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MAJOR ARTICLE

The Effects of Using a Clinical Prediction Rule to Prioritize Diagnostic Testing on Transmission and Hospital Burden: A Modeling Example of Early Severe Acute Respiratory Syndrome Coronavirus 2

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Background. Prompt identification of infections is critical for slowing the spread of infectious diseases. However, diagnostic testing shortages are common in emerging diseases, low resource settings, and during outbreaks. This forces difficult decisions regarding who receives a test, often without knowing the implications of those decisions on population-level transmission dynamics. Clinical prediction rules (CPRs) are commonly used tools to guide clinical decisions.

Methods. Using early severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) as an example, we used data from electronic health records to develop a parsimonious 5-variable CPR to identify those who are most likely to test positive. To consider the implications of gains in daily case detection at the population level, we incorporated testing using the CPR into a compartmentalized model of SARS-CoV-2.

Results. We found that applying this CPR (area under the curve, 0.69; 95% confidence interval, .68–.70) to prioritize testing increased the proportion of those testing positive in settings of limited testing capacity. We found that prioritized testing led to a delayed and lowered infection peak (ie, "flattens the curve"), with the greatest impact at lower values of the effective reproductive number (such as with concurrent community mitigation efforts), and when higher proportions of infectious persons seek testing. In addition, prioritized testing resulted in reductions in overall infections as well as hospital and intensive care unit burden.

Conclusion. We highlight the population-level benefits of evidence-based allocation of limited diagnostic capacity.

Keywords. clinical prediction rule; transmission dynamics; diagnostic testing.

The ongoing coronavirus disease 2019 (COVID-19) pandemic has demonstrated the importance of rapid identification of infections in managing an epidemic, as it allows for rapid isolation of cases, contact tracing and quarantining of contacts, thereby limiting onward transmission. However, as seen at the onset of the current pandemic, diagnostic testing capacity is often limited in the emergence of novel infections, in low resource settings, or during outbreaks [1–3].When diagnostic testing is unavailable, clinical case definitions are used instead in clinical management and public health response [4]. The rationing of diagnostic testing may result in those with more severe disease or at higher risks of complications receiving tests, as definitive diagnosis is critical to guide care [5]. However, because of their symptoms, severely ill patients may also be less mobile, thereby limiting the indirect benefit of their diagnostic testing on reducing onward transmission. Therefore, tools are needed to guide clinicians in the face of limited testing capacity.

Clinical prediction rules (CPRs) are commonly used tools to help to guide clinical management decisions, such as who should undergo testing or receive limited clinical resources. They provide standardization and consistency in care between physicians, as well as improved diagnostic accuracy [6]. Some widely used CPRs include the Centor criteria [7] for diagnosis and treatment of strep pharyngitis, the Ottawa ankle rule [8] for appropriate use of radiography in ankle trauma, and the CURB65 score [9] for triage of patients with pneumonia. Because CPRs are usually developed to improve patient care, their evaluation has been focused on their impact on patient-level outcomes; the impact of CPRs on population health, including on transmission dynamics of infectious pathogens, has not been widely studied.

Compartmental models such as the susceptible-exposed-infected-removed (SEIR) model, are often used to describe disease dynamics through a population. They combine

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epidemiological information (eg, transmissibility, duration of infectiousness, reproductive number) to provide a picture of the population-level disease dynamics over time [10, 11]; to our knowledge, compartmental models have not yet been used to evaluate the impact of CPRs on population-level public health outcomes.

Many diagnostic models for severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2) now exist [12], each specific to a given population and time, typically focused on achieving optimal patient care. Using a single health system in Utah as a proof of concept, we developed a CPR and incorporated it into an SEIR model of the ongoing SARS-CoV-2 pandemic to evaluate the population-level impact that could have been achieved by using a CPR to prioritize testing early in the pandemic, when testing capacity was limited. Many countries, including the United States, have experienced shortages in diagnostic testing capacity, and these shortages will likely continue in many settings worldwide [13–15], as well as in future outbreaks of emerging pathogens.

Our primary objective was to measure the impact that prioritized testing (using the CPR) could have had on the course of the SARS-CoV-2 pandemic, including the magnitude and timing of the outbreak peak as well as the associated impact on hospitalization and intensive care unit (ICU) burden. In addition, we determined the conditions (eg, test availability, test seeking volume, effective reproductive number) in which prioritized testing would have resulted in the greatest reduction in SARS-CoV-2 infections and hospitalizations. Potential benefits of CPR-guided testing continue to be relevant for surges in the SARS-CoV-2 pandemic, for future emerging infections, and for outbreaks of common infections (eg, cholera and measles) in settings with limited diagnostic capacity.

