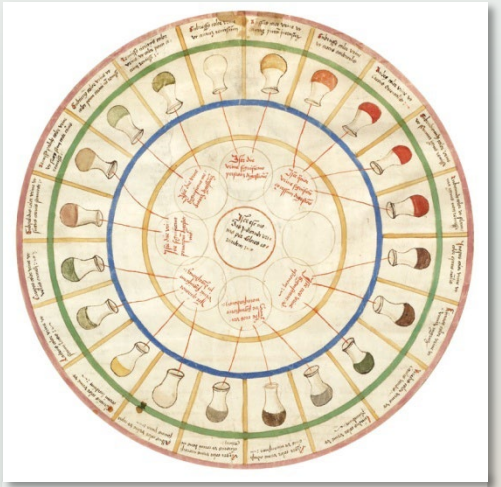
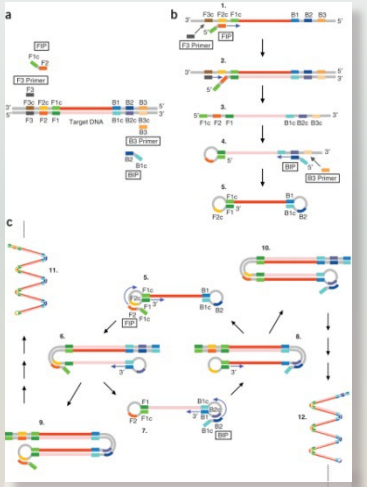




Point of Care Testing
(A little) Past and (more) Future

Sheldon Campbell M.D, Ph.D.,
F.C.A.P.
VA Connecticut Healthcare
Yale School of Medicine

Images from, respectively, Diagnosis, the doctor and the urine glass, Lancet (1999) 354,;http://www.medicine.nevada.edu/ddl/technology/lfa.html,; and Loop-mediated isothermal amplification (LAMP) of gene sequences and simple visual detection of products, Nature Protocols 3, 877 - 882 (2008)

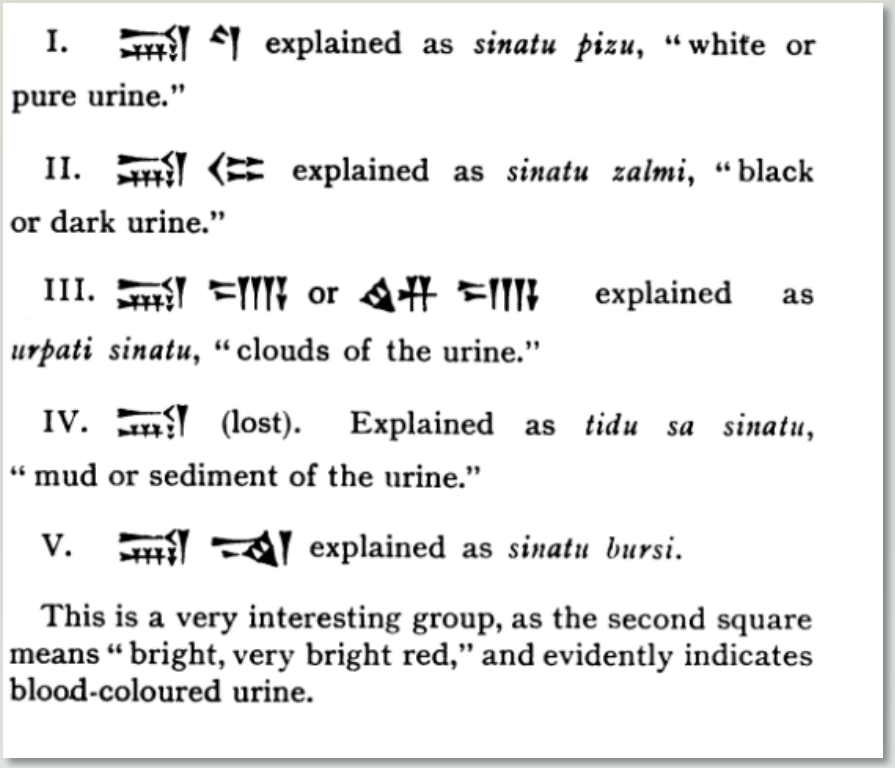
Learning Objectives

- Participants will be able to:
  - Recognize the evolution of modern Good Laboratory Practices in the history of uroscopy and other POCT.
  - Anticipate changes in patterns of health care and laboratory practice driven by technological change, including in POCT.

