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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 105.250 papers), viral COVID-19 infection is first characterized by fever, cough, shortness of breathing, sore throat, unusual fatigue and myalgia¹. 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 days², and contamination period, after appearance of the first symptoms, estimated to 8 days³. Some recent studies let suppose that patients, during the incubation period⁴, are able to transmit the virus. Even more asymptomatic patients⁵, estimated between 10-30% of cases⁶, 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 cases⁷. The only valid test to detect the presence of the virus is the reverse transcription-polymerase chain reaction (RT-PCR), usually associated with a nasopharyngeal swab, even if its sensitivity varies with the specimen types⁸, and seems more specific if anosmia is present⁹. Nevertheless, the main problems with RT-PCR are its expensive price, the need of trained healthcare professionals, and a specific and protected structure to practice the swab. Another 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 tests¹⁰. Cheaper and rapid antigen detection test became to be used as frontline testing for COVID-19 diagnosis, notably by symptomatic patients, but with lower

¹ Guan WJ, Ni ZY, Hu H et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708-1720.

² Shi J, Sun J, Hu Y. Enteric involvement of SARS-CoV2: implications for the COVID-19 management, transmission, and infection control. *Virulence* 2020;11(1):941-944.

³ Li Q, Guan X, Wu P et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382(13):1199-1207.

⁴ Yu P, Zhu J, Zhang Z et al. A familial cluster of infection associated with the 2019 novel coronavirus indicating possible person-to-person transmission during the incubation period. *J Infect Dis* 2020;221(11):1757-1761.

⁵ Rothe C, Schunk M, Sothmann P et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med* 2020;382:970-971. Bai Y, Yao L, Wei T et al. Presumed asymptomatic carrier transmission of COVID-19. *JAMA* 2020;323(14):1406-1407.

⁶ Yu C, Zhou M, Liu Y et al. Characteristics of asymptomatic COVID-19 infection and progression: A multicenter, retrospective study. *Virulence* 2020;11(1):1006-1014.

⁷ Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). *Science* 2020;368(6490):489-493.

⁸ Pokhrel P, Hu C, Mao H. Detecting the coronavirus (COVID-19). *ACS Sens* 2020 Jul 17:acssensors.0c01153. doi: 10.1021/acssensors.0c01153. Zitek T. The Appropriate Use of Testing for COVID-19. *West J Emerg Med* 2020;21(3):470-472. Fang Y, Zhang H, Xie J, Lin M, Ying L, Pang P, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology* 2020;296(2):E116-E117. Kanne JP, Little BP, Chung JH, Elicker BM, Ketani LH. Essentials for Radiologists on COVID-19: An Update—Radiology Scientific Expert Panel. *Radiology* 2020;296(2):E113-E114. Peros G, Gronki F, Molitor N et al. Organizing a COVID-19 triage unit: a Swiss perspective. *Emerg Microbes Infect* 2020;9(1):1506-1513.

⁹ Islek A, Balci MK. Analysis of factors causing false-negative real-time polymerase chain reaction results in oropharyngeal and nasopharyngeal swabs of patients with COVID-19. *Ear Nose Throat J* 2021 Feb 19:145561321996621. doi: 10.1177/0145561321996621.

¹⁰ Isikbay M, Henry TS, Frank JA et al. When to rule out COVID-19: How many negative RT-PCR tests are needed? *Respir Med Case Rep* 2020 Aug 18: 101192. doi:10.1016/j.rmcr.2020.101192.

performance (sensitivity) because it needs a higher viral load¹¹. Specimen are taken from nasopharyngeal or oropharyngeal secretions, or saliva.

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 720 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 occurrence¹². With COVID-19, the situation progressively became different. After some initial studies, the occurrence of olfaction dysfunction with COVID-19 is demonstrated to be frequent¹³, respectively in various studies from 33%¹⁴, 41%¹⁵, 44.2%¹⁶, 47%¹⁷, 48.47%¹⁸, 49.6%¹⁹, 60.7%²⁰, 61%²¹, 66.6%²², 68%²³, 70.1%²⁴, 70.2%²⁵, 72%²⁶, 74%²⁷, 74.9%²⁸, 79.2%²⁹, 79.7%³⁰, 83.9%³¹, 85.6%³², and 86%³³, of cases. Ethnicity also plays a role³⁴: Caucasians seem to have three times

¹¹ Scohy A et al. Low performance of rapid antigen detection test as frontline testing for COVID-19 diagnosis. *J Clin Virol* 2020. PMID:32485618.

¹² Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope* 2020;130(7):1787.

¹³ Sayin I, Yasar KK, Yazici ZM. Taste and smell impairment in COVID-19: An AAO-HNS anosmia reporting tool-based comparative study. *Otolaryngol Head Neck Surg* 2020 Jun 9:194599820931820. doi: 10.1177/0194599820931820. Lechien JR, Hopkins C, Saussez S. Sniffing out the evidence; It's now time for public health bodies recognize the link between COVID-19 and smell and taste disturbance. *Rhinology* 2020 Aug 1;58(4):402-403. doi: 10.4193/Rhin20.159. Sedaghat AR, Gengler I, Speth MM. Olfactory dysfunction: A highly prevalent symptom of COVID-19 with public health significance. *Otolaryngol Head Neck Surg* 2020;163(1):12-15.

