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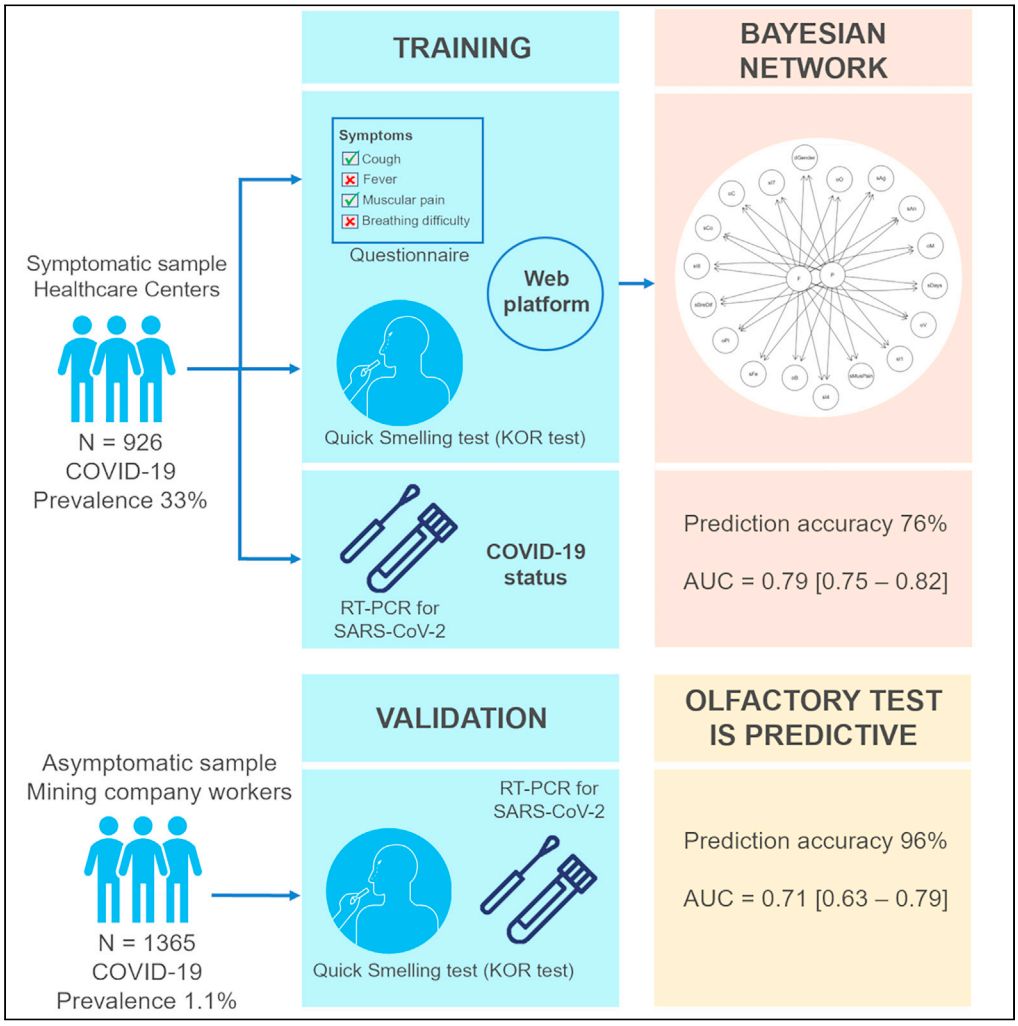

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Highlights

Total or partial loss of sense of smell is among the most prevalent COVID-19 symptoms

Partial olfactory impairment is seldom self-recognized, so a rapid test is developed

Bayesian net predicts COVID-19 status based on olfactory test and symptoms data

Results confirm measured olfactory loss as the most predictive COVID-19 symptom

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Screening of COVID-19 cases through a Bayesian network symptoms model and psychophysical olfactory test

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SUMMARY

The sudden loss of smell is among the earliest and most prevalent symptoms of COVID-19 when measured with a clinical psychophysical test. Research has shown the potential impact of frequent screening for olfactory dysfunction, but existing tests are expensive and time consuming. We developed a low-cost ($0.50/test) rapid psychophysical olfactory test (KOR) for frequent testing and a model-based COVID-19 screening framework using a Bayes Network symptoms model. We trained and validated the model on two samples: suspected COVID-19 cases in five healthcare centers (n = 926; 33% prevalence, 309 RT-PCR confirmed) and healthy miners (n = 1,365; 1.1% prevalence, 15 RT-PCR confirmed). The model predicted COVID-19 status with 76% and 96% accuracy in the healthcare and miners samples, respectively (healthcare: AUC = 0.79 [0.75–0.82], sensitivity: 59%, specificity: 87%; miners: AUC = 0.71 [0.63–0.79], sensitivity: 40%, specificity: 97%, at 0.50 infection probability threshold). Our results highlight the potential for low-cost, frequent, accessible, routine COVID-19 testing to support society's reopening.

INTRODUCTION

The COVID-19 pandemic has imposed an enormous global toll, with almost 200 million cases and about 4.2 million deaths globally as of July 2021 (Dong et al., 2020). So far, nonpharmaceutical interventions, such as wearing face masks, gathering restrictions, ventilation, and social distancing, have been the backbone of COVID-19 containment strategies (Li et al., 2021; Walker et al., 2020; Hsiang et al., 2020). Mass vaccination campaigns to prevent COVID-19 are now in place in several countries (Dagan et al., 2021; Vasileiou et al., 2021; Thompson et al., 2021). However, large-scale nonpharmaceutical interventions will continue to be important, particularly in low- and middle-income countries until a substantial proportion of the population is vaccinated (Kissler et al., 2020; Anderson et al., 2020; Aschwanden, 2021). These society-wide nonpharmaceutical strategies are socially and economically costly (Asahi et al., 2021; Baek et al., 2020). As countries reopen and lift restrictions, there is a risk of a resurgence of the epidemic as seen in several countries with the delta variant in Europe and Southeast Asia (Callaway, 2021). More focused interventions are essential to control viral transmission while reducing social and economic impact (Lavezzo et al., 2020; Karatayev et al., 2020; Hao et al., 2020). Controlling these transmission hotspots and effectively breaking the chain of viral transmission requires complementing nonpharmaceutical interventions with robust surveillance (Larremore et al., 2021b; Paltiel et al., 2020).

