pandemic.

Limitations to this study are related to the fact that the tested people were all employees of a healthcare structure and therefore nobody above 65 years of age was tested. Some elderly users over 65 years, or users that may be already suffering from anosmia, should have a vested interest to obtain / provide an alternative medical certificate, and thus avoid discrimination that may be caused by this test.

The concept, as Corowell promotes, of using anosmia as a key COVID-19 symptom associated to other symptoms is similar to the development of clinical scoring system, such as the one used in Brazil, even to replace PCR when the score was sufficiently high to predict the presence of COVID-19 infection[96].

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