¹⁴ Brendish NJ, Poole S, Naidu VV et al. Clinical characteristics, symptoms and outcomes of 1054 adults presenting to hospital with suspected COVID-19: a comparison of patients with and without SARS-CoV-2 infection. *J Infect* 2020. PMID: 32998038.

¹⁵ Agyeman AA, Chin KL, 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.

¹⁶ Avci H, Karabulut B, Farasoglu A et al. Relationship between anosmia and hospitalization in patients with coronavirus disease 2019: An otolaryngological perspective. *J Laryngol Otol* 2020;134:710-716.

¹⁷ Avci H, Karabulut B, Farasoglu A et al. Relation between anosmia and hospitalization in patients with coronavirus disease 2019: an otolaryngological perspective. *J Laryngol Otol* 2020 Aug 25:1-14. doi: 10.1017/S0022215120001851.

¹⁸ Ibekwe TS, Fasunla AJ, Orimadegun AE. Systematic review and meta-analysis of smell and taste disorders in COVID-19. *OTO Open* Sep 11;4(3):2473974X20957975. doi: 10.1177/2473974X20957975.

¹⁹ Lehrich BM, Goshtasbi K, Raad AR et al. Aggregate prevalence of chemosensory and sinonasal dysfunction in SARS-CoV-2 and related coronavirus. *Otolaryngol Head Neck Surg* 2020;163(1):156-161.

²⁰ Da Costa KVT, Carnauba ATL, Rocha KW et al. Olfactory and taste disorders in COVID-19: a systematic review. *Braz J Otorhinolaryngol* 2020 Jun 9;S1808-8694(20)30066-5. doi: 10.1016/j.bjorl.2020.05.008.

²¹ Hajikhani B, Calcagno T, Nasiri MJ et al. Olfactory and gustatory dysfunction in COVID-19 patients: A meta-analysis study. *Physiol Res* 2020 Sep;8(18):e14578. doi: 10.14814/phy2.14578.

²² Samimi Ardestani SH, Ardehali MM, Anari MR, et al. The coronavirus disease 2019: the prevalence, prognosis, and recovery from olfactory dysfunction (OD). *Acta Otolaryngol* 2020. PMID: 33176530.

²³ Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol* 2020;277(8):2251-2261.

²⁴ Rojas Lechuga MJ, Izquierdo-Dominguez A, Chiesa-Estomba C et al. Chemosensory dysfunction in COVID-19 out-patients. *Eur Arch Otorhinolaryngol* 2020 Aug 25;1-8. doi: 10.1007/s00405-020-06266-3.

²⁵ Lechien JR, Chiesa-Estomba CM, Place S et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020;288(3):335-344.

²⁶ Yan CH, Faraji F, Prajapati DP et al. Self-reported olfactory loss associated with outpatient clinical course in Covid-19. *Int Forum Allergy Rhinol* 2020;10(7):821-831.

²⁷ Horvath L, Lim JWJ, Taylor JW, et al. Smelle and taste loss in COVID-19 patients: assessment outcomes in a Victorian population. *Acta Otolaryngol* 2020 Dec 12;1-5. doi: 10.1080/00016489.2020.1855366.

²⁸ Samaranayake LP, Fakhruddin KS, Panduwawala C. Sudden onset, acute loss of taste and smell in coronavirus disease 2019(COVID-19): a systematic review. *Acta Odontol Scand* 2020;78(6):467-473.

²⁹ Ninchritz-Becerra E, Soriano-REixach MM, Mayo-Yanez M et al. Subjective evaluation of smell and taste dysfunction in patients with mild COVID-19 in Spain. *Med Clin (Barc)* 2020 Sep 25;S0025-7753(20)30666-7.

³⁰ Parma V, Ohla K, Valduizen MG et al. More than smell – COVID-19 is associated with severe impairment of smell, taste, and chemesthesis. *Chem Senses* 2020 June 20;bjaa041.

³¹ Baron-Sanchez J, Santiago C, Goizueta-San Martin G et al. Afectacion del sentido del olfato y el gusto en la enfermedad leve por coronavirus (COVID-19) en pacientes espanoles. *Neurologia* 2020. PMID: 32900532.

³² Maechler F, Gertler M, Hermes J et al. Epidemiological and clinical characteristics of SARS-CoV-2 infections at a testing site in Berlin, Germany, March and April 2020 – A cross-sectional study. *Clin Microbiol Infect* 2020 Aug 19; S1198-743X(20)30500-0. doi: 10.1016/j.cmi.2020.08.017.

³³ Yan CH, Faraji F, Prajapati DP et al. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol* 2020;10(7):806-813.