Two characteristics of SARS-CoV-2, the virus that causes COVID-19, makes frequent screening, rapid diagnosis, and early isolation of infected individuals critical. First, the virus spreads efficiently, with an average number of secondary cases caused by an infected individual of about 2.5 (Li et al., 2020; Wu et al., 2020). Second, a substantial proportion of onward transmission occurs before symptoms are apparent (He et al., 2020; Liu et al., 2020; Ganyani et al., 2020; Moghadas et al., 2020). The viral load is the major spreading factor. It remains low during incubation time and reaches a peak slightly before symptoms onset (He et al., 2020). This peak in infectiousness is followed by a rapid decline within about a week (He et al., 2020). These two characteristics hinder epidemic control efforts because detection and isolation of infectious individuals is challenging. So far, COVID-19 surveillance has been mainly based on

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Continued

reverse transcription-polymerase chain reaction (RT-PCR) assays, which is considered the gold standard for diagnosis (Wiersinga et al., 2020; Sethuraman et al., 2020). Yet, RT-PCR assays are expensive, and turnaround time, about 24–48 h or longer, make them impractical as a surveillance tool to curb community transmission. Modeling studies have shown that effective COVID-19 surveillance should prioritize the frequency of testing, accessibility, and immediate results (Larremore et al., 2021b; Bosetti et al., 2021, Pavelka et al., 2021). Infectious individuals might then be able to promptly isolate and stop onward transmission, which could be achieved through mass screening for specific high-prevalence symptoms of SARS-CoV-2 infection, such as olfactory dysfunction, or using antigen tests that can have a short turnaround time and cost about USD5-50 per test.

Another critical aspect of a robust surveillance is having a clear characterization of the clinical presentation of COVID-19. Clinical signs and symptoms related to COVID-19 are mostly nonspecific and include cough, fever, shortness of breath, dyspnea, myalgia, and fatigue (Guan et al., 2020; Long et al., 2020; Wang et al., 2020; de Souza et al., 2020). Initially overlooked, the sudden loss of smell has emerged as one of the earliest and most prevalent symptoms of COVID-19 (Borsetto et al., 2020, Menni et al., 2020; Ottaviano et al., 2020; Speth et al., 2020; Eliezer et al., 2020; Parma et al., 2020; Agyeman et al., 2020; Renaud et al., 2020). The mechanisms that explain the loss of smell probably relate to an inflammatory response of support and vascular cells that could affect odor conduction by obstructing the olfactory clefts (Sungnak et al., 2020) or modifying the function of olfactory sensory or olfactory bulb neurons (Brann et al., 2020). The function of olfactory sensory or olfactory bulb neurons could also be altered by damage to support cells (Plasschaert et al., 2018) or vascular damage (Chen et al., 2019). Recent studies have identified molecular factors involved in the sudden loss of smell (Chen et al., 2020). SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) and protease TMPRSS2 receptors to invade host cells (Brann et al., 2020). Both proteins are expressed in various cell types and are particularly abundant in the nose, throat, upper bronchial airways, and alveolar epithelial type II cells. Protein expression in the nose has only been determined in supporting cells and stem cells in the olfactory epithelium but not in olfactory neuronal receptors directly responsible for smell (Sungnak et al., 2020; Bilinska et al., 2020). These results suggest inflammation of cells in the olfactory epithelium leads to early loss and disturbance of the sense of smell in patients with COVID-19. Long-term symptoms could also be related to more extensive neural injury or virus persistence in the olfactory bulb (Lechien et al., 2020, 2021; Paderno et al., 2021). However, olfactory dysfunction is seldom self-recognized and reported except by patients with the most severe smell disorders (Xydakis and Bellusscio, 2017; Welge-Luessen et al., 2005; Lötsch and Hummel, 2019). Therefore, self-reported partial (hyposmia) and total (anosmia) olfactory impairment associated with COVID-19 infection may be unreliable and shows substantial variation (Agyeman et al., 2020; Gane et al., 2020; Giacomelli et al., 2020; Hopkins et al., 2020; Mao et al., 2020; Wehling et al., 2015). In contrast, when based on clinical psychophysical tests, the prevalence of olfactory impairment in patients with COVID-19 is high (Moein et al., 2020; Vaira et al., 2020a, 2020b).

We developed a model-based COVID-19 screening framework using a Bayes Network (BN) symptoms model and a low-cost (about USD 0.50/test) psychophysical olfactory function test (KOR, Kit Olfativo Rápido) for frequent and immediate prediction of COVID-19 status. Mass testing is supported by a web platform to track participants' health state with automated reports to facilitate testing implementation. As of October 2021, more than 270,000 KOR test have been performed at several companies in Chile. We present validation results of the Bayesian network model incorporating KOR test measurements on a sample of suspected COVID-19 individuals ($n = 926$, 33% prevalence of SARS-CoV-2 infection) and asymptomatic healthy mining workers ($n = 1,365$, 1.1% prevalence of SARS-CoV-2 infection). All participants had SARS-CoV-2 infection confirmation by RT-PCR assays. Our results highlight the potential for low-cost, frequent, and accessible screening for COVID-19 status.

RESULTS

KOR test and data

Figure 1A illustrates the application of the KOR test. An individual is presented with six familiar odors in a random sequence, one at a time. After each recognition, the individual is asked to select the term that best describes it. Details of the KOR test design as well as the application protocol can be found in the corresponding *Methods and materials* sections. Figure 1B shows the proportion of individuals who recognized aromas by RT-PCR status. For example, 79% of participants with a negative RT-PCR recognized the orange aroma, whereas 56% of participants with a positive RT-PCR recognized orange.

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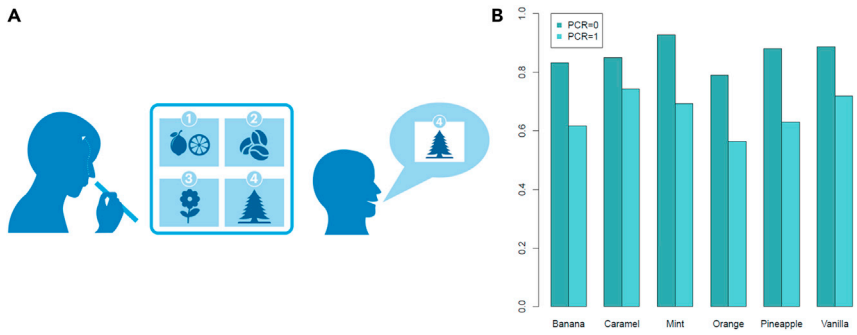

Figure 1. Implementation of the KOR test

(A) The KOR test consists of presenting individuals with six familiar odors, such as orange or vanilla, in a disposable piece of paper. Odors are presented in a random sequence. For each trial, we asked individuals to select in a tablet or mobile phone the term that best describes the odor from four options presented. If the individual does not recognize the odor, he/she selects "I do not recognize the odor." The test implementation takes less than three minutes per participant.
(B) Proportion of individuals from the UC-Christus sample (n = 936) with a positive or negative result from the RT-PCR assay who perceived each aroma: Banana, Caramel, Mint, Orange, Pineapple, and Vanilla.

