California shows the way for biosecurity in commercial gene synthesis

To the Editor — On 21 January, California took a major step to increase biosecurity in commercial gene synthesis, introducing legislation that requires all scientists purchasing gene synthesis products to use companies that perform screening on customers and the sequences they order. If enacted, this legislation would make it a competitive advantage for companies to take biosecurity seriously. Here, we argue that the US federal government and other governments should emulate California's actions.

Assembly member Rudy Salas (assembly district 32) introduced the legislation, which requires not only that customers use companies that perform biosecurity screening but also that companies offering DNA synthesis services in California perform sequence screening[1]. These restrictions would make it harder for a potential nefarious actor to access genetic material for making pathogenic viruses de novo, such as smallpox, Ebola or influenza. The de novo synthesis of known pathogens, particularly small viruses, is listed as one of the most pressing biodefense risks by a 2018 report from the National Academies of Sciences, Engineering and Medicine[2].

Many commercial gene synthesis companies already voluntarily screen customer orders to make sure that they are both selling to scientists working in regulated research institutions and not selling anything that could be potentially harmful. In 2010, the US Department of Health and Human Services issued voluntary guidance for companies, including steps to take if there is a sequence or customer of concern[3].

Because it costs time and money to perform biosecurity screening, responsible companies that voluntarily take this step have until now been at a competitive business disadvantage[4]. The California legislation seeks to tackle this by requiring that all DNA synthesis companies undertake sequence screening, thus leveling the playing field. The California legislation also has a mechanism for eventually requiring screening of smaller gene synthesis products than the current Department of Health and Human Services guidance calls for, a necessary step to keep up with advances in biotechnology[5].

Of course, there are limits to how much California can do by itself, as this legislation would apply only to California state funds and California gene synthesis companies. Although California is a biotech giant, with several gene synthesis companies, gene synthesis is international, with a global market valued at over $200 million in 2017 and projected growth to over $600 million by 2022 worldwide[6].

It is time for the US federal government and other governments to put in place regulations that ensure DNA sequences of pathogenic agents do not fall into the wrong hands. It is no longer sufficient for voluntary participation in guidance to oversee a matter of national and international biosecurity. Governments around the world should follow California's example by strengthening biosecurity rules that require synthetic DNA sequence screening. ❐

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Competing interests

The authors declare no competing interests.

The COVID-19 XPRIZE and the need for scalable, fast, and widespread testing

To the Editor — The US Food and Drug Administration (FDA) Emergency Use Authorization (EUA) and Instructions for Use (IFU) documents outlining the current approved virology tests for SARS-CoV-2 are largely unstandardized. As such, there remains an urgent need for a searchable interface allowing exploration of standardized information reported in these EUA and IFU documents. To gain an improved understanding of the current testing landscape and to galvanize future test development, we present here an online tool (http://www.resiliencehealth.com/tests) that profiles current and emerging virology tests for detecting SARS-CoV-2 (Figs. 1 and 2). We also call on the research community to respond to an open COVID-19 XPRIZE competition, OpenCovidScreen, seeking to identify cheap, high-quality, scalable testing solutions.

As of 27 July 2020, an analysis of the FDA data on EUA SARS-CoV-2 virology tests reveal a wide range of limit of detection (LoD), spanning >5 orders of $\log_{10}$ differences. These metrics are of critical importance because each 10-fold increase in the LoD of a COVID-19 viral diagnostic test is expected to increase the false negative rate by 13%[1].