MATERIALS AND METHODS

Clinical Prediction Rule

All patients tested for SARS-CoV-2 in the University of Utah Health (UHealth) system were eligible for our study. Data were gathered from a period when testing eligibility was based on presenting with ≥1 of the following: cough, fever, shortness of breath, or a high risk of exposure given recent travel or contact with a laboratory-confirmed case (1 March to 6 April 2020). We use the phrase "test eligible" to describe any person seeking a test who satisfies these conditions. We considered age, sex, state-ranked area deprivation index, smoking status, reported symptoms, healthcare worker status, travel history, and exposure to a confirmed SARS-CoV-2 case as predictive variables. Random forest regression and logistic regression models were considered for our CPR. Our final CPR was a logistic regression model using the top 5 predictors to output the probability of an individual testing positive for SARS-CoV-2. Full details on data processing, the predictive variables, and the construction of the CPR are available in the Supplementary Materials 1. This study was reviewed by the University of Utah Institutional Review Board and determined to be exempt.

Modeling Daily Testing

We first explored the effects of prioritized versus indiscriminate testing per day (Figure 1A). On a given day, we assumed a certain number, N_{eligible}, of people who seek testing and are test eligible (have cough, fever, shortness of breath, or known exposure and seek testing). Of those who seek testing, a certain proportion, q, would test positive for SARS-CoV-2 if given a test and the rest, $(1 - q)$, would test negative. We assumed a limited number, N_{tests}, of SARS-CoV-2 tests were available daily. Using simulations (details in Supplementary Materials 2), we measured the proportion of test-eligible, SARS-CoV-2–positive patients who received testing under the 2 testing regimens: prioritized and indiscriminate testing.

SEIR Modeling

We also considered the effect of prioritized testing on disease spread in the population over longer time scales (months to years). We incorporated the same processes described above into a stochastic SEIR model parametrized for COVID-19. On each modeled day, we simulated the steps shown in Figure 1B, with parameters as in Table 1. Further simulation details are provided in Supplementary Materials 3.

We ran simulations assuming a total population of 3.2 million, the approximate population of the state of Utah [16]. We assumed an initial condition of 15 people in the infectious class and all others in the susceptible class. We ran our simulations for a period of 2 years. For each set of parameters considered, we ran 1000 stochastic simulations and then calculated the mean value of each of the total susceptible ($S + T_S$), exposed ($E + T_E$), infectious ($I + T_I$), and removed ($R + T_R$) groups, as well as 95% prediction intervals.

We then calculated several metrics, including the timing of the peak of the mean infection curve; the peak value of the mean infection curve; and the mean total number of infections by the end of the simulation. These metrics allowed us to compare expected outcomes between the models with indiscriminate testing and prioritized testing.

To highlight the associated implications for healthcare demand, we also modeled the daily occupancy of hospital beds and ICU beds (details in Supplementary Materials 3) We then calculated the mean number of person-days (ie, the number of people on a given day) where demand for hospitalization exceeds Utah's capacity of 4869 hospital beds and the number of person-days where demand for ICU beds exceeds Utah's capacity of 687 ICU beds [17, 18]. Note that these numbers are for total hospital and ICU beds, not those set aside for patients