We used two samples for the analysis. First, we gathered data from 926 individuals with suspected COVID-19 infection or close contact with a laboratory-confirmed case in five medical centers in Santiago, Chile, hereafter called the "UC-Christus" sample. Our second sample consisted of 1,365 healthy asymptomatic participants from a large mining operation in Antofagasta, Chile, hereafter called the "miners" sample (asymptomatic). All participants in the "UC-Christus" and "miners" sample underwent an RT-PCR test following the KOR test as well as an epidemiological and clinical screening before the latter. We considered all RT-PCR positive results as lab-confirmed COVID-19 (Wiersinga et al., 2020; Sethuraman et al., 2020). Descriptive statistics of the training sample, COVID-19 symptoms prevalence, and RT-PCR status can be found in Table S9.

Anosmia score and classifier training

We developed an anosmia score for each individual based on the results of the KOR test. A higher score means a better sense of smell. Figure 2 compares anosmia score by RT-PCR status (Figure 2A) and by self-reported anosmia (Figure 2B), for all participants in the UC-Christus sample. Healthy individuals (RT-PCR negative) had a higher anosmia score than COVID-19 cases (Figure 2A) and also showed higher anosmia scores than participants who reported normal sense of smell (Figure 2B). The latter result suggests that some anosmic participants were not aware of their olfactory dysfunction, consistent with previous studies (Wehling et al., 2015). Participants with COVID-19 (RT-PCR positive) also showed a higher anosmia score than self-reported anosmic participants, suggesting there are normosmic participants among COVID-19 cases as reported elsewhere (Renaud et al., 2020; Agyeman et al., 2020).

Based on the anosmia scores, we developed a Gaussian mixture classifier to identify individuals with olfactory impairment. This classifier is composed of two Gaussian distributions: one describes the anosmia scores of individuals with olfactory impairment and the other represents the anosmia scores of individuals with a normal sense of smell.

A large proportion of COVID-19 cases develop some olfactory dysfunction (Moein et al., 2020; Vaira et al., 2020a, 2020b; Hornuss et al., 2020). We estimated the distribution of the anosmia scores for the truly anosmic participants based on the scores obtained from self-reported anosmic participants (mean = −1.81; std = 2.1). Similarly, we estimated the distribution of the anosmia scores for the nonanosmic participants based on the score of the participants with negative RT-PCR ignoring outliers from the left tail (mean = 1.22; std = 0.97). Briefly, we excluded 21 observations (3.4% of the sample) that were two SDs away from the left. Our goal here was was to exclude possible cases with anosmia and RT-PCR negative. Of note, the anosmia score means of the RT-PCR negative and self-reported nonanosmic groups were statistically different at a 95% confidence interval (Welch two-sample test, p value = 2.2×10^{-6}). We used these two distributions to build a Gaussian mixture classifier to identify individuals with olfactory dysfunction (refer to *Methods*). For a given anosmia score from a particular individual, the Gaussian mixture classifier

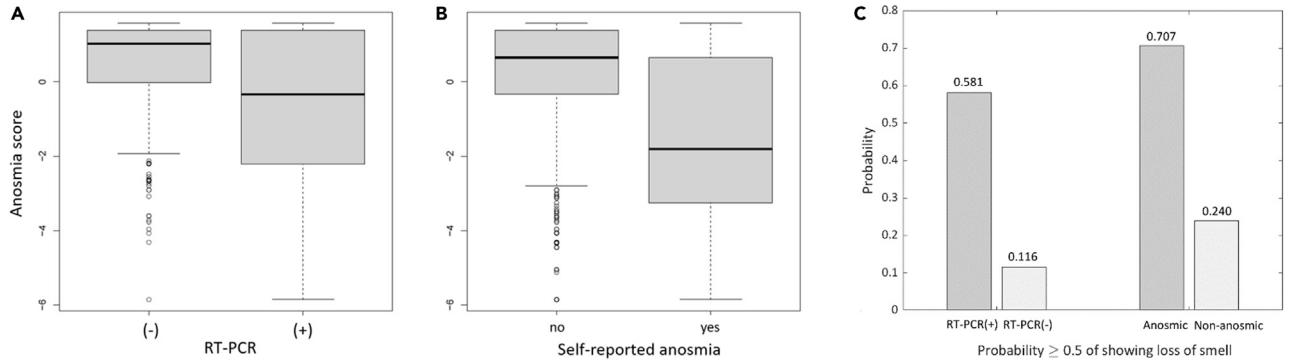

Figure 2. Anosmia score among participants

(A and B) Anosmia score distribution by RT-PCR status and (B) self-reported anosmia. Results include all UC-Christus participants (n = 926).

(C) Results from applying a Gaussian mixture classifier to identify individuals with olfactory dysfunction. The proportions 0.581, 0.116, 0.707, and 0.240 correspond to the proportion of individuals predicted to be anosmic in the group of RT-PCR +, RT-PCR −, self-reported anosmic, and self-reported nonanosmic, respectively.

outputs a probability for being anosmic. If this probability is higher than 0.5, we say the individual is predicted to be anosmic. Figure 2C shows the proportion of individuals with probability higher than 0.5 for being anosmic in four groups: the two bars on the left correspond to individuals with RT-PCR +/−, and the two bars on the right correspond to self-reported individuals as anosmic/nonanosmic. For example, among all individuals with RT-PCR positive, 58.1% were also predicted to be anosmic by the Gaussian mixture classifier, whereas among all individuals with negative RT-PCR, 24% were predicted to be anosmic.

Olfactory function measurement improves COVID-19 prediction by a Bayesian network model

We constructed a Bayesian network model to estimate whether a participant had COVID-19 (P) (Figure 3A). The model included self-reported cold (F) as a confounder, seven COVID-19 symptoms (cough, fever, muscular pain, breathing difficulty, self-reported anosmia, ageusia, and the anosmia score), five indicator variables (sI1 recognized more than four odors; sI4 reported more than one symptom among cough, fever, breathing difficulty, and muscular pain and sI1; sDays had 2-3 days with symptoms; sI7 had headache, diarrhea, or chest pain and recognized four or less odors; sI8 had ageusia, stomach pain, or fatigue and sI1), and gender. Conditions were individually assessed to determine their inclusion (Tables S3–S7). This network structure was the most predictive out of several other models considering different subsets of symptoms and conditions (refer to *Model structure learning*). The Brier score for this model was 0.2—the closer the score to zero, the better. Individual measures for this score, i.e., reliability, resolution, and uncertainty, are included in Table S2. Finally, the contribution of each variable to the probability of having COVID-19 can be found in Figures S9 and S10. For more details about the Bayesian network model, the reader is referred to the subsection in *Bayes network model*.