³⁴ Butowt R, Bilinska K, von Bartheld CS. Chemosensory dysfunction in COVID-19: Integration of genetic and epidemiological data points to D614G spike protein variant as a contributing factor. *ACS Chem Neurosci* 2020. PMID: 32997488.

higher prevalence than Asians³⁵, or Indians³⁶. These ethnic differences render the interpretation of the results of some meta-analysis quite confuse³⁷. Another problem is related to the combination of recent and older studies³⁸. The most recent one gives a global result of 47.85%, increased to 72.1% if anosmia is objectively measured³⁹. Another meta-analysis confirmed this number to be 77%⁴⁰. Nevertheless, few other studies hardly discuss these results⁴¹. The apparition of virus mutations could modify the incidence of anosmia, but no study demonstrates this fact until now. Viral loads were poorly correlated with COVID-19 symptoms and outcome, excepted for dyspnea and anosmia, which were significantly associated with lower viral loads⁴². It is significantly more frequent amongst COVID-19 patients than influenza patients⁴³. The sudden reduction of smell, especially if not associated with rhinitis symptoms and nasal obstruction, should be considered as highly suggestive of COVID-19 infection⁴⁴. To notice, nasal obstruction could be frequent (49.5%⁴⁵ up to 67.8%⁴⁶) 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 infection⁴⁷, which was documented between 26.6%⁴⁸, 33%⁴⁹, 38.3%⁵⁰, to 40%⁵¹ of patients, notably by pauci-

³⁵ Von Bartheld CS, Hagen MM, Butowt R. Prevalence of chemosensory dysfunction in COVID-19 patients: A systematic review and meta-analysis reveals significant ethnic differences. *ACS Chem Neurosci* 2020; Sep 17. doi: 10.1021/acscchemneuro.0c00460. Seo MY, Seok H, Hwang SJ et al. Trend of olfactory and gustatory dysfunction in COVID-19 patients in a quarantine facility. *J Korean Med Sci* 2020 Oct 26;35(41):e375. doi: 10.3346/jkms.2020.35.e375. Tham AC, Thein TI, Lee CS et al. Olfactory taste disorder as a presenting symptom of COVID-19: a large single-center Singapore study. *Eur Arch Otorhinolaryngol* 2020 Nov 7. doi: 10.1007/s00405-020-06455-0. Song J, Deng YK, Wang H, et al. Self-reported taste and smell disorders in patients with COVID-19: distinct features in China. *Curr Med Sci* Feb;41(1):14-23. doi: 10.1007/s11596-021-2312-7.

³⁶ Mishra P, Gowda V, Dixit S et al. Prevalence of new onset anosmia in COVID-19 patients: Is the trend different between European and Indian population? *Indian J Otolaryngol Head Neck Surg* 2020 Jul 21;1-4. Panda S, Mohamed A, Sikka K et al. Otolaryngologic manifestation and long-term outcome in mild COVID-19: Experience from a tertiary care centre in India. *Indian J Otolaryngol Head Neck Surg* 2020 PMID: 33078125. Sahoo PR, Sahu M, Surapenei PS, et al. Evolution of olfactory and gustatory dysfunctions in COVID-19 patients in India. *Eur Arch Otorhinolaryngol* 2021 Jan 3. doi: 10.1007/s00405-020-06563-x

³⁷ Tong JY, Wong A, Zhu D et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2020 Jul;163(1):3-11. Mair M, Singhavi H, PAi A et al. A meta-analysis of 76 studies with presenting symptoms and laboratory tests of COVID-19 patients. *Laryngoscope* 2020 Oct 17. doi: 10.1002/lary.29207.

³⁸ Aziz M, Goyal H, Hagbin H, et al. The association of "loss of smell" to COVID-19: A systematic review and meta-analysis. *Am J Med Sci* 2020 Nov 1: S0002-9629(20)30427-4.

³⁹ Saniasiaya J, Islam MA, Abdullah B. Prevalence of olfactory dysfunction in coronavirus disease 2019 (COVID-19): A meta-analysis of 27492 patients. *Laryngoscope* 2020 Nov 20. doi: 10.1002/lary.29286.

⁴⁰ Hannum ME, Ramirez VA, Lipson SJ, et al. Objective sensory testing methods reveal a higher prevalence of olfactory loss in COVID-19-positive patients compared to subjective methods: A systematic review and meta-analysis. *Chem Senses* 2020 Sep 29;bjaa064. doi: 10.1093/chemse/bjaa064.

⁴¹ Villerabel C, Makinson A, Jaussent A, et al. Diagnostic value of patient-reported and clinically tested olfactory dysfunction in a population screened for COVID-19. *JAMA Otolaryngol Head Neck Surg* 2021 Jan 7;e205074. doi: 10.1001/jamaoto.2020.5074.

⁴² Biguenet A, Bouillier K, Marty-Quinternet S et al. SARS-CoV-2 respiratory viral loads and association with clinical and biological features. *J Med Virol* 2020 Sep 5. doi: 10.1002/jmv.26489.

⁴³ Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *Eur J Neurol* 2020;10.1111/ene.14273. doi:10.1111/ene.14273

⁴⁴ Hopkins C, Vaira LA, De Riu G. Self-reporting olfactory loss in COVID-19: is it really a favorable prognostic factor? *Int Forum Allergy Rhinol* 2020 May 12: 10.1002/alr.22608.

⁴⁵ Speth MM, Singer-Cornelius T, Oberle M et al. Olfactory dysfunction and sinonasal symptomatology in COVID-19: Prevalence, severity, timing, and associated characteristics. *Otolaryngol Head Neck Surg* 2020;163(1): 114-120. doi: 10.1177/0194599820929185.

⁴⁶ Lechien JR, Chiesa-Estomba CM, Place S et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020;288(3):335-344.