- Why would you ask an old guy to talk about the future?

Uroscopy as POC in the Ancient World

- A Sumerian Syllibarium (dictionary) c. 4000 BCE lists body parts, and alludes to changes in color and constitution of urine observed by physicians.



I. explained as *sinatu pizu*, "white or pure urine."

II. explained as *sinatu zalmi*, "black or dark urine."

III. explained as *urpati sinatu*, "clouds of the urine."

IV. (lost). Explained as *tidu sa sinatu*, "mud or sediment of the urine."

V. explained as *sinatu bursi*.

This is a very interesting group, as the second square means "bright, very bright red," and evidently indicates blood-coloured urine.

No, I was not personally around for this.

Advances in Urine Analysis

- Theophilus (610-641 AD) employed heat to further the analysis of urine; arguably the first analytic technique in medicine.
- Alsahavarius (c. 1085) noted the effect of certain foods on the color of the urine, and cautioned physicians against being fooled by intentional ingestions.
- Actuarius (d. 1283) recommended the use of a graduated glass for measuring sediments.

A Greek Physician examining the Urine
and
a Diagram showing the Various
Colours of Morbid Urine
From an illuminated MS. of the XIV century

Comprehensive QA for Uroscopy

Gilles de Corbeil, early 12th Century

Poem written in dactylic hexameter, which I dare anyone here to write a scientific publication in today.