We evaluated the performance of our model based on the UC-Christus dataset (n = 926, 33% positive RT-PCR). A 10-fold cross-validation was performed in order to have a robust estimator of the errors in the identification of positive and negative COVID-19 individuals. Figure 3B displays the average receiver operating characteristic (ROC) curve of the full model in black. To assess the contribution to the model of the objective measurements of olfactory impairment, we estimated the model with all variables except the ones that include information from the KOR test. Figure 3B shows the ROC curve of this model in red. The complete model displayed an area under the curve (AUC) of 0.785 with 95% confidence interval (0.754; 0.816) and 76% accuracy, whereas the partially complete model yielded an AUC of 0.733 with 95% confidence interval (0.696; 0.768) and 72% accuracy. The difference in the AUC is not significant at a 95% confidence level but an 87% level (De Long test, p value = 0.13).

We further looked at the subset of individuals from the UC-Christus sample with no reported symptoms (n = 288) to assess model performance based solely on the anosmia score. From this subset, 39 individuals had an RT-PCR positive, of which 9 had a predicted probability above 0.5 for being infected. All recognized three or less odors among a total of six, except for one that recognized four odors. The two odors not

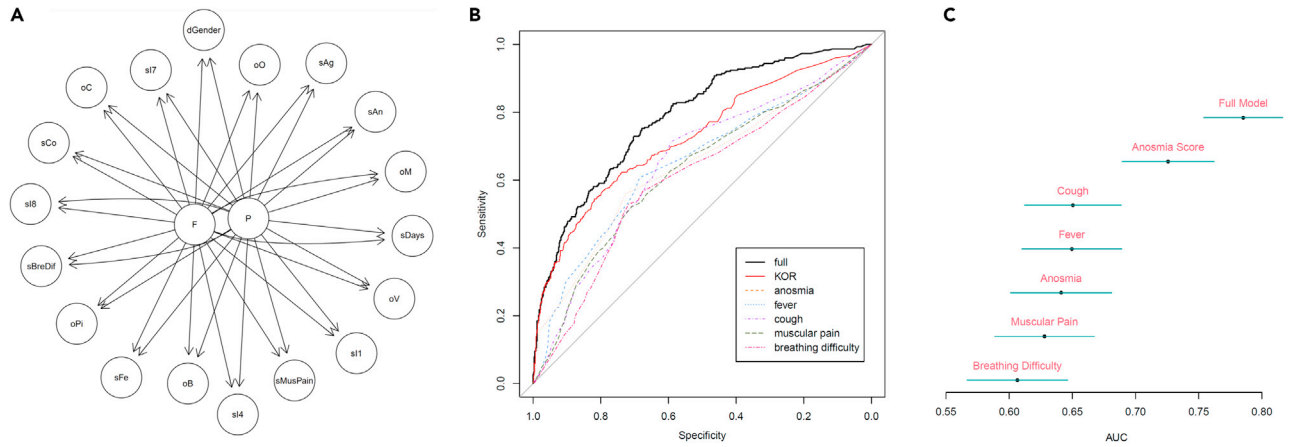

Figure 3. Training of the Bayesian network model for COVID-19 prediction

(A) Structure of the model. P represents the result of the RT-PCR assay, and F represents self-reported cold. The six different odors are represented with the variables: oB (Banana), oC (Caramel), oM (Mint), oO (Orange), oPi (Pineapple), oV (Vanilla). The six different symptoms are represented by sCo (cough), sFe (fever), sMusPain (muscular pain), sBreDif (breathing difficulty), sAn (self-reported anosmia), and sAg (self-reported ageusia). Five indicator variables are represented by sI1, sI4, sI7, sI8, and sDays. dGender represents the gender of the individual. All variables are dichotomous.

(B) Average receiver operating characteristic (ROC) curve, as estimated through cross-validation ($K = 10$), for predicting a COVID-19 case using the full model (black line), only the KOR test (red line), and single self-reported symptoms.

(C) Mean and 95% confidence intervals for the AUC of the ROC curves shown in (B). These analysis were performed using the UC-Christus sample ($n = 926$). The complete model displayed an area under the curve (AUC) of 0.785 with 95% confidence interval (0.754; 0.816) and 76% accuracy, whereas the model with only the KOR test yielded an AUC of 0.733 with 95% confidence interval (0.696; 0.768) and 72% accuracy. The difference in the AUC is not significant at a 95% confidence level but an 87% level (De Long test, p value = 0.13).

recognized were mint and orange. The remaining 30 individuals with a positive RT-PCR recognized at least four odors and were not captured by the model at the infection probability threshold of 0.5. From the 249 individuals with a negative RT-PCR, 13 obtained a probability of being infected above 0.5, 11 of them recognized three or fewer odors, and 2 recognized four, with mint among the nonrecognized.

Anosmia score predicts COVID-19 status with higher fidelity than self-report

We further applied the KOR test to 1,365 workers from a mining company that had not been previously infected and did not present any symptoms. These workers were also tested with RT-PCR. Among all the workers, only 15 had a positive RT-PCR, of which the BN model identified 6. These six individuals identified less than four odors from the KOR test. The remaining nine individuals identified five out of the six odors ($n = 4$) or identified the six odors ($n = 5$). Overall, the model exhibited 96% accuracy, 97% specificity, and 40% sensitivity at a 0.5 infection probability threshold (refer to Table S8 for details.)

As the only predictor of COVID-19 status in asymptomatic individuals is their olfactory function, we compared the anosmia score of this sample and the probability of having olfactory dysfunction using the anosmia classifier trained with the UC-Christus dataset. The latter showed great agreement between the anosmia negative individuals and the miners cohort as observed by the overlapping between both densities (Figure 4), confirming its suitability for describing the olfactory function of the general population. Finally, we compared the anosmia classifier results against the anosmia self-report of a sub-sample from the miners cohort for which this information was available ($n = 825$). There were 52 individuals likely of having olfactory dysfunction as determined by their anosmia score and the corresponding infection probability (>0.5). This corresponds to 6.3% of the total sample. Of those, only 8 (approx. 1%) individuals self-reported an olfactory dysfunction. Roughly, 85% of individuals with olfactory impairment were not aware of their loss of the sense of smell. This result confirms that olfactory impairment is typically underestimated or not perceived by healthy individuals (Wehling et al., 2015), rendering the self-report of a "healthy olfactory function" unreliable.