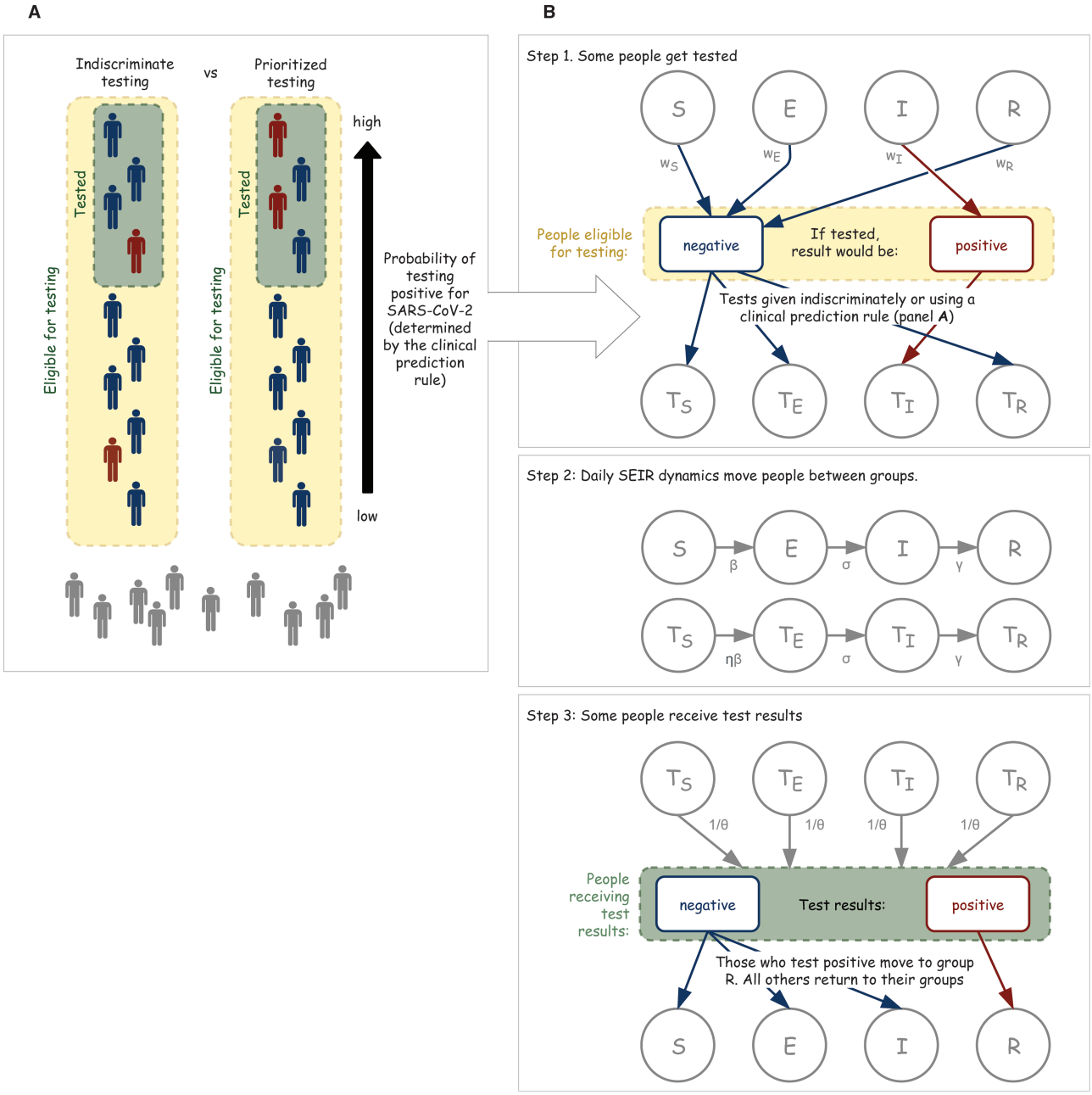

Figure 1. Effects of prioritized testing on daily testing outcomes and incorporation into a susceptible-exposed-infected-removed (SEIR) model. (*A*), Schematic comparing the testing of a subset of test-eligible people using either indiscriminate testing or prioritized testing. Red figures would test positive for severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2), blue figures would test negative, and gray figures are not seeking tests. Please refer to the online version of this manuscript to view color figures. For prioritized testing, people are arranged and then tested according to their probability of testing positive, as determined by the clinical prediction rule. (*B*), Visual depiction of how prioritized testing was incorporated into the daily stochastic SEIR model. In step 1, people in each compartment seek testing with probabilities w_S, w_E, w_I, and w_R. Individuals waiting for test results are in state T_S, T_E, T_I, or T_R. In step 2, after testing, daily SEIR dynamics occur with transmission rate β, incubation rate σ, and removal rate γ. Those waiting for test results (states T_S, T_E, T_I, and T_R) have reduced transmission by a factor of η. In step 3, a proportion of those in states T_S, T_E, T_I, and T_R receive their test results, after an average delay of θ days.

with COVID-19, and thus provide an upper bound for hospital capacity. All analyses and simulations were conducted using R statistical software (version 3.6.0; [19]). All code is archived and available online (doi:10.5281/zenodo.3924186).

RESULTS

During the period from 1 March to 6 April 2020, a total of 1983 patients were tested for SARS-CoV-2 at UHealth. After removing observations with missing covariate data, we obtained an

Table 1. Summary of the Parameters (and Available Sources) Used in the Stochastic Susceptible-Exposed-Infected-Removed (SEIR) Model[a]

Symbol	Interpretation	Value	Source(s)	Other Values Considered[b]
w_S	Proportions of individuals in susceptible, exposed, infected, and removed states (listed in that order) who are test eligible each day	0.0013	Estimated; details in Supplementary Materials 4	…
w_E		0.0013		…
w_I		0.072		0.029–0.144
w_R		0.00084		…
N_{tests}	No. of tests available daily	1000	…	500, 3000, 5000
σ	Incubation rate	1/5.2	[20, 21]	…
γ	Recovery ("removal") rate	Uniform random variable over 1/7 to 1/4	[22–25]	…
R_e	Effective reproductive number	1.75	…	1.5–2.5
β	Frequency-dependent transmission rate	$\gamma \cdot R_e$	[26]	…
θ	Average test result delay	2 days	…	0–4
η	Reduction in transmission due to isolation	0.2 (ie, isolation reduces transmission by 80%)	[27]	…

[a]For full details on model parametrization, see Supplementary Materials 4.
[b]This column shows the range of values presented for that sensitivity analysis.

analytic sample size of 1928. Our final parsimonious 5-variable CPR had a cross-validated area under the curve (AUC) of 0.69 (95% confidence interval, .68–.70). In all the results that follow, we used this 5-variable CPR. We explored using additional variables but found this only marginally improved predictive ability (AUC up to 0.71; Supplementary Figure 1 and Supplementary Table 2), at the expense of requiring much greater data entry effort by clinicians. We also considered alternative versions of the CPR in light of varying predictor availability in different clinical contexts. We explored models excluding symptoms, including vital signs, and including a race/ethnicity variable (Supplementary Table 1). Again, these did not meaningfully improve predictive ability (AUC up to 0.72; Supplementary Table 2). Finally, we explored using random forest regression to fit the models, but logistic regression estimates had consistently higher AUCs.