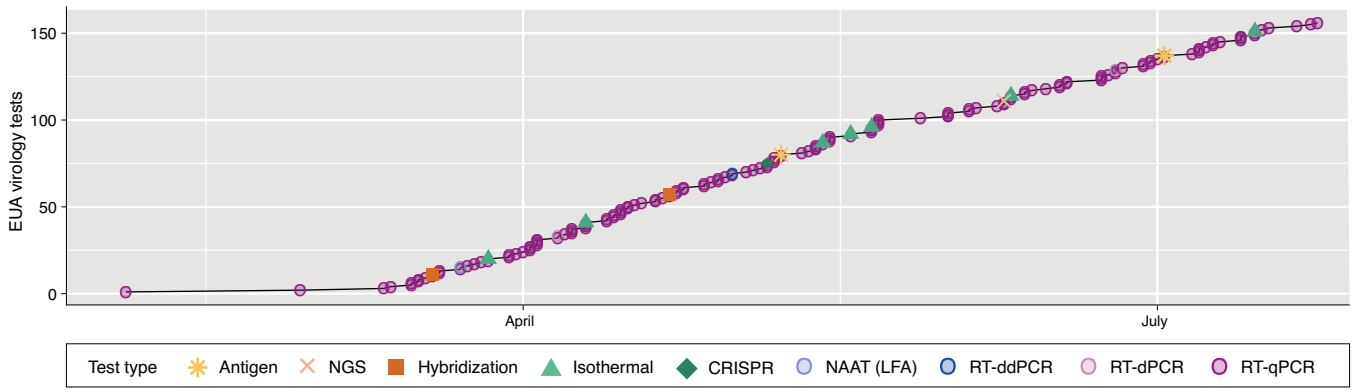


Fig. 1 | Cumulative number of EUA virology tests approved from February to July 2020. NGS, next-generation sequencing; NAAT, nucleic acid amplification test; LFA, lateral flow assay; RT, reverse transcription; ddPCR, Droplet Digital PCR; dPCR, digital PCR; qPCR, quantitative PCR.

Beyond this variable performance reported in IFUs for EUA tests, key attributes of many tests, such as primer sequences, protocol steps or viral gene targets, are either unclear or missing. Also, most approved EUAs use large multipliers (2- to 200-fold) on their own LoD for contrived or clinical samples to pass the minimum threshold for approval, based on a 95% positive/negative percentage agreement across at least 30 positive and 30 negative samples. As submissions stand, it is difficult to directly compare results and even understand how a test will actually translate into real-world or clinical settings.

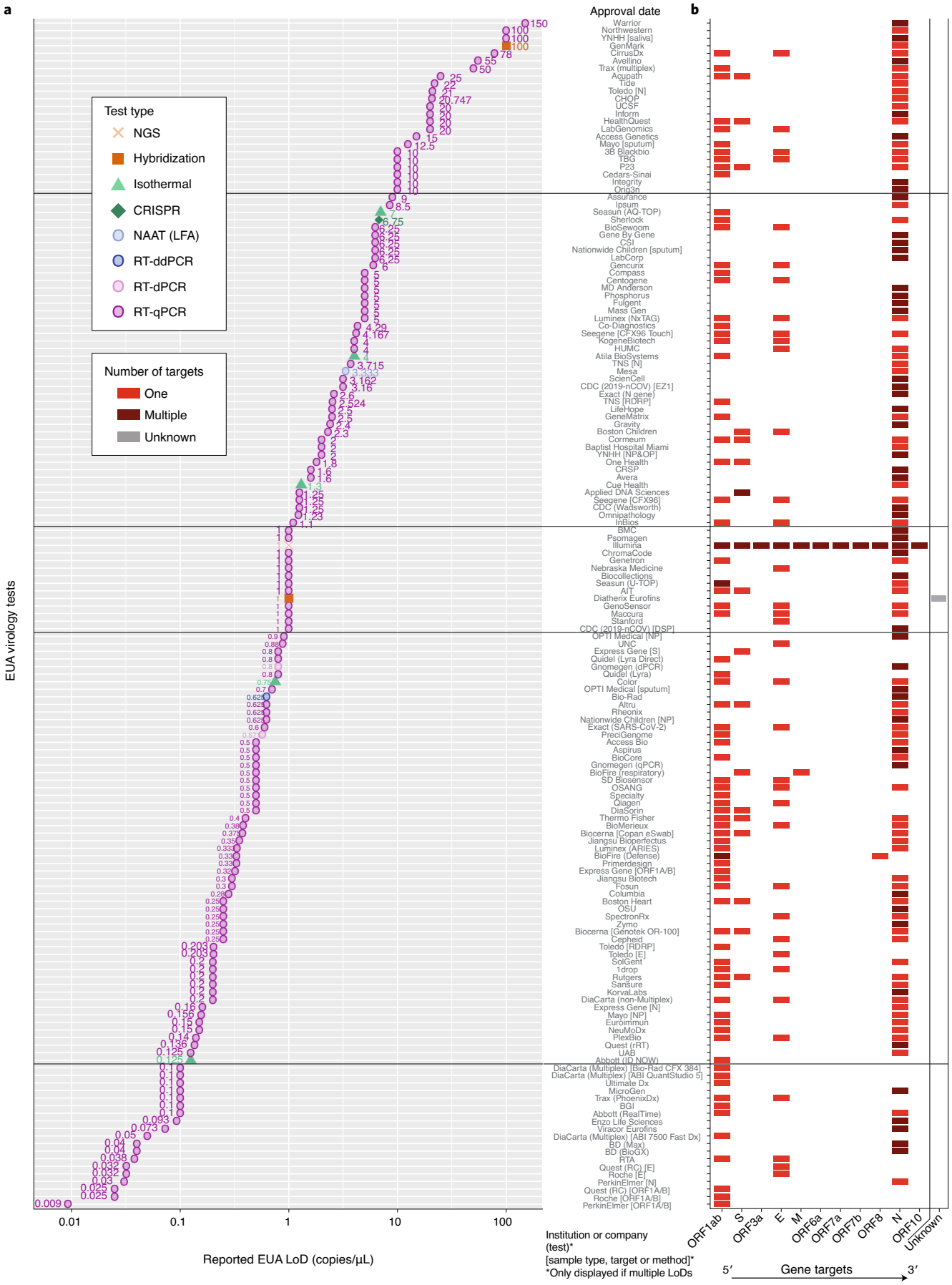
Moreover, there has not been an independent assessment of these tests' abilities or a comprehensive benchmarking of their strengths and weaknesses in different clinical settings, nor a consistent sample type (for example, nasopharyngeal, nasal, saliva) used across the EUAs. Thus, a comprehensive benchmarking effort on all methods on the market would be helpful, similar to ones conducting head-to-head studies of serological tests[2] and other sites that annotate and analyze some of these tests, such as FindDx (https://www.finddx.org/), the US National Institute for Standards and Technology (NIST)'s Rapid Microbial Testing Methods Consortium (https://www.nist.gov/programs-projects/nist-rapid-microbial-testing-methods-consortium) and the COVID-19 Testing Project (https://covidtestingproject.org/index.html).