PHYSICIAN EXAMINING A SAMPLE OF URINE BROUGHT BY A PATIENT

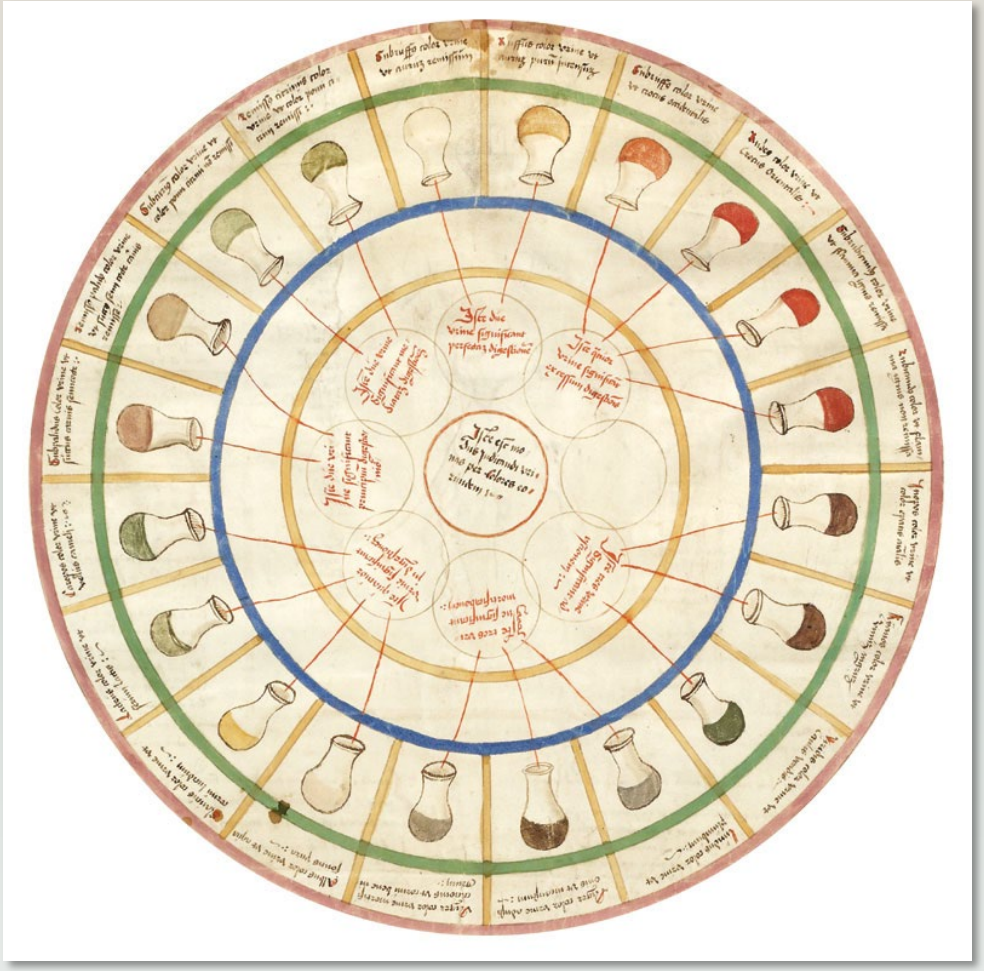
From a woodcut of the XVI century

Gilles de Corbeil, who graduated at the School of Salerno at the beginning of the twelfth century, and was first physician to Phillipe Auguste, wrote an elaborate poem on the urine, entitled "Liber de urinis," which gives a good idea of the state of medical knowledge at the period in which he lived. He begins by studying the etymology of the word urine, and then, referring to the composition of this excretion, remarks that "urine is composed of the residue left in the blood and other humours in the kidneys." Next, he proceeds to lay down in detail, rules for its examination, placing, for the guidance of the uroscopist, special emphasis on the aspects, the consistence, the quantity, the nature, and the things contained therein. He enjoins the physician to take into consideration, also, the circumstances of place, the number, the time, the age, the sex, the exercises indulged in, as well as the temperament and diet of his patient.

Gilles de Corbeil and his poetical treatise on urine

Historical Attempts to Comply with CLIA

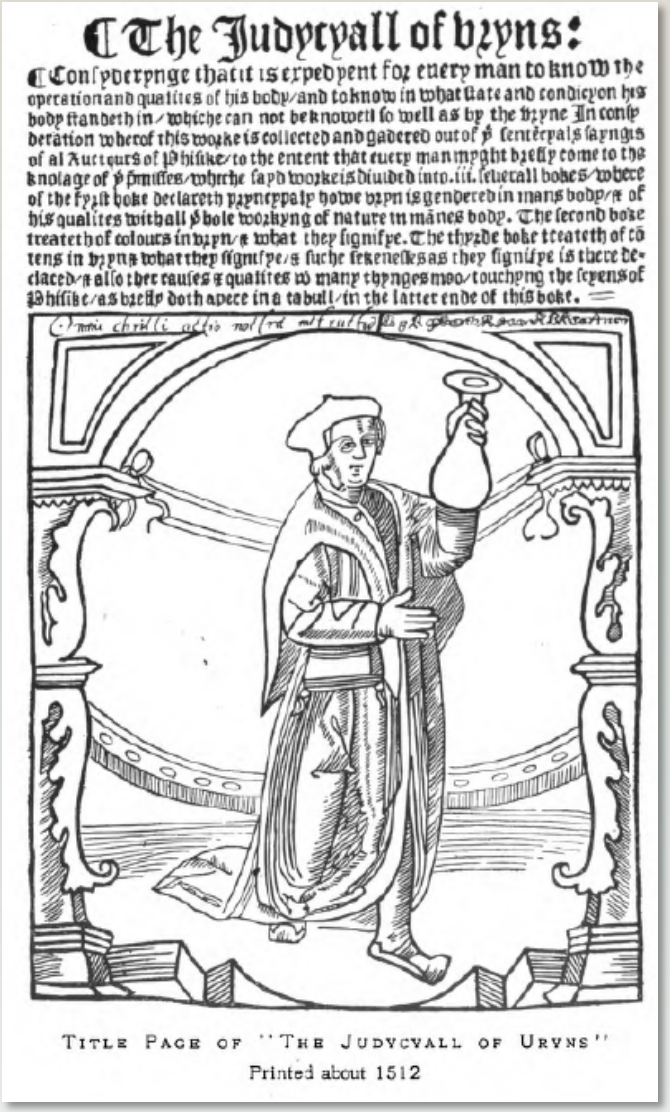
- The urine-glass disc was used as a colorimetric standard (the first ones known date from 1400 or before) in urine diagnosis.



published in 1506 by Ullrich Pinder, in his book *Epiphanie Medicorum*, from http://blogs.scientificamerican.com/oscillator/2012/10/18/the-urine-wheel/

History of Uroscopy – Lessons

- Like us, the ancient uroscopists:
  - Paid attention to pre-analytical, analytical, and post-analytical components of testing.
  - Attempted to standardize procedures and practices
  - Attempted to train, and assess and ensure competency
  - Attempted to improve the practice of their craft



Title Page of "The Judycvall of Vryns"
Printed about 1512

What has been will be again, what has been done will be done again; there is nothing new under the sun.
Ecclesiastes 1:9

The Modern Era of POCT: Rapid Antigen Tests

- In the infectious disease world, the first antigen tests for POC use were rapid strep latex tests.
- A major advance over existing methods.
- Required a simple extraction followed by latex agglutination on a glass slide.
- WHY Group A Strep!!?
  - A single test allows for treatment.
  - Limited differential
  - No need for imaging or other tests to **complete the encounter**.