When comparing indiscriminate testing to prioritized testing, the absolute difference in the number of people infected with COVID-19 who were tested was greatest for intermediate levels of testing availability, achieving the greatest benefit to disease detection when 40%–60% of test-eligible people received testing (vertical difference between solid lines in Figure 2). However, the proportional increase in the number of people with COVID-19 who were tested was greatest for low testing capacity, with the largest fold changes seen when <20% of test-eligible people received testing (dotted line in Figure 2). For example, if the rate of SARS-CoV-2 positivity among test-eligible people was 5% and there was test capacity for only 10% of those people, we would expect to see a nearly 3-fold increase in the number of patients testing positive on a given day if using prioritized testing instead of indiscriminate testing (Figure 2A). These results were sensitive to the proportion of SARS-CoV-2–positive patients who are test eligible, with greater differences between prioritized and random testing strategies seen for low rates of SARS-CoV-2 positivity (compare Figure 2A–2E). Results were robust to the total number of test-eligible persons.

Using our stochastic SEIR compartmental model, we show that prioritized testing delays the timing and reduces the prevalence at the infection peak and reduces final size of the pandemic (Figure 3 and Table 2). For our base parameter set, prioritized testing compared with indiscriminate testing resulted in a 30-day delay in the timing of the infection peak and a 22% decrease in the peak number of infections.

The differences in the timing and numbers of infections between a model with prioritized versus indiscriminate testing were greatest for lower values of the effective reproductive number, R_e (Figure 3 and Table 2). When alternate CPRs with similar AUC values were considered, results varied only marginally (Supplementary Table 2). Alternate CPRs with higher AUCs did not necessarily perform better on all metrics (Supplementary Table 3). Increasing the proportion of infectious test-eligible people (w_I) had a positive impact on the magnitude of the differences between the indiscriminate and prioritized testing models (Figure 3 and Table 2). Increasing the number of tests available (N_{tests}) increased the differences for low values of N_{tests} but then had reduced benefits for higher values (Table 2), consistent with Figure 2. Varying the delay in test results, θ, from 0 to 4 days, we observed only small differences in overall disease dynamics (Table 2). Increasing η from 0.2 to 0.5 (ie, with those awaiting test results isolating less effectively) did not notably increase the effect of varying θ (Supplementary Table 3).

Finally, we explored the impact of prioritized testing on hospital and ICU bed occupancy, basing our parameters on the outbreak in Utah (Figure 4). We demonstrated that prioritized testing resulted in reductions in the number of people-days (ie, sum of the number of people on each day needing a hospital or ICU bed) where demand exceeded capacity for both hospital