DISCUSSION

The results from our study suggest that olfactory dysfunction is one of the earliest and most discriminant symptoms to predict COVID-19 status when the loss of the sense of smell is measured through a

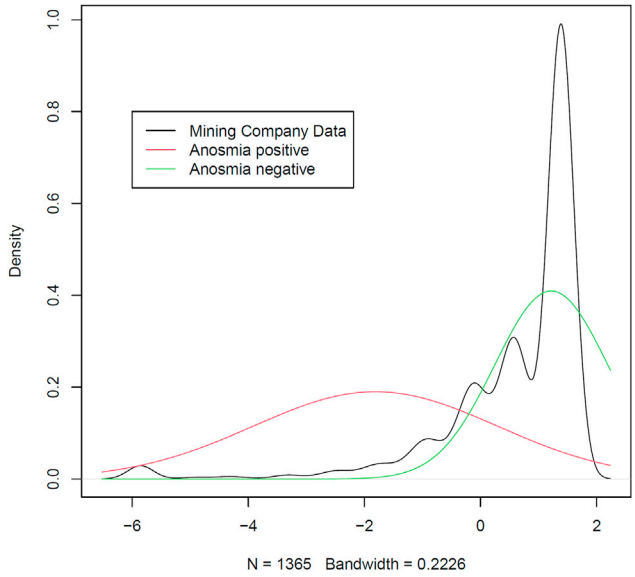

Figure 4. Anosmia prevalence in the healthy workers cohort

Anosmia score density in the asymptomatic sample from the mining company (black line). The red and green lines correspond to the distribution for anosmic and nonanosmic individuals, respectively, as estimated in the UC-Christus data.

psychophysical olfactory test. We report a novel model for predicting the COVID-19 status of individuals based on self-reported symptoms (subjective measures) and the degree of olfactory dysfunction (anosmia score) as determined from psychophysical odor recognition trials from a rapid smelling test (Figure 1). This anosmia score overcomes the known limitations of olfactory dysfunction self-report, i.e., usually underestimation of olfactory dysfunction severity (Figure 2B), and furthermore, it substantially increases the predictive power of the model (Figures 3B and 3C). We found that the full model incorporating this index yielded COVID-19 status predictions with high fidelity (AUC 0.785), which worsened when this index was left out (AUC 0.733). In the case of asymptomatic individuals (miners data), where the only measurements were obtained from the KOR test, the model was able to detect positive COVID-19 cases that otherwise would have gone undetected. Among the 15 individuals who were RT-PCR positive, 6 of them recognized less than four odors, and the remaining 9 recognized at least five out of the six different odors. We obtained a similar performance on the asymptomatic participants from the UC-Christus sample. The model recognized all individuals with RT-PCR positive who identified less than four odors and one individual who identified four odors. For the model to recognize an individual infected that identified four odors, mint has to be among the unrecognized odors.

Unfortunately, we were not able to monitor participants in time because of funding constraints. However, it is possible that some cases classified as false positives due to a negative RT-PCR result could have been SARS-CoV-2 infections. Despite being the gold standard, RT-PCR positivity varies among SARS-CoV-2-infected patients. Several studies have raised concerns about potential false-negative RT-PCR results in patients with COVID-19 (Arevalo-Rodriguez et al., 2020; Woloshin et al., 2020), which may depend, for example, on the timing of sample collection or sampling technique (Sethuraman et al., 2020; Watson et al., 2020). Therefore, even with a low probability of exposure, a negative RT-PCR cannot rule out an SARS-CoV-2 infection (Jara et al., 2021; Woloshin et al., 2020). This also underscores the importance of frequent testing for COVID-19 (Larremore et al., 2021b; Paltiel et al., 2020; Service, 2020).

As opposed to conventional olfactory function tests, KOR does not place the same weight on all the odors for the determination of the olfactory function state. A clear example is mint. Mint has two features that are especially attractive in a smell test. First, mint has a very distinctive smell and is rarely confused with other odors. Second, mint is a familiar smell to most people. In the KOR test, mint was correctly recognized by a majority of participants with a negative RT-PCR (93%). Hence, mint has a larger contribution to the model. If mint is not recognized, there is a higher probability that the participant is infected (Figure 1B). It is possible

that some of the proposed odors may not be readily recognized across different sociocultural settings, despite being used and validated in international medical studies (Schriever et al., 2018). Cross-cultural validity would be, nevertheless, straightforward to address by piloting the test and choosing odors that satisfy the two features mentioned earlier before implementation.

We designed the KOR smell test and web platform as a low-cost public health tool for screening a large number of people, frequently, with a short sample-to-answer reporting time. Two aspects of SARS-CoV-2 infection make this epidemic difficult to control. First, the virus is efficiently transmitted between individuals, and transmissibility has increased in several places due to new circulating variants (Centre for Disease Control and Prevention, 2021; Callaway, 2021). Second, a substantial portion of onward transmission occurs before symptoms are apparent, and the peak in infectiousness declines quickly, typically in about a week (Cevik et al., 2020; He et al., 2020; Jefferson et al., 2020). Further, a substantial proportion of infected individuals do not have apparent symptoms (Long et al., 2020; Johansson et al., 2021). Several studies have stressed the importance of frequent, mass testing, with a short sample-to-answer reporting time to limit viral transmission in this epidemic (Larremore et al., 2021b; Paltiel et al., 2020; Bosetti et al., 2021, Pavelka et al., 2021). Because a large proportion of patients have olfactory dysfunction (Lechien et al., 2020; Beltrán-Corbellini et al., 2020; Tong et al., 2020; Moein et al., 2020; Menni et al., 2020), several studies have highlighted the public health potential of screening for hyposmia or anosmia (Gautier and Ravussin, 2020; Xydakis et al., 2020; Larremore et al., 2021a). Modeling suggests that frequent screening for olfactory dysfunction could substantially reduce viral spread at a comparatively low cost (Larremore et al., 2021a).

One relevant consideration is that it is possible that false positives would be put under quarantine unnecessarily, at least until they can access a more sensitive test such as an RT-PCR. False positives may also occur because some patients with COVID-19 have also reported persistent anosmia or hyposmia (Lechien et al., 2021; Carfì et al., 2020; Yan et al., 2020; Reiter et al., 2020) and may test positive after the virus has been cleared. It is worth noting that patients may also show positive RT-PCR results for weeks (van Kampen et al., 2021), with an average of 17 days (Cevik et al., 2020) and a median of 22–33 days (Sun et al., 2020). From an epidemiological standpoint, false positives are preferable to having community transmission, especially for a gradual reopening of society. Perhaps more worryingly, using a psychophysical smell test for mass screening would probably result in false negatives and in the onward transmission of SARS-CoV-2. However, in a counterfactual scenario without mass screening, those individuals would not be tested and transmit the virus. The potential use of this test requires adequate risk communication and is not intended to replace other nonpharmaceutical strategies for the control and prevention of viral transmission, such as social distancing or wearing face masks.