Gerber, M. A., L. J. Spadaccini, L. L. Wright, and L. Deutsch. 1984. Latex agglutination tests for rapid identification of group A streptococci directly from throat swabs. J. Pediatr. 105:702-705.

ORIGINAL ARTICLES

Latex agglutination tests for rapid identification of group A streptococci directly from throat swabs

A comparison of the accuracy and practicality of two new latex agglutination tests for the rapid identification of group A β-hemolytic streptococci directly from throat swabs was performed in a busy pediatric office. The Directigen Group A Strep Test kit had a sensitivity of 84%, specificity 99%, positive predictive value 99%, and negative predictive value 93% when compared with blood agar cultures. The Culturette Brand 10-Minute Group A Strep ID Kit had a sensitivity of 83%, a specificity 99%, positive predictive value 97%, and negative predictive value 93% when compared with blood agar cultures. When cultures with less than 10 colonies of group A β-hemolytic streptococci per plate were not considered positive, both rapid tests had a sensitivity of 95%. The Culturette Brand test required considerably less time, equipment, supplies, and skill than the Directigen test. Only the Culturette Brand test appeared to be practical for routine use in a pediatrician's office. Further investigations of the accuracy of both of these rapid tests need to be performed before either is accepted as a substitute for the throat culture. (J PEDIATR 105:702, 1984)

Michael A. Gerber, M.D., Linda J. Spadaccini, R.N., Laura L. Wright, B.S., and Larry Deutsch, M.D. *Farmington, Connecticut*

THROAT CULTURES on blood agar plates have been used to confirm the diagnosis of group A β-hemolytic streptococcal pharyngitis for more than three decades[1]; however, physicians disturbed by the 24- to 48-hour delay inherent in this procedure have sought alternative methods. For example, fluorescent antibody staining of throat swabs has been suggested as a possible substitute for throat cultures.[2] Although fluorescent antibody staining has become an acceptable method of grouping streptococci after isolation on blood agar plates, it has been unreliable when used as a primary method of identification directly from throat swabs.[3] Gram staining of smears of pharyngeal secretions has also been proposed as a possible adjunct to clinical evaluation and throat cultures in the diagnosis of GABHS pharyngitis[4]; however, this procedure requires considerable technical expertise and is relatively insensitive when compared with blood agar cultures.

From the Department of Pediatrics, University of Connecticut School of Medicine.

Submitted for publication June 8, 1984; accepted July 20, 1984.

Reprint requests: Michael A. Gerber, M.D., Department of Pediatrics, University of Connecticut Health Center, Farmington, CT 06032.

Recently several serologic methods have been developed that use either coagglutination or latex agglutination for the rapid identification of GABHS directly from throat swabs. Within the past year, two of these procedures, Directigen Group A Strep Test Kit (Hynson, Westcott, & Dunning, Baltimore, Md.) and Culturette Brand 10-Minute Group A Strep ID Kit (Marion Scientific, Kansas City, MO.), have been released commercially. We compared the accuracy and practicality of these two rapid tests in a busy pediatric office.

GABHS	Group A β-hemolytic streptococci
MCT	Micronitrous acid extraction-coagglutination test

METHODS

Children between 2 and 16 years of age seen at the Department of Pediatrics, Kaiser Foundation Health Plan of Connecticut, East Hartford, with clinical findings suggesting GABHS pharyngitis were enrolled in the study after informed consent had been obtained. Throat swabs were obtained by simultaneously rubbing two sterile rayon-tipped swabs (Culturette II, Marion Scientific) over the posterior pharynx and both tonsils (or tonsillar fossae). This procedure was then repeated so that two pairs of

POC In the COVID Pandemic

(Controversial, like everything else)

- Molecular
  - Sensitive, maybe too sensitive.
  - Expensive when lots of tests needed.
  - Labs are connected to LIS and report to public health.
- Antigen
  - Insensitive; except maybe not.
  - Cheap, except not really.
  - Home-based testing is widely and rapidly available.

My daughter's (+) COVID test; did not get reported to public health. Did get loaded to Instagram.