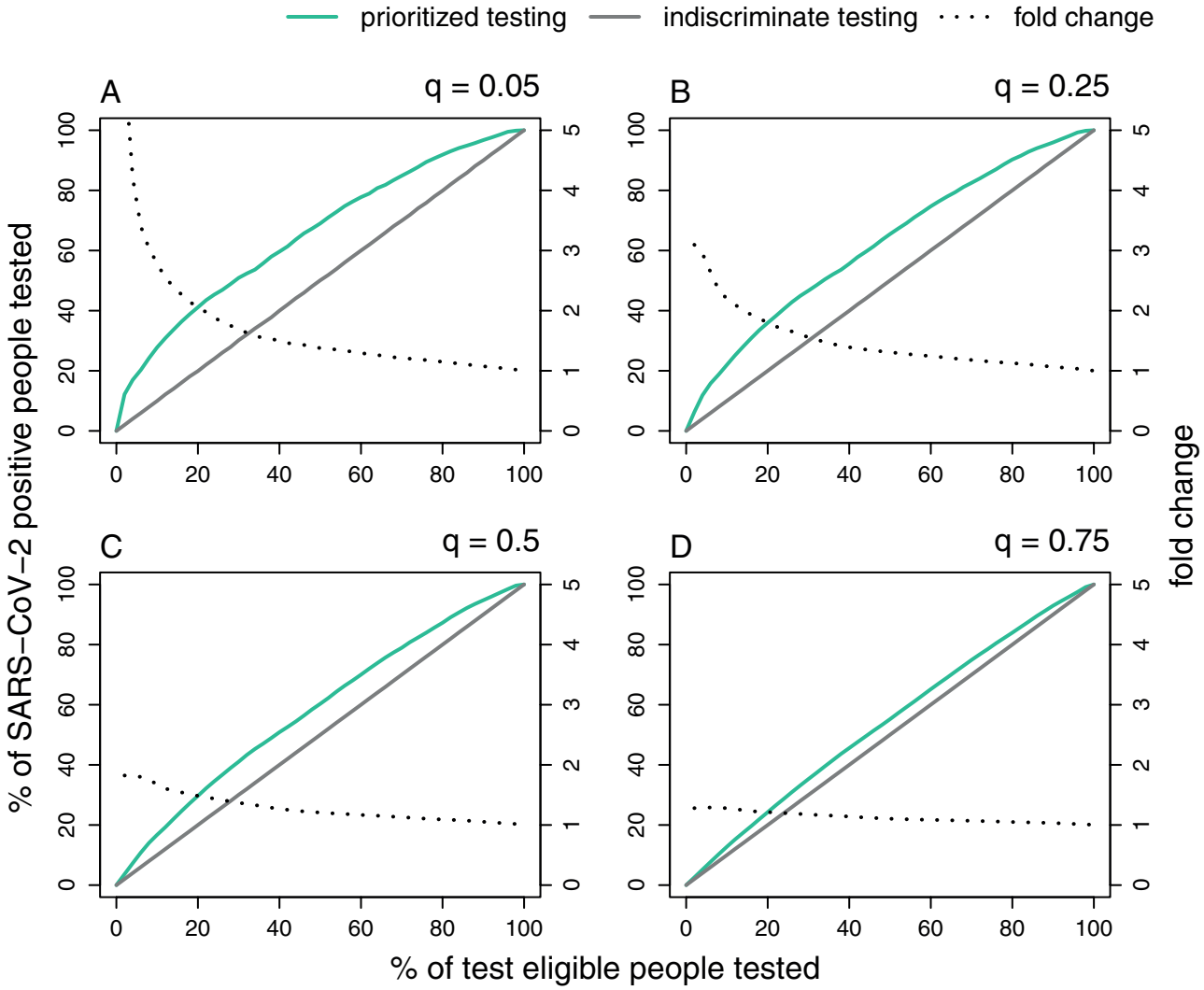

Figure 2. Effect of prioritized testing compared with indiscriminate testing on the proportions of severe acute respiratory syndrome coronavirus disease 2 (SARS-CoV-2)–positive and test-eligible people who are tested. The horizontal axis allows comparison between different testing capacities. The vertical axis shows the percentages of SARS-CoV-2–positive and test-eligible people tested. Dotted lines denote the fold changes between the gray and green lines. Refer to the online version of this manuscript to view color figure. The percentages of test-eligible people who are SARS-CoV-2 positive (proportion *q*) are 5% in *A,* 25% in *B,* 50% in *C,* and 75% in *D.*

and ICU beds (Table 2). For our base parameter set, prioritized testing as compared with indiscriminate testing resulted in 63% and 96% reductions in the numbers of people-days above hospital and ICU capacity, respectively.

DISCUSSION

The availability of diagnostic testing may be limited during the initial phase of an outbreak with an emerging pathogen, or even in later phases in under-resourced settings resulting in rationing of diagnostic tests, which can have unintended population-level implications. Using SARS-CoV-2 in Utah as a proof of concept, we found that a CPR to prioritize testing positively affects both the number of laboratory-confirmed cases per day and long-term disease dynamics when testing is scarce. We incorporated our model of prioritized testing into an SEIR model and showed the value of our CPR, with appreciable delays in the timing and height of the infection peak, decreases in the total number of infections, and reductions in the number of people-days above hospital and ICU capacity. This novel combination of analytic methods allowed us to highlight both the individual-level and population-level benefits of the CPR.

In spite of our CPR's having only moderate discriminatory performance (AUC, 0.69), our results show that prioritizing diagnostic testing, even based on less-than-perfect CPRs, still has a meaningful impact on individual and population disease burden. Furthermore, future predictive models built after more extensive and improved data collection (eg, standardized collection by clinicians over a longer time) may improve CPR performance, thereby further improving the impact of prioritized testing on community disease burden.