⁴⁷ Karimi-Galougahi M, Raad N, Mikaniki N. Anosmia and the Need for COVID-19 Screening during the Pandemic. *Otolaryngol Head Neck Surg* 2020;163(1):96-97. Kang YJ, Cho JH, Lee MH et al. The diagnostic value of detecting sudden smell loss among asymptomatic COVID-19 patients in early stage: The possible early sign of COVID-19. *Auris Nasus Larynx* 2020;47(4):565-573.

⁴⁸ Kaye R, Chang CWD, Kazahaya K, Brereton J, Denny JC 3rd. COVID-19 Anosmia Reporting Tool: Initial Findings. *Otolaryngol Head Neck Surg* 2020;163(1):132-134.

⁴⁹ Karimi-Galougahi M, Naini AS, Ghorbani J et al. Emergence and evolution of olfactory and gustatory symptoms in patients with COVID-19 in the outpatient setting. *Indian J Otolaryngol Head Neck Surg* 2020 PMID: 33014751.

⁵⁰ Biadsee A, Baidsee A, Kassem F et al. Olfactory and oral manifestations of COVID-19: Sex-related symptoms – A potential pathway to early diagnosis. *Otolaryngol Head Neck Surg* 2020 Oct;163(4):722-728.

⁵¹ Ugurlu BN, Akdogan O, Yilmaz AY, et al. Quantitative evaluation and progress of olfactory dysfunction in COVID-19. *Eur Arch Otorhinolaryngol* 2021 Jan 1. doi: 10.1007/s00405-020-06516-4.

symptomatic ones⁵², and in the young population⁵³, or sometimes the sole symptom⁵⁴, or even unnoticed⁵⁵. In a case report of a reinfection, it is mentioned as the unique symptom⁵⁶. The next step was the establishment that anosmia could be the initial indicator of the infection, including otherwise asymptomatic patients⁵⁷. Even more, it became considered as a possible predictor for COVID-19 infection, with a better sensibility and specificity than fever⁵⁸. Finally, smell testing might help, in some cases, to identify COVID-19 patients in need of early treatment or quarantine⁵⁹. Even more, because of its highly specificity as COVID-19 symptom⁶⁰, olfactory dysfunction has been shown to be the strongest predictor of COVID-19 positivity when compared to other symptoms in logistic regression analysis⁶¹. It could also be used as an indicator of the COVID-19 pandemic⁶². In other studies, anosmia is considered, with fever and myalgia, as the strongest independent predictors of positive assays⁶³, even anosmia alone as the most discriminative symptom between seropositive (53%) and seronegative persons (4%)⁶⁴. To notice, anosmia is more frequent in non-hospitalized COVID-19 patients than in hospitalized ones⁶⁵, letting suppose a milder form of disease⁶⁶.

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 app⁶⁷. One limitation is that self-reporting is not confirmed with objective

⁵² Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. *Laryngoscope* 2020;130(7):1787. Lechien JR, Chiesa-Estombs CM, Varia LA, et al. Epidemiological, otolaryngological, olfactory and gustatory outcomes according to the severity of COVID-19: a study of 2579 patients. *Eur Arch Otorhinolaryngol* 2021 Jan 16 doi: 10.1007/s00405-020-06548-w.

⁵³ Maechler F, Gertler M, Hermes J et al. Epidemiological and clinical characteristics of SARS-CoV-2 infections at a testing site in Berlin, Germany, March and April 2020 – A cross-sectional study. *Clin Microbiol Infect* 2020 Aug 19; S1198-743X(20)30500-0. doi: 10.1016/j.cmi.2020.08.017. Paderno A, Schreiber A, Grammatica A et al. Smell and taste alterations in Covid-19: a cross sectional analysis of different cohorts. *Int Forum Allergy Rhinol* 2020 May 14: 10.1002/alar.22610. Agyeman AA, Chin KL, 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.

⁵⁴ Fantozzi PJ, Pampena E, Di Vanna D et al. Xerostomia, gustatory and olfactory dysfunctions in patients with COVID-19. *Am J Otolaryngol* 2020. PMID: 32977063.

⁵⁵ Hornuss D, Lange B, Schröter N et al. Anosmia in COVID-19 patients. *Clin Microbiol Infect* 2020;26(10):1426-1427.

⁵⁶ Jain A, Kaur J, Rai AK, et al. Anosmia: A clinical indicator of COVID-19 reinfection. *Ear Nose Throat J* 2020 Dec 9;145561320978169.

⁵⁷ Wagner T, Shweta F, Murugadoss K, et al. Augmented curation of clinical notes from a massive HER system reveals symptoms of impending COVID-19 diagnosis. *Elife*. 2020;9:e58227. Published 2020 Jul 7.

⁵⁸ Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent smell loss is the best predictor of COVID-19: a preregistered, cross-sectional study. *medRxiv* 2020 Jul 26:2020.07.22.20157263.

⁵⁹ Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020;10(8):944-950. Makaronidis J, Mok J, Bolagun N et al. Seroprevalence of SARS-CoV-2 antibodies in people with an acute loss in their sense of smell and/or taste in a community-based population in London, UK: an observational cohort study. *PLoS Med* 2020;17(10): e1003358.

⁶⁰ Makaronidis J, Mok J, Bolagun N et al. Seroprevalence of SARS-CoV-2 antibodies in people with an acute loss in their sense of smell and/or taste in a community-based population in London, UK: an observational cohort study. *PLoS Med* 2020;17(10): e1003358.