Similar to our smell test, antigen tests can have a sample-to-answer response time as low as 15 min. The performance of antigen tests varies substantially, and they are particularly susceptible to sampling quality (Dinnes et al., 2021). For example, in the United Kingdom, the Innova test showed sensitivities for symptomatic patients of 79%, 73%, and 58% when used by trained laboratory scientists, trained healthcare staff, and pharmacy employees, respectively (Torjesen, 2021; England, 2020). Although sensitivity is substantially lower in individuals without apparent symptoms (Ferguson et al., 2021; Wise, 2020), rapid antigen tests can detect at least 66% of cases with high viral loads (Wise, 2020; Mina et al., 2021). At USD 5–50 per test, rapid antigen tests can substantially limit COVID-19 transmission through frequent mass testing. Although the performance of our smell test is comparable with some antigen tests, our test is not intended for use as a diagnostic tool, but rather to serve as a low-cost (USD 0.50) psychophysical screening tool.

In addition to the frequent use of olfactory tests and rapid antigen tests to reduce viral transmission (Dinnes et al., 2021; Larremore et al., 2021a; Peeling et al., 2021), the use of routine blood exams has the potential to help identify SARS-CoV-2 infections quickly and at a low cost. Cabitza et al. (Cabitza et al., 2021a) applied machine learning models to hematochemical values of routine blood tests, showing good performance in detecting SARS-CoV-2 infections. These models could be used, for example, in settings with limited availability of other diagnostic tests (e.g., RT-PCR), reagents, or testing capabilities, such as in low-income countries or during rapid COVID-19 surges.

Limitations of the study

Our analyses are based on a sample of individuals from medical centers with probable COVID-19 and a sample of asymptomatic workers in a large mining operation. Neither sample is representative of the broader population. Nevertheless, the overrepresentation of positive cases in the UC-Christus data enabled us to estimate the

relationship between symptoms and disease using a moderate sample size. The underrepresentation of positive cases in the miners' data challenged the model to capture infected individuals with just KOR test measurements. Furthermore, contexts such as a mining operation are relevant as they resemble a type of scenario where the test is more likely to be used as additional screening for individuals who do not have other apparent COVID-19 symptoms, such as fever. Test deployment in different conditions, such as a different sociocultural setting or changes in disease dynamics (e.g., a new variant), could theoretically affect test results. Therefore, continuous monitoring and external validation on different datasets are recommended (Cabitza et al., 2021b). Diagnosis for symptomatic patients in a clinical setting usually requires high accuracy and sensitivity, as it defines a patient's treatment. In contrast, given the transmission dynamics of SARS-CoV-2, rapid results and frequency of testing are much more critical for effective surveillance with the potential of controlling viral transmission (Larremore et al., 2021b; Paltiel et al., 2020; Bosetti et al., 2021, Pavelka et al., 2021).

STAR★METHODS

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2021.103419.

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AUTHOR CONTRIBUTIONS

Conceptualization, S.E., P.A.S., E.A.U., L.M., J.P., A.F., S.S., and E.A.; Methodology, S.E., P.A.S., E.A.U., and E.A.; Investigation, C.V. and C.L.; Formal Analysis, S.E.; Resources, S.S., M.U., N.S., and P.B.; Data Curation, P.A.S., S.E., and C.V.; Validation, S.E., P.A.S., E.A.U., and C.V.; Writing—Original Draft, S.E., P.A.S., and E.A.U.; Writing—Review & Editing, S.E., P.A.S., E.A.U., M.A., and E.A.; Supervision, M.A. and E.A.; Funding Acquisition, E.A.

DECLARATION OF INTERESTS

DICTUC SA. has interest in commercial application of the olfactory test. E.A. is an advisor for DICTUC SA. C.V. and C.L. are employed by DICTUC SA.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Chemicals, peptides, and recombinant proteins		
Banana scent	https://alfagroup.cl/en/	PTMEZ382401
Caramel scent	https://alfagroup.cl/en/	PTMEZ382701
Mint scent	https://alfagroup.cl/en/	PTMEZ381801
Orange scent	https://alfagroup.cl/en/	PTMEZ381901
Pineapple scent	https://alfagroup.cl/en/	PTMEZ382101
Vanilla scent	https://alfagroup.cl/en/	PTMEZ383177
Deposited data		
UC Christus and miners cohort data	This paper	Mendeley Data: https://doi.org/10.17632/z4ktvcwfp6.2
Software and algorithms		
RStudio 1.4	RStudio	https://www.rstudio.com/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Eduardo Agosin (agosin@ing.puc.cl).

Materials availability

This study did not generate new unique reagents.

Data and code availability

De-identified human data for model training and validation have been deposited at Mendeley Data and are publicly available as of the date of publication. DOIs are listed in the key resources table. This paper does not report original code. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Samples for model training and validation were collected only from voluntary, non-remunerated, individuals who provided written informed consent to be part of this study. All the collected data was anonymized for the purpose of this study. The study protocol was reviewed and approved by the Ethics Committee of the Pontificia Universidad Católica de Chile on April 2020. Details of the samples are shown below.

Model training dataset: COVID-19 suspects cohort from healthcare system

This sample of participants was obtained from five medical centers of the UC-Christus healthcare network in Santiago. The sample consisted of 926 individuals, 48% women and 52% men, with an average of 37 $\pm$ 13 years of age. These individuals had either symptoms compatible with SARS-CoV-2 infection, or were in close contact with confirmed cases. The individuals took the olfactory KOR and the RT-PCR tests. In this sample, 9 individuals were unaware of their anosmia status, i.e., failed to recognize any smell and did not report loss of smell. COVID-19 prevalence was 33% in this sample. Individuals who reported base olfactory dysfunction due to previous trauma and/or acute/chronic health issues (e.g., chronic sinusitis, allergic rhinitis) were excluded from the sample. Before the application of the test, we used a questionnaire to obtain participants' COVID-19-related symptoms (fever, cough, muscular pain, breathing difficulty), demography (age, gender), comorbidities (allergy, cold, diabetes, hypertension, Parkinson, rhinitis and Alzheimer), and smoking status. We also registerred other self-reported symptoms or conditions such as anosmia/hyposmia, ageusia, headache, diarrhea, fatigue, chest and stomach pain.

Model validation dataset: Workers cohort from mining company

We employed a sample of 1365 workers from a mining company in Antofagasta, Chile for model validation. Inclusion criteria imposed by the mining company to the employees to be allowed to work were the following: i) the person did not have a positive RT-PCR for COVID-19, and ii) at the moment of the test, the person did not have fever or any other apparent COVID-19 symptom. Therefore, only asymptomatic individuals were included in this sample. Participants were tested for their olfactory function status using the KOR test and also took an RT-PCR at a sanitary checkpoint. The prevalence of COVID-19 was 1.1% in this sample. Participants (825) also reported at the time of the screening if they recently suffered from olfactory impairment.