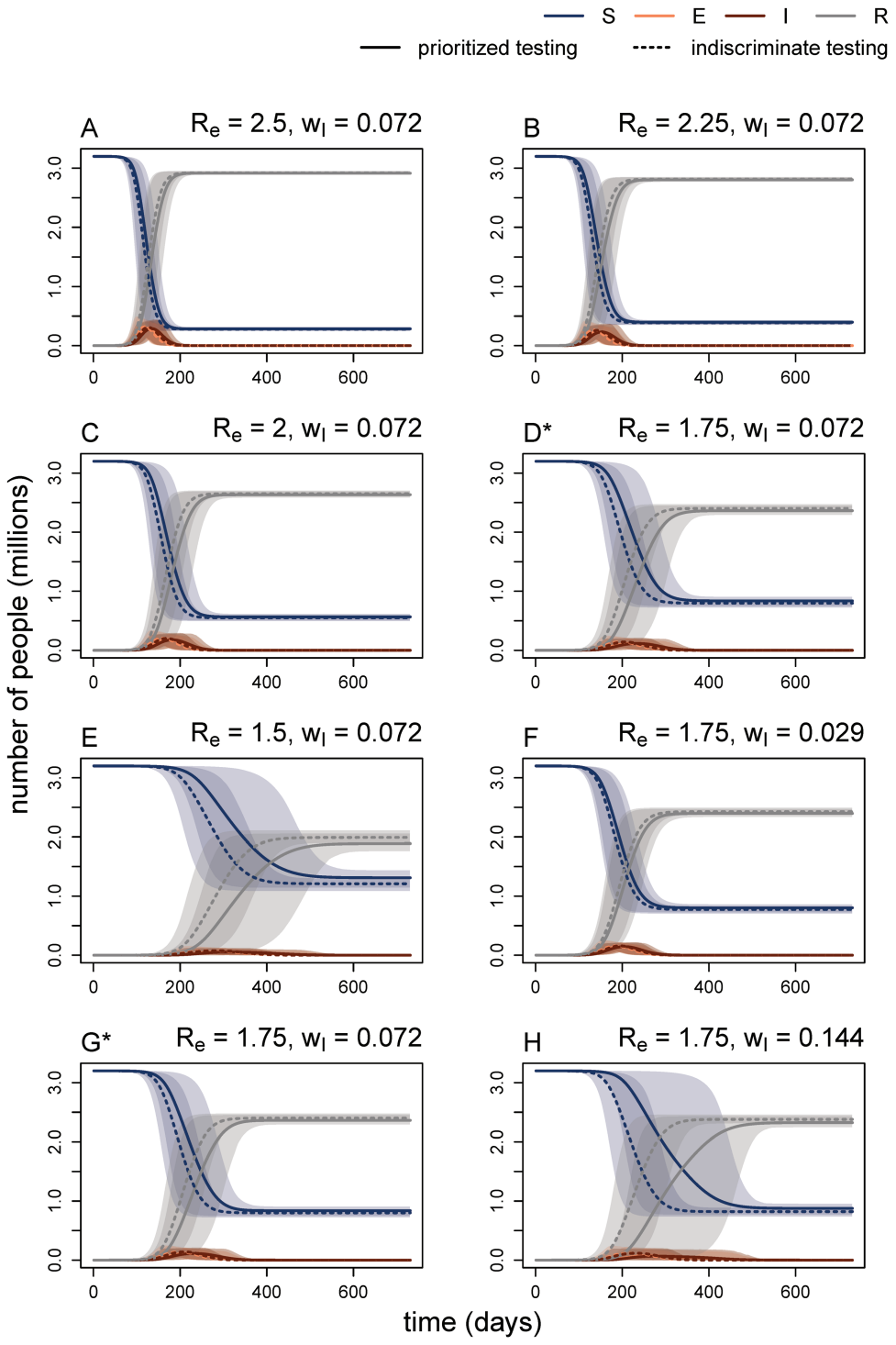

Figure 3. Comparison of susceptible-exposed-infected-removed (SEIR) curves between models with prioritized versus indiscriminate testing for decreasing values of the effective reproductive number, R_e, (*A–E*), and decreasing rates of test seeking among infectious individuals, w_I (*F–H*). Solid lines represent means of 1000 stochastic simulations with prioritized testing, and dotted lines, means for the model with indiscriminate testing. Shaded regions represent corresponding middle 95th percentiles of simulations. *A*, $R_e = 2.5$. *B*, $R_e = 2.25$. *C*, $R_e = 2.0$. *D*, $R_e = 1.75$. *E*, $R_e = 1.5$. *F*, $w_I = 0.029$. *G*, $w_I = 0.072$. *H*, $w_I = 0.144$. Note that *D* and *G* have the same parameters, but have both been included to show sequential change as we vary R_e and w_I. Refer to the online version of this manuscript for the full color figure.

When considering the individual-level impact of the CPR on test-eligible individuals, we found that prioritized testing yielded the greatest absolute gains for intermediate testing capacity (capacity to test 40%–60% of test-eligible people) and the highest proportional gains for low testing capacity. Improved diagnostic triage through prioritized testing leads to diagnosis

Table 2. Effects of Prioritized Testing on Infection Dynamics of Susceptible-Exposed-Infected-Removed (SEIR) Model Over a Range of Parameter Values[a]

Parameter	Delay in Peak Timing, d	Mean Reduction, No. (%)			
		Peak Height	Total Infections	Person-Days Above Hospital Capacity	Person-Days Above ICU Capacity
R_e					
2.5	8	21 192 (7)	6478 (0)	21 619 (5)	145 802 (72)
2.25	10	27 197 (12)	9891 (0)	35 371 (10)	138 734 (76)
2.0	13	24 418 (14)	17 081 (1)	48 960 (20)	128 623 (83)
1.75[b]	30	25 592 (22)	38 415 (2)	62 794 (63)	108 918 (96)
1.5	36	22 855 (43)	101 938 (5)	NA[c]	45 747 (100)
w_I					
0.029	10	12 592 (9)	29 584 (1)	27 768 (20)	108 691 (88)
0.072[b]	30	25 592 (22)	38 415 (2)	62 794 (63)	108 918 (96)
0.144	45	49 559 (74)	54 434 (2)	40 246 (100)	98 663 (100)
N_{tests}					
500	21	20 832 (15)	24 751 (1)	45 297 (33)	111 538 (90)
1000[b]	30	25 592 (22)	38 415 (2)	62 794 (63)	108 918 (96)
3000	21	24 499 (46)	141 657 (6)	NA[c]	49 329 (100)
5000	4	2910 (8)	127 200 (7)	NA[c]	NA[c]
θ					
0	25	25 734 (23)	38 314 (2)	63 136 (73)	107 319 (97)
2[b]	30	25 592 (22)	38 415 (2)	62 794 (63)	108 918 (96)
4	23	24 646 (21)	40 993 (2)	61 139 (63)	108 912 (95)

