

Point of Care Testing – From Sumer to Star Trek

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A BEDSIDE DIAGNOSIS FROM URINE

From a woodcut of the XVI century

From: The evolution of urine analysis; an historical sketch of the clinical examination of urine. Wellcome, Henry S. Sir, 1853-1936. London, Burroughs Wellcome [1911]

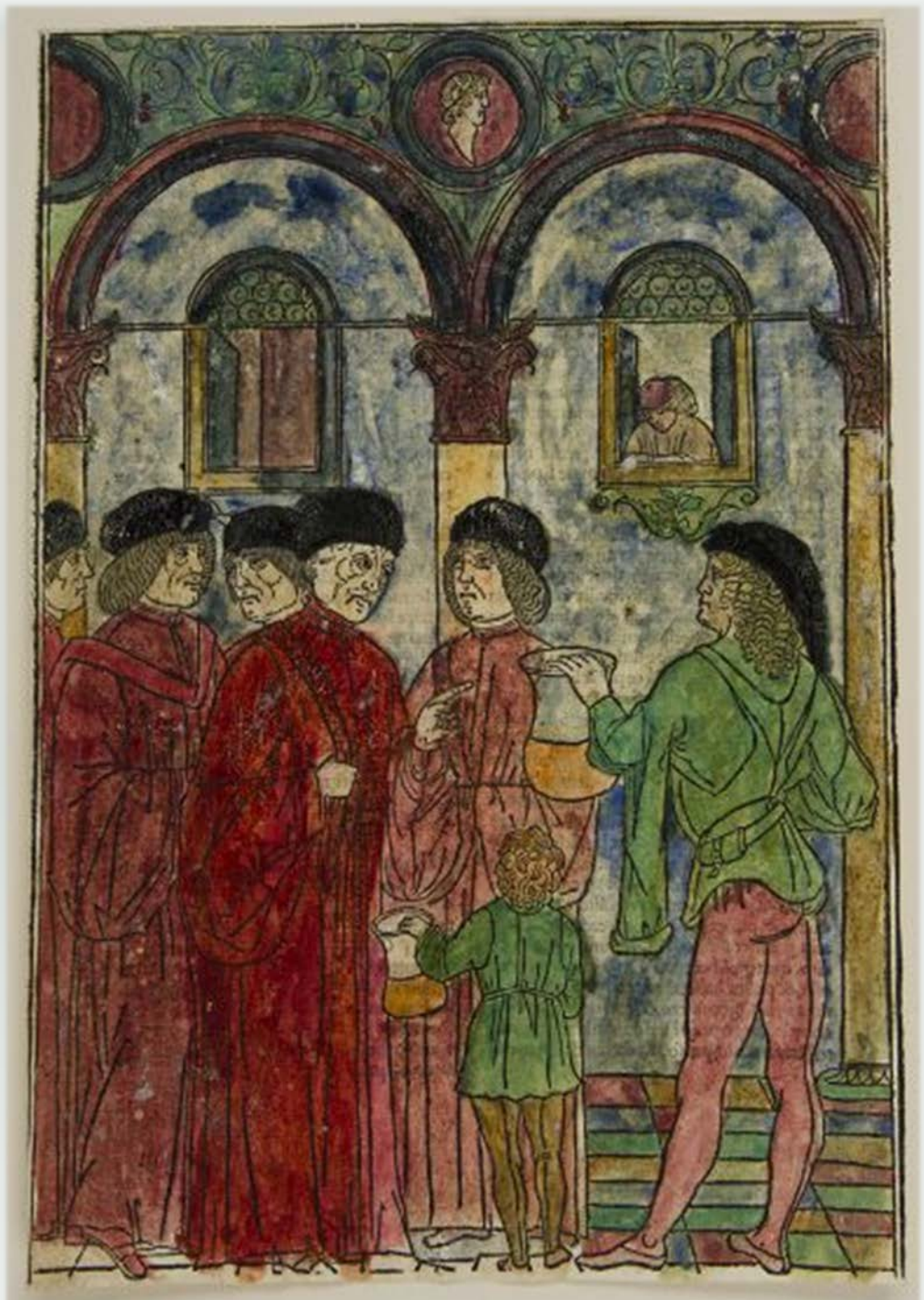
Learning Objectives

- Participants will be able to:
 - Recognize the evolution of modern Good Laboratory Practices in the history of uroscopy.
 - Demonstrate the evolution of infectious-disease POCT from the first rapid Strep to current molecular flu tests.
 - Explain the characteristics of the ideal point-of-care infectious-disease test.
 - Explain how Campbell's Laws will impact the implementation of emerging point-of-care platforms.

Petrus, his students and an attendant with a flask of urine, c. 1500

From Fasciculus Medicinae, Venice,
C. Arrivabenus, 1522

Harvard Art Museums/Fogg
Museum, Gray Collection of
Engravings Fund, G5121.2



Ancient POCT: Urine Examination (Uroscopy)

CHAPTER I

UROSCOPY IN ANTIQUITY



THERE is perhaps no excretion of the human body which possesses more interest to the medical practitioner, and probably none which throws so strong a light on the organic processes of the diseased as well as the healthy body, as the urine.



The origin of uroscopy, or the art of diagnosing disease from the inspection and examination of the urine, is practically co-eval with the genesis of the art of healing itself, and, after a careful investigation of the subject, one must conclude





Antiquity of
uroscopy


Uroscopy in the Ancient World



- A Sumerian Syllibarium (dictionary) c. 4000 BC 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.   or   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.

Some Sanskrit diagnoses:

- *Iksumeha*, cane-sugar juice urine.
- *Ksuermeḥa*, potash urine.
- *Sonitamēha*, urine containing blood.
- Pistameha, floury-white urine.
 - When the patient passes this type of urine the hair on the body becomes erect, and the urine looks as though mixed with flour. Urination is painful.
- *Hastimeḥa*, elephant urine.
 - “The patient continuously passes turbid urine like a mad elephant.”
- *Madhumēha*, honey urine.
 - Trains of long black ants are attracted by the urine.

Hippocrates on Urine Analysis

Emphasized the importance of examining the urine with all five senses.

Thank goodness for technology.