⁶¹ Rocke J, Hopkins C, Philpott C et al. Is loss of smell a diagnostic marker in COVID-19: A systematic review and meta-analysis. *Clin Otolaryngol* 2020 Aug 1: 10.1111/coa.13620. doi: 10.1111/coa.13620. Owsu M, Sylverken AA, Ankrah ST, et al. Epidemiological profile of SARS-CoV-2 among selected regions in Ghana: A cross-sectional retrospective study. *PLoS One* 2020 Dec 10;15(12):e0243711.

⁶² Pierron D, Pereda-Loth V, Mantel M et al. Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness. *Nat Comm* 2020 Oct 14;11(1):5152. doi: 10.1038/s41467-020-18963-y.

⁶³ Lan FY, Filler R, Mathew S et al. COVID-19 symptoms predictive of healthcare worker's SARS-CoV2 PCR results. *PLoS One* 2020;15(6): e0235460. Ebinger JE, Botwin GJ, Albert CM, et al. Seroprevalence of antibodies to SARS-CoV-2 in healthcare workers: a cross-sectional study. *BMJ Open* 2021 Feb 12;11(2):e043584. doi: 10.1136/bmjopen-2020-043584.

⁶⁴ Vos ERA, den Hartog G, Schepp RM, et al. Nationwide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave. *J Epidemiol Community Health* 2020 Nov 28;jech-2020-215678. doi: 10.1136/jech-2020-215678.

⁶⁵ Giorli A, Ferretti F, Biagini C et al. A literature systematic review with meta-analysis of symptoms prevalence in Covid-19: the relevance of olfactory symptoms in infection not requiring hospitalization. *Curr Treat Options Neurol* 2020;22(10):36.

⁶⁶ Sanli DET, Altundag A, Kandemirli SG et al. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. *Am J Otolaryngol* 2020 Oct 28;42(1):102796. doi: 10.1016/j.amjoto.2020.102796.

⁶⁷ Menni C, Valdes AM, Freidin MB et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med* 2020;26(7):1037-1040.

testing⁶⁸, notably because of the low affective response and attention to odors⁶⁹, showing the importance to have an objective test⁷⁰. The smell loss as a screening symptom was found to show a high specificity and moderate sensitivity for the detection of COVID-19 infection⁷¹. In another study, data stress the necessity for an awareness of loss of smell as a cardinal symptom⁷². The development of the ODoR-19, a 1-10 scale to screen for recent smell loss, supports this affirmation⁷³. A machine-learning approach utilizing this visual analog scale (VAS) reached an average accuracy of 80%, a sensitivity of 82% and a specificity of 78%⁷⁴. In conclusion and as demonstrated in the greatest part of the most recent studies⁷⁵, smell testing is justified as a screening tool for COVID-19, and might be valuable for early diagnosis⁷⁶, notably when rapid screening is needed⁷⁷. A recent study demonstrated a negative predictive value of 89.01%⁷⁸; and three others that in case of recent anosmia, 91.18%⁷⁹, 93%⁸⁰, 95%⁸¹, and 97%⁸² of cases were

⁶⁸ Lechien JR, Chiesa-Estomba CM, Place S et al. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020;288(3):335-344. Prajapati DP, Shahrivini B, MacDonald BV et al. Association of subjective olfactory dysfunction and 12-item odor identification testing in ambulatory COVID-19 patients. *Int Forum Allergy Rhinol* 2020. PMID: 32964657. Rajkumar I, Anand KH, Revathishree K et al. Contemporary analysis of olfactory dysfunction in mild to moderate covid 19 patients in a tertiary health care centre. *Indian J Otolaryngol Head Neck Surg* 2020. PMID: 33020732. Mazzatenta A, Neri G, D'Ardes D, et al. Smell and taste in severe COVID-19: Self-reported vs. testing. *Front Med (Lausanne)* 2020 Dec 2;7:589409.

⁶⁹ Wrzesniewski A, McCauley C, Rozin P. Odor and affect: Individual differences in the impact of odor on liking for places, things and people. *Chem Senses* 1999;26(6):713-721.

⁷⁰ Rodriguez S, Cao L, Rickenbacher GT et al. Innate immune signaling in the olfactory epithelium reduces odorant receptors levels: modeling transient smell loss in COVID-19 patients. *medRxiv* 2020 Jun 16;2020.06.14.20131128. doi: 10.1101/2020.06.14.20131128. Fucillo E, Saibene AM, Canevini MP et al. Olfactory disorders in coronavirus disease 2019 patients: a systematic literature review. *J Laryngol Otol* 2020 Sep 15:1-10. doi: 10.1017/S0022215120002005. Rouadi PW, Idriss SA, Bousquet J. Olfactory and taste dysfunctions in COVID-19. *Curr Opin Allergy Clin Immunol* 2021 Feb 3. doi: 10.1097/ACI.0000000000000735.

⁷¹ Printza A, Constantinidis. The role of self-reported smell and taste disorders in suspected COVID-19. *Eur Arch Otorhinolaryngol* 2020;277(9):2625-2630.