Abbreviations: θ, average test result delay (in days); ICU, intensive care unit; NA, not available; N_{tests}, number of tests available daily; R_e, effective reproductive number; w_I, proportion of infected individuals who are test eligible each day.

[a]All parameter values are as stated in the text, except where stated otherwise in the table. Each column compares the mean results from 1000 stochastic simulations of the model with prioritized testing to one with indiscriminate testing.

[b]Results for the base parameter set described in the text (ie, R_e = 1.75; w_I = 0.072; N_{tests} = 1000; and θ = 2), and are repeated for reference in each subsection.

[c]Values are NA where hospital or ICU demand did not exceed capacity for either the prioritized or indiscriminate testing model.

of individuals earlier in their course of disease, with potential for benefit through earlier initiation of therapies or medical monitoring, and isolation or contact-tracing precautions [28].

At the population level, we found notable impact of prioritized testing on COVID-19 dynamics, leading to reductions in infections, hospitalizations, and ICU use, as well as delaying the infection peak, providing more time for health systems to prepare for the surge. The magnitude of this impact was sensitive to several key parameters. For example, when R_e was lowered, as may happen with the introduction of other public health interventions such as social distancing, the effects of prioritized testing increased. This suggests a synergistic effect between prioritized testing and other nonpharmaceutical interventions, since implementing prioritized testing concurrently with other nonpharmaceutical interventions that reduce R_e, can help maximize potential gains. Increasing the proportion of infectious people who seek testing (w_I) increases the effects of prioritized testing because of the indirect benefit (reduction of R_e) of isolating those individuals quickly. This may occur in populations with a higher proportion of symptomatic individuals, such as older populations [29] or those with other known risk factors [30]. Alternatively, the proportion of infectious individuals seeking testing could be increased intentionally through interventions such as contact tracing or campaigns to encourage test-seeking behavior.

For any given level of testing, when SARS-CoV-2 is prevalent and comprises a large fraction of the test-eligible population, either testing strategy can be impactful in reducing transmission by speeding up isolation. For any given level of testing, when SARS-CoV-2 comprises only a small fraction of the test-eligible population, prioritized testing using the CPR leads to greater population-level benefit. Thus, in settings with both SARS-CoV-2 and high prevalence of influenzalike illness (eg, a possible fall and winter scenario), prioritized testing may be of increased value.

Use of prioritized testing is most useful in situations with limited test capacity, as the benefits of prioritized testing become negligible when test demand does not exceed test availability. While some health systems had increased their testing capacity to meet demands, as the United States experiences a new surge in cases, demand for testing has continued to increase. Furthermore, many countries and regions with lower resources may continue to have limited capacity for testing. Investment in a system of prioritized testing may be more cost-effective than the manufacturing or purchasing of more tests to meet demand. In addition, this approach can be useful in future pandemic preparedness, as a similar approach implemented in a timely manner may help maximize finite testing resources during the initial stages of a future outbreak, until adequate, affordable testing is available.