SCIENCE ADVANCES | RESEARCH ARTICLE

CORONAVIRUS

Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening

Daniel B. Larremore[1,2]*, Bryan Wilder[3], Evan Lester[4,5], Soraya Shehata[5,6], James M. Burke[4], James A. Hay[7,8], Milind Tambe[3], Michael J. Mina[7,8,9]*†, Roy Parker[2,4,6,10]*†

The COVID-19 pandemic has created a public health crisis. Because SARS-CoV-2 can spread from individuals with presymptomatic, symptomatic, and asymptomatic infections, the reopening of societies and the control of virus spread will be facilitated by robust population screening, for which virus testing will often be central. After infection, individuals undergo a period of incubation during which viral titers are too low to detect, followed by exponential viral growth, leading to peak viral load and infectiousness and ending with declining titers and clearance. Given the pattern of viral load kinetics, we model the effectiveness of repeated population screening considering test sensitivities, frequency, and sample-to-answer reporting time. These results demonstrate that effective screening depends largely on frequency of testing and speed of reporting and is only marginally improved by high test sensitivity. We therefore conclude that screening should prioritize accessibility, frequency, and sample-to-answer time; analytical limits of detection should be secondary.

SCIENCE ADVANCES | RESEARCH ARTICLE

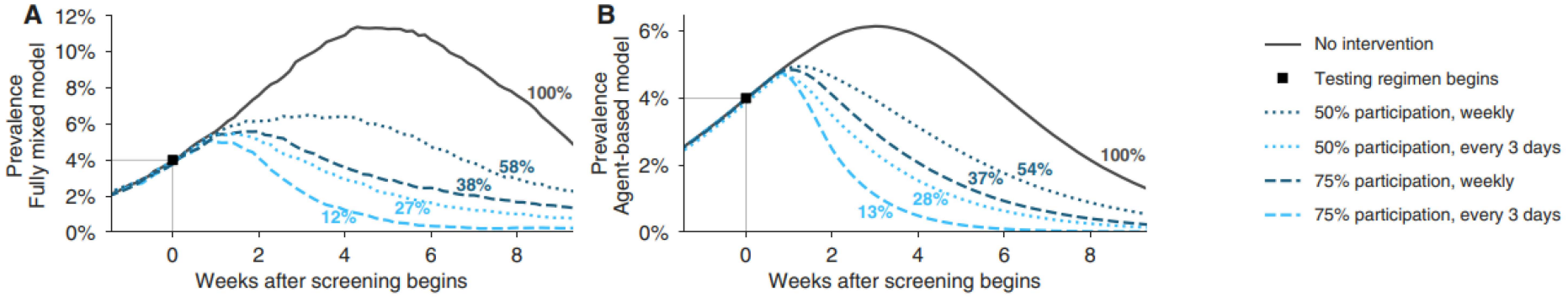


Fig. 6. Repeated population screening suppresses an ongoing epidemic. Widespread testing and isolation of infected individuals drive prevalence downward for both (**A**) the fully mixed compartmental model and (**B**) the agent-based model. Time series of prevalence, measured as the total number of infectious individuals, are shown for no intervention (solid) and population screening scenarios (various dashed lines; see legend) for individual stochastic simulations. Screening began only when prevalence reached 4% (box), and time series are shifted such that testing begins at $t = 0$. Scenarios show the impact of a test with LOD 10^5, no delay in results, and with 10% of samples assumed to be incorrectly collected (and therefore negative) to reflect decreased sensitivity incurred at sample collection in a mass testing scenario. Annotations show total number of post-intervention infections, as a percentage of the no-intervention scenario, labeled as 100% (see fig. S8 for identical simulations using a test with LOD 10^6).

So, Where Are We Going?

- Drivers of POCT
- SWOT Analysis of POCT going forward
- POC and the environment of care
- POC and the information environment

(Non) Drivers of POCT

Box 2
Campbell's laws of POCT, and corollaries

The Laws

1. Almost nobody goes into medicine or nursing to do diagnostic testing.
2. No POCT, however simple, is easier than filling in one more box on a laboratory order.

The Inpatient Corollary

An inpatient POC test is useful only if:
The time for transport to the laboratory for THAT SINGLE ANALYTE significantly and negatively impacts care, OR
The test is performed on an easily obtained sample (eg, fingerstick blood) MORE FREQUENTLY than routine blood draws are obtained.