⁷² Zens M, Brammertz A, Herpich J et al. App-based tracking of self-reported COVID-19 symptoms. *J Med Internet Res* 2020 Jul 26. doi: 10.2196/21956.

⁷³ Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent smell loss is the best predictor of COVID-19: a preregistered, cross-sectional study. *medRxiv* 2020 Jul 26;2020.07.22.20157263.

⁷⁴ Callejon-Leblic MA, Moreno-Luna R, Del Cuvillo A, et al. Loss of smell and taste can accurately predict COVID-19 infection: A machine-learning approach. *J Clin Med* 2021 Feb 3;10(4):570. doi: 10.3390/jcm10040570.

⁷⁵ Lechien JR, Barillari MR, Jouffe L et al. Anosmia is a key symptom of COVID-19 infection and should be used as a diagnostic tool. *Ear Nose Throat J* 2020 May 21: 145561320925191. doi: 10.1177/0145561320925191. Boscolo-Rizzo P, Borsetto D, Hopkins C et al. Challenges in interpreting the diagnostic performance of symptoms to predict COVID-19 status: the case of anosmia. *Int Forum Allergy Rhinol* 2020 June25: 10.1002/alr.22650. doi: 10.1002/alr.22650. Borsetto D, Hopkins C, Philips V et al. Self-reported alteration of sense of smell or taste in patients with COVID-19: a systematic review and meta-analysis on 3563 patients. *Rhinology* 2020 Jul 6. doi: 10.4193/Rhin20.185. Boscolo-Rizzo P, Polesel J, Spinat G et al. Predominance of an altered sense of smell or taste among long-lasting symptoms in patients with mildly symptomatic COVID-19. *Rhinology* 2020 Jul 19. doi: 10.4193/Rhin20.263. Roland LT, Gurrola II JG, Loftus PA et al. Smell and taste symptom-based predictive model for COVID-19 diagnosis. *Int Forum Allergy Rhinol* 2020 Jul;10(7):832-838. doi: 10.1002/alr.22602. Lechien JR, Hopkins C, Saussez S. Letter to the editor about the Beltran-Corbellini et al. publication: 'Acute-onset smell and taste disorders in the context of Covid-19: a pilot multicenter PCR-based case-control study (Eur J Neurol 2020. Doi:10.1111/ene.14273.)' *Eur J Neurol* 2020 May 22 : 10.1111/ene.14357. Iravani B, Arshamian A, Ravia A et al. Relationship between odor intensity estimates and COVID-19 prevalence prediction in a Swedish population. *Chem Senses* 2020 May 22; bja0034. doi: 10.1093/chemse/bjaa034. Seden N, Yigit E, Yigit O et al. Objective evaluation of odor loss in COVID-19 and other suspected case. *Am J Otolaryngol* 2020 PMID: 33080550. Shah NN, Hussain RT, Mustafa H et al. Evaluation of olfactory acuity in patients with Coronavirus disease 2019 (COVID-19). *Indian J Otolaryngol Head Neck Surg* 2020 Oct 27:1-8. doi: 10.1007/s12070-020-02241-w.

⁷⁶ Abalo-Lojo JM, Pouso-Diz JM, Gonzalez F. Taste and smell dysfunction in COVID-19 patients. *Ann Otol Rhinol Laryngol* 2020;129(10):1041-1042. Pang KW, Chee J, Subramaniam S et al. Frequency and clinical utility of olfactory dysfunction in COVID-19: a systematic review and meta-analysis. *Curr Allergy Asthma Rep* 2020 Oct 13;20(12):76. doi: 10.1007/s11882-020-00972-y. Marchese-Ragona R, Restivo DA, De Corso E et al. Loss of smell in COVID-19 patients: a critical review with emphasis on the use of olfactory tests. *Acta Otorhinolaryngol Ital* 2020 Aug;40(4):241-247. doi: 10.14639/0392-100X-N0862. Qiu C, Cui C, Hautefort C, et al. Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: An international multicenter study. *Otolaryngol Head Neck Surg* 2020;163(4):714-721.

⁷⁷ Butowt R, von Bartheld CS. Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. *Neuroscientist* 2020 Sep 11:1073858420956905. doi: 10.1177/1073858420956905.

⁷⁸ Boudjema S, Finance J, Coulibaly F et al. Olfactory and gustative disorders for the diagnosis of COVID-19. *Travel Med Infect Dis* 2020 Sep 5: 101875. doi: 10.1016/j.tmaid.2020.101875.

⁷⁹ Baron-Sanchez J, Santiago C, Goizueta-San Martin G et al. Afectacion del sentido del olfato y el gusto en la enfermedad leve por coronavirus (COVID-19) en pacientes espanoles. *Neurologia* 2020. PMID: 32900532.

⁸⁰ Saussez S, Lechien JR, Hopkins C. Anosmia: an evolution of our understanding of its importance in COVID-19 and what questions remains to be answered. *Eur Arch Otorhinolaryngol* 2020 Sep 9. doi: 10.1007/s00405-020-06285-0.

⁸¹ Wells PM, Doores KJ, Couvreur S et al. Estimates of the rate of infection and asymptomatic COVID-19 disease in a population sample from SE England. *J Infect* 2020 Oct 14:S0163-4453(20)30653-8. doi: 10.1016/j.jinf.2020.10.011.