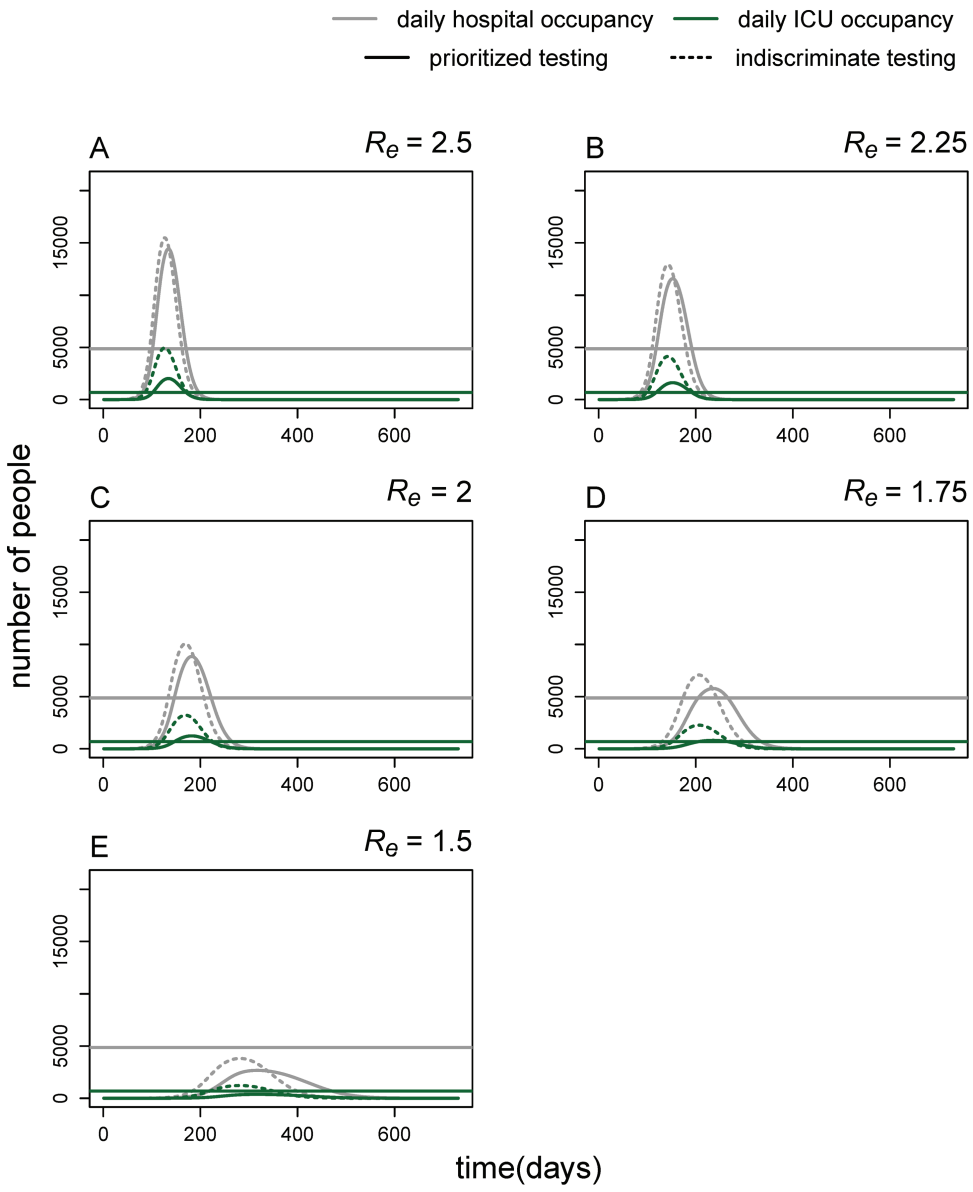

Figure 4. Comparison of simulated demand for daily hospital and intensive care unit (ICU) occupancy between models with prioritized versus indiscriminate testing. Solid lines represent means of 1000 stochastic simulations with prioritized testing, and dotted lines, means for the model with indiscriminate testing. The effective reproductive number, *Re*, decreases from 2.5 to 1.5 in increments of 0.25 in plots *A*–*E*. Refer to the online version of this manuscript for the full color version of this figure.

Our study has several limitations. Our CPR was derived using data from a single health system servicing primarily non-Hispanic white patients, with test eligibility criteria that followed Centers for Disease Control and Prevention guidance from early in the pandemic; thus, as with other diagnostic CPRs for SARS-CoV-2 [12], our CPR should not be considered generalizable and requires validation in other settings. For different populations or for later periods in Utah, the CPR should be updated with the most appropriate available data. Furthermore, specific population subgroups (eg, age and sex) may benefit from individualized CPRs, and this was not explored in the current analysis. Instead, we highlight the generalizability of the approach we have presented and note that the individual-level and population-level impacts of prioritized testing are robust to the specific CPR used (Supplementary Table 3).

There are also several logistical challenges. Implementation of such a prioritization system would require its incorporation into a telephone- or Web-based triage, or through a health worker–based assessment. In addition, our model assumes that all individuals seeking testing would present at the same time. In most clinical settings, the implementation of such a CPR would involve the use of a probability threshold, set based on data from the previous day(s) and the expected number of test-eligible people. The optimal setting of this threshold, given stochastic testing demands

and infection dynamics, would be an area for future exploration during clinical trials. We also did not consider the implications of the sensitivity and specificity of SARS-CoV-2 tests; low sensitivity and specificity in the diagnostic tests would reduce the utility of testing in general, and thus also of prioritized testing. Finally, our SEIR model was chosen as a tool to demonstrate the relative impact of the CPR using a generalizable framework familiar to our intended audience, and it thus omitted explicit consideration of some SARS-CoV-2 transmission mechanisms (eg, superspreader events). As knowledge about any emerging pathogen continues to evolve, additional details that could help with detailed forecasting can and should be included for specific populations, appropriate for a specific time and place.

The limited availability of SARS-CoV-2 testing has hampered disease mitigation efforts in many locations. By incorporating a diagnostic CPR into a transmission dynamics model, we have demonstrated the potential efficacy of prioritized testing for delaying and reducing peak infections and the consequent healthcare demand. By highlighting parameter regimens in which these effects are greatest, we have suggested situations in which it may be most efficacious to use a CPR to prioritize testing of testing shortages caused by the emergence of a novel infectious disease such as SARS-CoV-2.

Notes

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