METHODS DETAILS

KOR test design

The KOR test is a rapid, six-odor, forced multiple-choice identification test. While previous rapid tests have shown to be reasonably effective for detecting total loss of olfactory function (i.e., anosmia) through the identification of only three odors (Hummel et al., 2001), they are ineffective for the identification of partial olfactory function loss. As there is good evidence of COVID-19 cases suffering from partial olfactory impairment (Moein et al., 2020), we increased the number of odors in the test (6) to improve its sensitivity. The proposed six odors were based on previous odor recognition reports (Hummel et al., 2001) and clinical olfactory studies for infants in several countries including Chile (Schriever et al., 2018). To minimize recognition bias, candidate odors were evaluated and validated in a pilot trial. Only odors with a high recognition level of at least 85% (Figure S11) were selected. The sample of the pilot study consisted of 79% and 21% healthy men and women, respectively, with ages between 18 and 65 years of age in a sample of 2289 volunteers. Selected odors showed no significant differences in their recognition between men and women at 5% significance level (two-sided *t* test, critical *p* value = 0.21), displayed a high recognition level in all cases ($_{>}$ 85% one-sided *t* test, minimum critical *p* value = 0.41), and showed no significant differences in the average recognition level for individuals between 18 and 60 years at 5% significance level (ANOVA, critical *p* value = 0.10). Details of the pilot study sample can be found in Table S10.

KOR test application protocol

The KOR test is managed through an online platform, hosted in www.testkor.com. To carry out an olfactory test, the evaluator first enters the information of the individual to undergo the olfactory test. All this information is requested and stored in the KOR platform and includes:

- Personal information: national identification number (or passport number), name, date of birth, nationality and gender.
- Information about previous SARS-CoV-2 test: the individual is asked whether he/she has undergone the SARS-CoV-2 RT-PCR test, and if the answer is yes, then he/she is asked the date of the test and whether the result was either negative or positive or still pending.
- Information of comorbidities: the individual is asked about his/her comorbidities. There is a predefined list that the evaluator can refer to, which includes: loss of smell, respiratory allergies, hypertension, rhinitis or sinusitis, Parkinson's disease, Alzheimer's disease, and diabetes. In addition, the platform provides an open question where the evaluator can enter any additional comorbidities.
- Information on smoking: the individual must indicate if he/she smokes.

This information is only requested once; the next time the individual undergoes the olfactory test, he/she only needs to provide the identification number in the platform for his/her information to be displayed. It is important to note that all the personal information is anonymized upon storing in the platform.

Then, the olfactory test is carried out as follows: a paper strip is impregnated with one drop (0.03 mL $\pm$ 4 uL) of an aromatic solution, as indicated by the platform, and presented to the participant to be smelled. The individual must identify the corresponding odour among 4 options, shown in the platform. Before evaluating the next odour, the subject is asked to neutralize eventual remaining fragrance in the nasal cavity by smelling his own body odor (wrist or forearm). All 6 aromas, i.e. banana, caramel, mint, orange, pineapple and vanilla, were evaluated in a random sequence, as determined by the platform, one at a time, with an inter stimulus interval of 15 s. Figure S15 shows an example of the selection panel for each scent.

The aromas were supplied by Alfa Group (https://alfagroup.cl/), a Chilean company specialized in providing food ingredients. The company's safety procedures are certified for HACCP and FSSC22000. All raw materials were FEMA/GRAS. Each aroma is contained in a 30 mL amber, glass dropper. Table S11 indicates the composition and concentration of main odorants of the six solutions. The variability of the volume delivered by the glass dropper was measured in an analytical balance (n = 70), yielding a coefficient of variation lower than 15%, which is acceptable for odor recognition purposes.

COVID-19 RT-PCR test

Individuals were tested following the World Health Organization guidelines for real-time reverse-transcriptase PCR testing using validated diagnostics reported elsewhere (Corman et al., 2020).

Model structure learning

To evaluate and identify the best structure for the Bayesian Network, several network structures were assessed for their predictive performance. The variables considered in the models are described in what follows. P represents the result of the RT-PCR assay, F represents self-reported cold, R represents the presence or absence if rhinitis, A represents the presence or absence of allergies, and S whether the person smokes or not. These five variables P, F, A, S and R are considered either diseases or conditions that can lead to different symptoms which are the variables described next. The perception or not of six different odors are represented with the variables: oB (Banana), oC (Caramel), oM (Mint), oO (Orange), oPi (Pineapple), oV (Vanilla). Six different symptoms are represented by: sCo (cough), sFe (fever), sMusPain (muscular pain), sBreDif (breathing difficulty), sAn (self-reported anosmia), and sAg (self-reported ageusia). Additionally, five indicator variables are included and represented by (described in the *Methods* section of the main article): sI1, sI4, sI7, sI8, sDays. Finally, dGender represents the gender of the individual.

The evaluated structures are shown in Figures S1–S6. These structures differ only in the diseases and/or conditions included in the model, whereas the remaining structures consider subsets of the symptoms (Figures S7 and S8). Table S1 displays the performance of the evaluated network structures for the prediction of COVID-19 status in the training dataset, whereas Table S2 shows the performance indicators of the final model. Tables S3–S7 show respectively the effect of the covariates for the dependent variables *allergies*, *rhinitis*, *cold*, *RT-PCR* and *smoking*, when a logistic regression model was fitted to the data. This model was employed as a starting point for identifying a smaller set of significant variables to be included in the final Bayesian Network model (see next).

Bayes network model

To predict an individual's COVID-19 status, we built a model that considers an RT-PCR positive result as a COVID-19 case (Y_1), and incorporates *cold* (Y_2) as a possible confounder variable, seven symptoms (cough (X_7), fever (X_8), muscular pain (X_9), breathing difficulty (X_{10}), self-reported anosmia (X_{14}), ageusia (X_{15}) and the anosmia score), five indicator variables ($X_{11}, X_{12}, X_{13}, X_{16}, X_{17}$) and gender ($X_{18}$). To compute the anosmia score, we evaluate the identification of six odours: banana (X_1), caramel (X_2), mint (X_3), orange (X_4), pineapple (X_5) and vanilla (X_6). The five indicator variables were defined in the following way: X_{11} measures whether the individual recognized more than four odours or not (this score yielded the best COVID-19 prediction performance when the odors have equal weight, see Figure S13); X_{12} indicates whether the individual suffers from more than one symptom among cough, fever, muscular pain, breathing difficulty, headache, diarrhea and fatigue, and satisfies X_{11} = 1; X_{13} measures whether the individuals had 2-3 days with symptoms (this variable represents the days where the RT-PCR is most effective); X_{16} measures whether the individuals had X_{11} = 0 and one or more symptoms among headache, diarrhea and chest pain; and X_{17} measures whether the individual satisfies X_{11} = 1 and one or more symptoms among ageusia, stomach pain and fatigue. These indicator variables aim to identify group of symptoms that by occurring together increase the effect on the model. The structure of the model is depicted in Figure 3A. Note that the structure of the model assumes that all the X variables are conditionally independent given Y_1 and Y_2. The joint probability distribution of all variables is given by:

$$\Pr(Y_1, Y_2, X_1, \ldots, X_{18}) = \Pr(Y_1)Pr(Y_2)\prod_{i=1}^{18} \Pr(X_i|Y_1, Y_2) \qquad \text{(Equation 1)}$$

and we are interested in calculating the probability of positive RT-PCR given the other variables, i.e.