⁸² Karni N, Klein H, Asseo K, et al. Self-rated smell ability enablers highly specific predictors of COVID-19 status: a case-control study in Israel. *Open Forum Infect Dis* 2020 Dec 28;8(2):ofaa589. doi: 10.1093/ofid/ofaa589.

COVID-19 positive. A Swedish study demonstrates a high odds ratio of 28.4 by seropositive COVID-19 persons⁸³. Simple and cheap solution to test smell function began to be proposed⁸⁴. Some are in development in various places. Nevertheless, as time is progressing, many publications highlight the importance of such a test⁸⁵ 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.”⁸⁶ Even more, it could reduce the reproduction number of 55%, thus better than most of the lockdown techniques⁸⁷.

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 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”.

⁸³ Rudberg AS, Havervall S, Manberg A et al. SARS-CoV-2 exposure, symptoms and seroprevalence in healthcare workers in Sweden. *Nat Comm* 2020 Oct 8;11(1):5064. doi: 10.1038/s41467-020-18848-0.

⁸⁴ Zhu H, Zhang H, Ni S et al. The vision of point-of-care PCR tests for the COVID-19 pandemic and beyond. *Trends Analyt Chem* 2020;130:115984. Bagnasco D, Passalacqua G, Braido F, et al. Quick olfactory Sniffin’ Sticks test (Q-tests) for the detection of smell disorders in COVID-19 patients. *World Allergy Organ J* 2021 Jan;14(1):100497. doi: 10.1016/j.waojou.2020.100497.

⁸⁵ Bhattacharjee AS, Joshi SV, Naik S, et al. Quantitative assessment of olfactory dysfunction accurately detects asymptomatic COVID-19 carriers. *EClinicalMedicine* 2020 Nov;28:100575.

⁸⁶ Larremore DB, Toomre D, Parker R. Modeling the effectiveness of olfactory testing to limit SARS-2-CoV transmission. *medRxiv* 2020 Dec 2 doi.org/10.1101/2020.11.30.20241174

⁸⁷ Li Y, Campbell H, Kulkarni D, et al. The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number R_t of SARS-CoV-2: a modelling study across 131 countries. *Lancet Inf Dis* 2020; Oct 22 doi.org/10.1016/S1473-3099(20)30785-4

The second part of the test is a questionnaire related to COVID-19 classical presentation and anosmia.

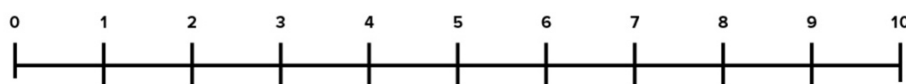
Question 1 is related to the transmission time of COVID-19 which is accepted to be less than 8 days after the onset of the first symptoms: *“Have you been tested “positive” for COVID-19 in the last 10 days?”*

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 test⁸⁸: *“Rate your recent ability to smell on the following scale, 0 being no smell and 10 excellent smell.”*



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 persons⁸⁹. The incidence of olfactory dysfunction in the general population is a matter of discussion⁹⁰. Most investigations identified increasing aging⁹¹, and smoking habits in a dose-related manner⁹², as important factors in terms of the occurrence of smell dysfunction. A

⁸⁸ Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent smell loss is the best predictor of COVID-19: a preregistered, cross-sectional study. *medRxiv* 2020 Jul 26:2020.07.22.20157263.

⁸⁹ Rebolz H, Braun RJ, Ladage D et al. Loss of olfactory function-early indicator for Covid-19, other viral infections and neurodegenerative disorders. *Front Neurol* 2020 Oct 26;11:569333. doi: 10.3389/fneur.2020.569333. eCollection 2020. Hopkins C, Smith B. Widespread smell testing for COVID-19 has limited application. *Lancet* 2020 Oct;163(4):722-728. doi: 10.1177/0194599820934380. Menni C, Sudre CH, Steves CJ et al. Widespread smell testing for COVID-19 has limited application – Authors’ repli. *Lancet* 2020 Nov 3;S0140-6736(20)32316-3. doi: 10.1016/S0140-6736(20)32316-3.

⁹⁰ Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *Laryngoscope* 2004;114(10):1764-1769.

⁹¹ Doty RL, Shaman P, Applebaum SL et al. Smell identification ability: changes with age. *Science* 1984;226(4681):1441-1443. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997;278(16):1357-1362. Oleszkiewicz A, Hummel T. Whose nose does not know? Demographical characterization of people unaware of anosmia. *Eur Arch Otorhinolaryngol* 2019;276:1849-1852.

⁹² Fryre RE, Schwartz BS, Doty RL. Dose-related effects of cigarette smoking on olfactory function. *JAMA* 1990;263(9):1233-1236.

difference exists between patients under 60 years of age, the incidence being around 5%⁹³, and over 60 years of age, incidence being more than 15%⁹⁴. Some pathologies⁹⁵ can play a role, essentially in older age, especially Parkinson and Alzheimer⁹⁶, but also medications⁹⁷. A recent study demonstrated a significant difference between the prevalence of anosmia among old black adults (22.3%) and old white adults (10.4%)⁹⁸. Even more recent COVID-19 infected persons can have a persistent anosmia many weeks after the onset of the disease⁹⁹. In such kind of situation, other methods of screening need to be used (official medical certificate, recent negative PCR, etc.) Another limitation is the presence of known COVID-19 symptoms before the test, because, all these persons will fail Corowell. In other words, Corowell is efficient only with persons which feel in good health or which are not symptomatic for a COVID-19 infection, thus pauci-symptomatic or asymptomatic ones.