However, even if all current EUA tests for the SARS-CoV-2 virus performed with >95% sensitivity and >95% specificity, their combined capacities would still fall short of enabling large-scale, ubiquitous temporal monitoring (tens of millions per day), involving samples with varying viral load and substrates[3]. Also, tests with a higher LoD would not be readily applicable to pooling strategies, in which samples are by definition diluted before testing. Even the lower LoD tests, while promising for pooling, have not had independent LoD assessments. Moreover, truly city-scale or even national-level testing to decrease and control infection rates would require fast turnaround times (test result in less than one day), easy processing, and a low cost (per test and capital expense), such that a consumer, employer or government body could easily pay for multiple tests a week for each person.

To address the above issues, we have designed the COVID-19 XPRIZE competition, OpenCovidScreen (https://opencovidscreen.org/), to identify economically viable, high-quality, scalable testing options (Fig. 3). After competitors are selected on the basis of their results, methods, cost, scalability and speed, they will then be sent blinded samples to analyze. Results will be uploaded to the XPRIZE site and analyzed for overall performance, LoD and false positives. The finalists, based on their overall methods, results and innovation, will go into the clinical validation round, in which OpenCovidScreen will follow the methods laid out by the competitors to assess the reproducibility of their results. Top teams from this validation round will be awarded a prize and selected to set up and deploy testing sites, wherein OpenCovidScreen will help scale their tests and expand them into more locations, as well as to coordinate with government, industry and non-profit efforts (for example, the NIH RADx Program and Testing for America; https://www.nih.gov/research-training/medical-research-initiatives/radx).