The Outpatient Corollary

An outpatient POC test is useful only if:
The test result is available during the patient visit AND a decision can be made or action taken on the basis of it without waiting for other laboratory results, OR
If you can make money doing it.

SWOT Analysis of Future POCT

Strengths	Weaknesses
• **Everything everyone loves about POC** • **Not a novel concept to MDs and Pts; accustomed to GAS and Flu Ag tests** • **Current state of the art assays (e.g. NAAT, more sensitive Ag assays) have improved performance over past** • **Some POC NAAT comparably sensitive to culture and lab-based methods** • **Many clinically relevant specimens readily available: urine, mucosal swabs, whole blood**	• Instrumentation costs • Assay / Reagent costs • Specimen type restrictions (e.g. eSwab v. conventional swab) • Serum or plasma beyond POC scope • Limited ID conditions where AST is not relevant • Quality of testing performance by non-laboratory staff. • Arbitrary / limited menus limit clinical impact • Small number of analytes per platform limit scaleability
Opportunities	Threats
• **Continuing advances in testing: NAAT workflow, TAT, "Lab on a Chip"** • **Antimicrobial stewardship (AMS) gaining increased importance nationally with regulatory bodies** • **Development of biomarkers for AMS → Negative Predictive Value** • **Development of new antivirals to broaden clinical actions (e.g. RSV)** • **Implementing replacement tests at specific, off-site clinics (e.g. public health / STI clinics)** • **Ability to facilitate new models of care** • **Microbiology laboratory consolidation may necessitate more local infectious disease testing**	• Changes in reimbursement models • Inertia in physician offices • Theranos-effect → Disproportionally increased scrutiny of assays / methods and/or disproportionate fear of regulatory oversight for novel tests / methods • Turf wars between pharmacies, urgent cares, offices, EDs and potential regulation

The Environment…

Table 1
Microbiological POC in various environments

Care Setting	Clinical Environment	Types of Infections and Problems Seen	Turnaround Time for Impact	Other
Inpatient	Clinical laboratory on-site; often clinically complex patients.	Sepsis; HAI.	Transport time to laboratory has to be long enough to make it worth doing the test at the POC.	Wide range of potential pathogens in many cases.
Emergency	Clinical laboratory on-site	Acute infectious syndromes; some screening.	Test turnaround time strongly impacts throughput.	Tests that can speed discharge strongly favored.
Urgent care	No dedicated laboratory; test availability impacts scope of care available. Space and personnel limited. Volume of testing must justify capital expenses.	Acute infectious syndromes.	Test turnaround time strongly impacts throughput.	Availability of some tests may allow expansion of scope of care available on-site.
Ambulatory	POL on site, or only CLIA-waived tests. Space and personnel limited. Volume of testing must justify capital expenses.	Common health maintenance, screening, and acute ambulatory illnesses.	Test results must be available during the encounter to streamline care.	
Telemedicine	Laboratory may or may not be on-site, depending on the telemedicine model.	Common health maintenance, screening, and acute ambulatory illnesses.	Depends on care model.	Evolving models for telemedicine. In some cases will be linked to other services—pharmacy, imaging. Extent of laboratory tests available at POC may impact scope of care.
Outreach	Specific programs, targeting particular diseases or vulnerable populations. No on-site laboratory; limited, often temporary space.	STI; HIV, HCV.	Rapid—30 min or less for success.	
Home	Patient centered; clinical and interpretive support limited.	STI; acute infectious syndromes; chronic disease screening.	Somewhat flexible; some mail-in testing has been successful.	An evolving area; will expert systems increase the possibilities for home testing?

Abbreviations: HAI, healthcare-associated infection; HCV, hepatitis C virus; HIV, human immunodeficiency virus; POC, point-of-care; POL, physician's office laboratory; STI, sexually transmitted infection.