Over the last 3 months clinical evidence was collected with the Corowell Symptom Screening Test in the Clinique de Montchoisi in Lausanne, Switzerland. Three different sets of data collection were performed. In total we analyzed 534 Tests.

First data set:

- In the first data set 50 subjects were screened for 8 consecutive test days with Corowell at the entrance of our clinic, which yielded 384 Test Results.
- During the 8 days 374 Tests were successfully "PASSED" as "NOT COVID-19-infection-suspected" by the subjects.
- 10 Tests resulted in "COVID-19-infection-suspected" subjects.
- 3 subjects of 10 subjects were confirmed RT-PCR Positive.
- This represents 6% of the group.
- During the same period "normal" practiced screening and testing methods of the entire population in Switzerland only yielded 1% confirmed RT-PCR Positive subjects.

Second data set:

- In the second data set a group of 26 subjects was tested, that were scheduled to undergo certain medical interventions, with Corowell first at the entrance of our clinic and subsequently tested all subjects as well with RT-PCR.
- 23 Tests were successfully "PASSED" as "NOT COVID-19-infection-suspected" by the subjects.
- 3 Tests resulted in "COVID-19-infection-suspected" subjects.
- 2 subjects of 3 subjects were confirmed RT-PCR Positive.
- This represents 7.7% COVID-Positive of the group.

Third data set:

- In the third data set a group of 124 subjects were tested, that were scheduled to undergo certain medical interventions, with Corowell first at the entrance of our clinic and subsequently tested all subjects as well with RT-PCR.

⁹³ Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *Laryngoscope* 2004;114(10):1764-1769. Rouby C, Thomas-Danguin T, Vigouroux M et al. The Lyon clinical olfactory test : Validation and measurement of hyposmia and anosmia in healthy and diseased population. *Int J Otolaryngol* 2011;2011:203805.

⁹⁴ Landis BN, Konnerth CG, Hummel T. A study on the frequency of olfactory dysfunction. *Laryngoscope* 2004;114(10):1764-1769. Rouby C, Thomas-Danguin T, Vigouroux M et al. The Lyon clinical olfactory test : Validation and measurement of hyposmia and anosmia in healthy and diseased population. *Int J Otolaryngol* 2011;2011:203805.

⁹⁵ Schiffman SS. Taste and smell in disease (first of two parts). *N Engl J Med* 1983;308(21):1275-1279. Schiffman SS. Taste and smell in disease (second of two parts). *N Engl J Med* 1983;308(22):1337-1343.

⁹⁶ Rouby C, Thomas-Danguin T, Vigouroux M et al. The Lyon clinical olfactory test : Validation and measurement of hyposmia and anosmia in healthy and diseased population. *Int J Otolaryngol* 2011;2011:203805.

⁹⁷ Schiffman SS. Influence of medications on taste and smell. *World J Otorhinolaryngol Head Neck Surg* 2018;4(1):84-91. Ferraro S, Tuccori M, Convertino I et al. Olfactory and gustatory impairments in COVID-19 patients: Role in early diagnosis and interferences by concomitant drugs. *Br J Clin Pharmacol* 2020 Nov 13. doi: 10.1111/bcp.14634. Martins Castro LG, Parente Almeida I. My patient refers smell/taste disturbance. It may not be COVID-19. *Dermatological drugs associated with olfactory and/or gustative disorders. J Dermatolog Treat* 2021 Feb 10;1-5. doi: 10.1080/09546634.2021.1887797.

⁹⁸ Dong J, Pinto JM, Guo X et al. The prevalence of anosmia and associated factors among U.S. Black and White older adults. *J Gerontol A Biol Sci Med Sci* 2017;72(8):1080-1086.

⁹⁹ Boscolo-Rizzo P, Menegaldo A, Fabbris C, et al. Six-month psychological evaluation of olfactory dysfunction in patients with COVID-19. *Chem Senses* 2021 Feb 12;bjab006. doi: 10.1093/chemse/bjab006.

- 111 Tests were successfully "PASSED" as "NOT COVID-19-infection-suspected" by the subjects.
- 13 Tests resulted in "COVID-19-infection-suspected" subjects.
- 3 subjects of 13 subjects and only 1 of the 111 "Passed" Tests were confirmed RT-PCR Positive

As we use Anosmia and targeted Questionnaires as PASS/FAIL criteria, an overall yield of 88.88% to identify COVID-19 TRUE Positives was found, especially and substantially more COVID-19 infected subjects than the national average.

In all of the data presented above only 1 False Negative subject was missed by the Corowell screening method, which represents 11% overall of all True Positives.

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 infection¹⁰⁰.

¹⁰⁰ Cadegiani FA, Zimerman RA, Campello de Souza B, et al. The AndroCov clinical scoring for COVID-19 diagnosis: A prompt, feasible, costless, and high sensitive diagnostic tool for COVID-19 based on a 1757-patient cohort. *Cureus* 2021 Jan 7;13(1):e12565. doi: 10.7759/cureus.12565.