We invite readers to submit solutions for this XPRIZE, which is open to participants from all around the world (https://xprize.org/testing). This prize can serve as a springboard for both new and established technologies that can enable truly global viral testing and surveillance. Successful methods will depend on the availability of reagents, resources and automation, and as such, these metrics will also be used to identify the finalists. Winning methods will help regions increase testing capabilities by orders of magnitude and thus empower schools, businesses and cities to rapidly reopen safely, as well as pioneer technologies and platforms that can be used for future outbreaks. It is crucial to deploy rapid, scalable methods capable of tracking viruses to mitigate their detrimental impacts on society. All are encouraged to help in this fight. ❐

Fig. 2 | Performance and targets of different EUA virology tests. a, Limit of detection (LoD) for tests that reported copies/μL or copies/mL (presented in copies/μL throughout). **b**, EUA virology test targets. SARS-CoV-2 5′–3′ genome[4] on horizontal axis, with tests on the vertical axis and colors indicating whether the test has one target (red) or multiple targets (brown) in the specified region. Each line indicates a test source (company or institution). If an EUA reported different LoDs for different targets, sample types or methods, each is displayed as a separate row. NGS, next-generation sequencing; NAAT, nucleic acid amplification test; LFA, lateral flow assay; RT, reverse transcription; ddPCR, Droplet Digital PCR; dPCR, digital PCR; qPCR, quantitative PCR; RDRP, RNA-dependent RNA polymerase; DSP, diagnostic sample preparation; NP, nasopharyngeal; OP, oropharyngeal; rRT, real-time reverse transcriptase.


a
b
Approval date
Test type
NGS
Hybridization
Isothermal
CRISPR
NAAT (LFA)
RT-ddPCR
RT-dPCR
RT-qPCR
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Multiple
Unknown
EUA virology tests
Reported EUA LoD (copies/µL)
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0.1
1
10
100
Warrior
Northwestern
YNHH [saliva]
GenMark
CirrusDx
Avellino
Trax (multiplex)
Acupath
Tide
Toledo [N]
CHOP
UCSF
Inform
HealthQuest
LabGenomics
Access Genetics
Mayo [sputum]
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TBG
P23
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Phosphorus
Fulgent
Mass Gen
Luminex (NxTAG)
Co-Diagnostics
Seegene [CFX96 Touch]
KogeneBiotech
HUMC
Atila BioSystems
TNS [N]
Mesa
ScienCell
CDC (2019-nCOV) [EZ1]
Exact (N gene)
TNS [RDRP]
LifeHope
GeneMatrix
Gravity
Boston Children
Cormeum
Baptist Hospital Miami