Information Technology and the Future of POCT

Opportunities

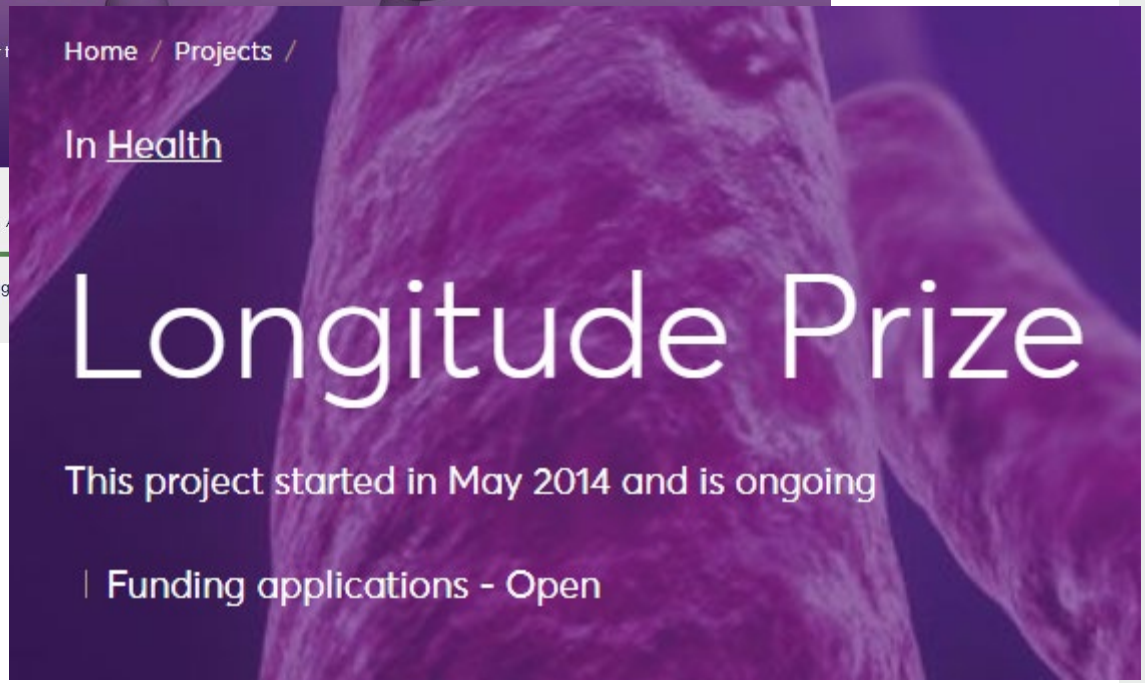
- Outreach to underserved populations via widely available devices, e.g. smart phones.
- Run complex analytics; computer vision, interpretation, NGS data analysis, remotely.
- Rapid reaction to emerging infections.

Challenges

- How can the variety of POCT plug into the EMR and the public health system?
- Development of heterogeneous data universe would be bad.
- Validation of complex multisite testing at POC.
- Security. Also security and security.

The Distant Future

- POCT and changes in care models will interact. Note that POL testing exists in large practices now; how different is this?
- Decentralized testing, along with decentralized imaging and other diagnostic support services, may drive decentralization of care.
- Highly-complex analyses will be laboratory performed for the foreseeable future, but new models of laboratory practice will likely evolve as decentralized testing becomes more prevalent.
- However ***do*** you manage QC for analyzers in fifty decentralized telemedicine / pharmacy sites?
  - In ten thousand homes?
- POC will still need to **close the clinical encounter** to have impact; but perhaps the clinical encounter will change, too.



$17.1 million Longitude prize for POCT for bacterial infections

Point-of-care test kits will allow more targeted use of antibiotics, and an overall reduction in misdiagnosis and prescription. Effective and accurate point of care tests will form a vital part of the toolkit for stewardship of antibiotics in the future. This will ensure that the antibiotics we have now will be effective for longer and we can continue to control infections during routine and major procedures.

Sources and Acknowledgements

- Much of the discussion and tables are from:
  - Peaper DR, Durant T, Campbell S. Distributed Microbiology Testing: Bringing Infectious Disease Diagnostics to Point of Care. Clin Lab Med. 2019 Sep;39(3):419-431.
- For information on uroscopy:
  - Melissa Grafe, Ph.D.
    John R. Bumstead Librarian for Medical History
    Cushing/Whitney Medical Library, Yale University
  - The evolution of urine analysis; an historical sketch of the clinical examination of urine. Wellcome, Henry S. Sir, 1853-1936. London, Burroughs Wellcome [1911].
    - Of this 305-page monograph, only the first 92 pages pertain to uroscopy; the rest consists of advertisements for Wellcome products.

A Breakthrough in Testing!

- **Credit:** Wellcome Library, London
- A physician examining a urine specimen in which a faint figure of a baby is visible, a female patient is crying and being shouted at by her angry mother, indicating that she is pregnant.
- Watercolour by I.T., 1826.