$$\Pr(Y_1 = 1|Y_2, X_1, \ldots, X_{18}) \quad \text{(Equation 2)}$$

where all variables are dichotomous Bernoulli distributed. We assume a Binomial distribution for the joint probability of RT-PCR and self-reported cold.

$$\Pr(Y_1) \sim Bern(\theta_1) \quad \text{(Equation 3)}$$
$$\Pr(Y_2) \sim Bern(\theta_2) \quad \text{(Equation 4)}$$
$$\Pr(X_i|Y_1, Y_2) \sim Bern(\theta_{i,k}) \quad i = 1, \ldots, 18; k = 1, \ldots, 4 \quad \text{(Equation 5)}$$

Here k denotes the four different outcomes that the joint variables (Y_1, Y_2) can take. Note that there are a total of 75 parameters that need to be estimated. θ_k represents the probability of belonging to group k for the variables Y_1, Y_2. $\theta_{i,k}$ represents the probability that an individual is positive for the condition/disease/variable i given that she/he is in group k for the variables Y_1, Y_2. We trained this model using a dataset of 926 individuals. In order to gain some degrees of freedom, and because we observed a clear tendency between the symptoms and the outcome of the variables Y_1 and Y_2 as shown in Figure S10, we set the following linear constraint on the parameters,

$$\theta_{i,k} \sim \alpha_i + \beta_i R_{ik} \quad i = 1, \ldots, 18; k = 1, \ldots, 4 \quad \text{(Equation 6)}$$

thereby reducing the number of parameters to be estimated to 36. We either plug-in Equations 3 and 4, or 3 and 5 into 1 to obtain via maximum likelihood the estimators of the parameters. The variables R_{ik} are known and set to fit the tendency of the parameters as shown in Figure S12.

Finally, for a new individual with variables $X_1 = x_1, \ldots, X_{18} = x_{18}$ we compute:

$$m_3 = \frac{s_3}{s_0} = \Pr(Y_1 = 1, Y_2 = 1|X_1 = x_1, \ldots, X_{18} = x_{18}) / \Pr(Y_1 = 0, Y_2 = 0|X_1 = x_1, \ldots, X_{18} = x_{18})$$
$$m_2 = \frac{s_2}{s_0} = \Pr(Y_1 = 1, Y_2 = 0|X_1 = x_1, \ldots, X_{18} = x_{18}) / \Pr(Y_1 = 0, Y_2 = 0|X_1 = x_1, \ldots, X_{18} = x_{18})$$
$$m_1 = \frac{s_1}{s_0} = \Pr(Y_1 = 0, Y_2 = 1|X_1 = x_1, \ldots, X_{18} = x_{18}) / \Pr(Y_1 = 0, Y_2 = 0|X_1 = x_1, \ldots, X_{18} = x_{18})$$

From these three equations we can obtain the probabilities s_0, s_1, s_2, s_3. If $Y_2 = 1$ then

$$\Pr(Y_1 = 1|Y_2 = 1, X_1 = x_1, \ldots, X_{18} = x_{18}) = \frac{s_3}{s_1 + s_3},$$

when $Y_2 = 0$ then

$$\Pr(Y_1 = 1|Y_2 = 0, X_1 = x_1, \ldots, X_{18} = x_{18}) = \frac{s_2}{s_0 + s_2}.$$

which represent the probability of being a positive case of Covid-19.

Anosmia score and classifier

For an individual with outcomes from the KOR test given by $(x_1, x_2, x_3, x_4, x_5, x_6)$ where x_i can take the value 1 if the individual identified odour i or 0 if the individual did not, its anosmia score is calculated in the following way.

- For individuals with cold:

$$\text{anosmiaScore} = \sum_{i=1}^{6} x_i \log\left(\frac{\theta_{i1}}{\theta_{i3}}\right) + (1 - x_i)\log\left(\frac{1 - \theta_{i1}}{1 - \theta_{i3}}\right)$$

- For individuals without cold:

$$\text{anosmiaScore} = \sum_{i=1}^{6} x_i \log\left(\frac{\theta_{i0}}{\theta_{i2}}\right) + (1 - x_i)\log\left(\frac{1 - \theta_{i0}}{1 - \theta_{i2}}\right)$$

The distribution of the anosmia score, say y, is assumed to be a Gaussian mixture of two distribution:

$$f\left(y;\pi,\mu_1,\sigma_1^2,\mu_2,\sigma_2^2\right) = \pi f\left(y;\mu_1,\sigma_1^2\right) + (1-\pi) f\left(y;\mu_2,\sigma_2^2\right)$$

where $f(y;\mu,\sigma^2)$ denotes a Gaussian distribution with mean μ and variance σ^2, the parameters μ_1,σ_1^2 represent the parameters of the distribution for the anosmia score for individuals suffering from olfactory dysfunction, and the parameters μ_2,σ_2^2 represent the parameters of the distribution for the anosmia score for individuals that do not suffer from olfactory dysfunction. The estimators for these parameters were obtained from the UC-Christus data: $\widehat{\mu}_1 = -1.81$, $\widehat{\sigma}_1^2 = 4.41$, $\widehat{\mu}_2 = 1.22$ and $\widehat{\sigma}_1^2 = 0.94$.

KOR web platform

The KOR test web platform was designed to enable a rapid administration of the test. We developed a data model to store test information efficiently, paying attention to how often data about organizations, members, and screening tests are updated. The platform's data access layer (back-end) was developed in Django (open-source framework), while its user interface (front-end) was developed in the JavaScript library ReactJS (open-source). High scalability and security concerns are handled by the deployment of the platform in Amazon Elastic Compute Cloud. As of October 2021, over 270,000 tests have been performed in the platform by several chilean companies (Figure S14). General statistics on platform use, such as total tests, tests per day, and average time per test, can be found at http://metabase.imfd.cl/public/dashboard/2801acac-8414-43be-871d-dad441026d3a.

QUANTIFICATION AND STATISTICAL ANALYSIS

Data pre-processing and analysis as well as training of the Bayesian network model was performed in the R v.3.5.2 environment (R Foundation, Austria) using RStudio 1.4 IDE.