YNHH [NP&OP]
One Health
CRSP
Avera
Cue Health
Applied DNA Sciences
Seegene [CFX96]
CDC (Wadsworth)
Omnipathology
InBios
BMC
Psomagen
Illumina
ChromaCode
Genetron
Nebraska Medicine
Biocollections
Seasun (U-TOP)
AIT
Diatherix Eurofins
GenoSensor
Maccura
Stanford
CDC (2019-nCOV) [DSP]
OPTI Medical [NP]
UNC
Express Gene [S]
Quidel (Lyra Direct)
Gnomegen (dPCR)
Quidel (Lyra)
Color
OPTI Medical [sputum]
Bio-Rad
Altru
Rheonix
Nationwide Children [NP]
Exact (SARS-CoV-2)
PreciGenome
Access Bio
Aspirus
BioCore
Gnomegen (qPCR)
BioFire (respiratory)
SD Biosensor
OSANG
Specialty
Qiagen
DiaSorin
Thermo Fisher
BioMerieux
Biocerna [Copan eSwab]
Jiangsu Bioperfectus
Luminex (ARIES)
BioFire (Defense)
Primerdesign
Express Gene [ORF1A/B]
Jiangsu Biotech
Fosun
Columbia
Boston Heart
OSU
SpectronRx
Zymo
Biocerna [Genotek OR-100]
Cepheid
Toledo [RDRP]
Toledo [E]
SolGent
1drop
Rutgers
Sansure
KorvaLabs
DiaCarta (non-Multiplex)
Express Gene [N]
Mayo [NP]
Euroimmun
NeuMoDx
PlexBio
Quest (rRT)
UAB
Abbott (ID NOW)
DiaCarta (Multiplex) [Bio-Rad CFX 384]
DiaCarta (Multiplex) [ABI QuantStudio 5]
Ultimate Dx
MicroGen
Trax (PhoenixDx)
BGI
Abbott (RealTime)
Enzo Life Sciences
Viracor Eurofins
DiaCarta (Multiplex) [ABI 7500 Fast Dx]
BD (Max)
BD (BioGX)
RTA
Quest (RC) [E]
Roche [E]
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Roche [ORF1A/B]
PerkinElmer [ORF1A/B]
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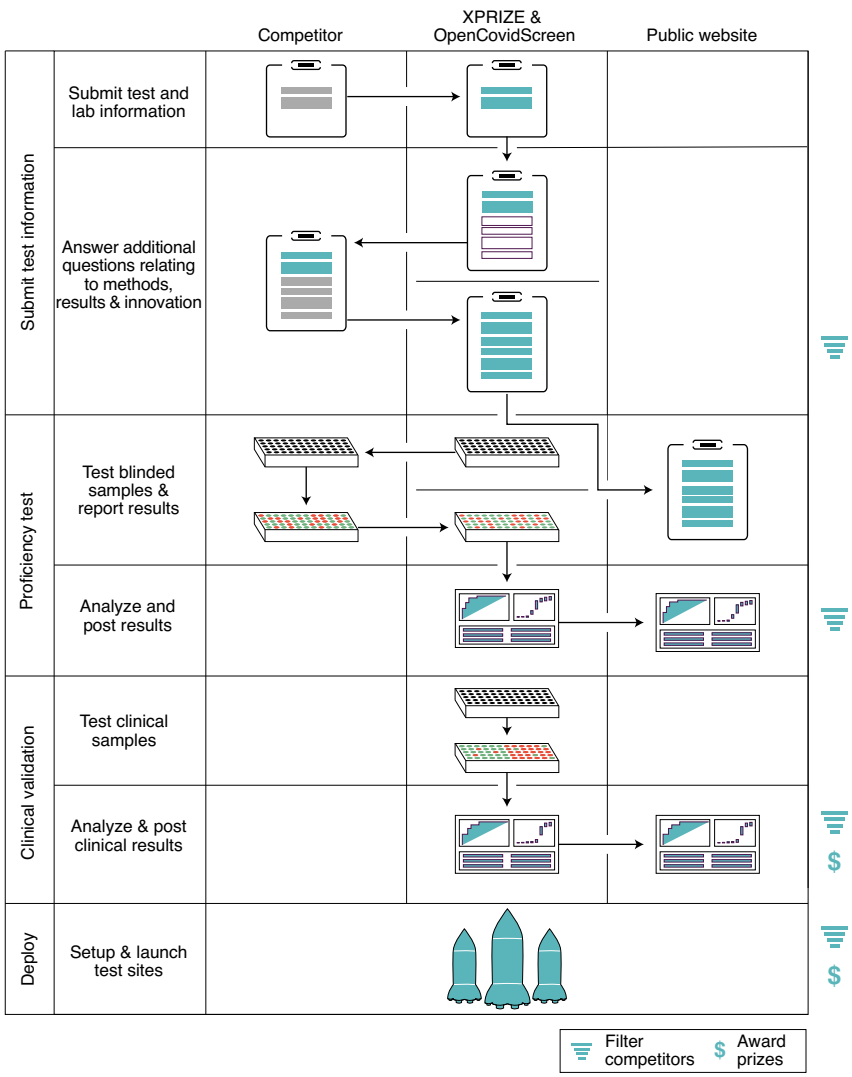

Fig. 3 | The XPRIZE/OpenCovidScreen competition. The OpenCovidScreen competition is intended to identify fast, scalable, and cheap SAR-CoV-2 virology tests through a series of phases, starting with submitting test and method information (top), a proficiency test including blinded samples, and a clinical validation phase (middle). The top competitors identified on the basis of their methods, results and scalability will then be chosen for deployment to enable widespread usage of their tests (bottom).

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Competing interests

J.K. is cofounder and board member for Gingko Bioworks. C.E.M. is a cofounder and board member for Aevum, Biotia and Onegevity, as well as an advisor or compensated speaker for Abbvie, Acuamark Diagnostics, ArcBio, Bio-Rad, DNA Genotek, Genialis, Genpro, HomoDeus, Karius, Illumina, MilliporeSigma, Nanostring, New England Biolabs, Qiagen, Promega, Resilience Health, Tempus Labs, Whole Biome, and Zymo Research. A.C.H., H.P.J., C.E.M. and M.J.M. advise Resilience Health. J.H. is a board member or shareholder for Grail and Illumina. G.C. has conflicts: http://arep.med.harvard.edu/gmc/tech.html.