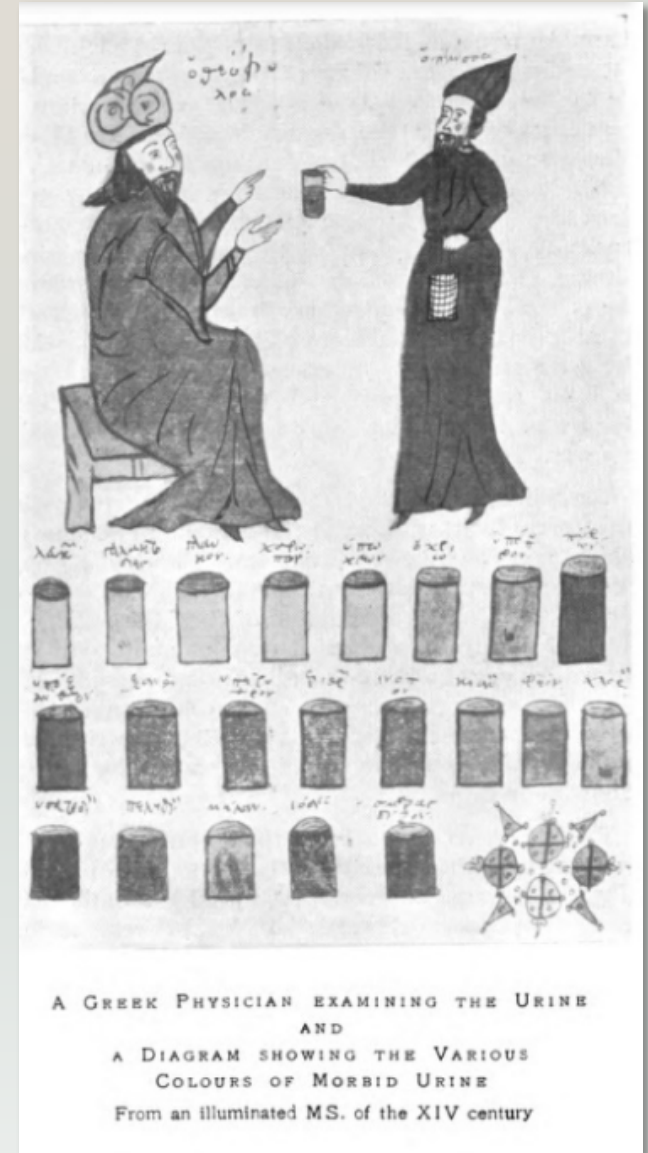


HIPPOCRATES INSTRUCTING STUDENTS IN THE "JUDGMENT"
OF DISEASE FROM THE URINE
From a woodcut of the XV century

He pointed out the effect of food and drink on the secretion, its variation in colour, odour and transparency, and taught the symptomatic and prognostic signification of these changes. "Urine is best," he states, "when the sediment is white, smooth and consistent, during the whole time until the disease comes to a crisis, for it indicates freedom from danger and an illness of short duration ; but if deficient, and if it be sometimes passed clear and sometimes with a white and smooth sediment, the disease will be more protracted and not so void of danger. If the urine be reddish and the sediment consistent and smooth, the affection in this case will be more protracted than the former, but still not fatal. Farmacious sediments in the urine are bad, and still worse are the leafy ; the white and thin are very bad ; but the furfuraceous are still worse than these. Clouds carried about in the urine are good when white, but bad if black. When the urine is yellow and thin, it indicates that the disease is unconcocted. The most deadly of all kinds of urine are the fetid, watery, black and thick ; in adult men and women the black is of all kinds of urine the worst, but in children, the watery.

Advances in Urine Analysis

- Theophilus (610-641 AD) employed heat to further the analysis of urine; arguably the first analytic technique in medicine.
- Alisahavarius (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.



Specimen Guidelines

Ismail of Jurjani (c. end of 11th century), a Persian physician

Includes container specifications, time of collection, storage conditions, and patient instructions.

Goes on to provide detailed recommendations for examination of urine.

“The urine which is for the physician to examine,” he states, “must be collected in a bottle, which must be large, transparent and clean, and if possible should be in the shape of a bladder. It should be of a large size, so as to contain the whole of the urine (24 hours), for the reason, if there be something (sediment) in it, it should be detected at once. The shape of the bottle is devised like a bladder for the reason that the urine should be in natural position as in that viscus. Urine should be well guarded against heat, cold and the sun, because extremes of temperature change its natural state, and heat makes it burn, and its thin sediments are consumed thereby. Cold makes urine congealed.

“Urine sent for examination should be that of the early morning after a good sleep. It should be passed before eating or drinking anything, because partaking of certain foods changes the colour of the urine. One should not rely upon urine that has been passed during starvation, sorrow, weakness or sleeplessness, or after coition, because above conditions change its colour. After food and wine the natural heat of the body increases for the purpose of digestion, the urine becomes colourless. Often in hot diseases it becomes white and puts the physician off his guard. After hunger, sleeplessness, sorrow and trouble, urine changes its colour, because heat (bodily) in such conditions moves about (in the body) and makes the urine appear coloured. Often one passes colourless urine after sleeplessness, because heat (bodily) is dissipated through insomnia, the urine passed is rather turbid and not clear and light, because food cannot be well digested in sleeplessness; food remains kham (uncooked, unasssimilated); that is also the reason why one gets darkish and muddy water from uncooked food.

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

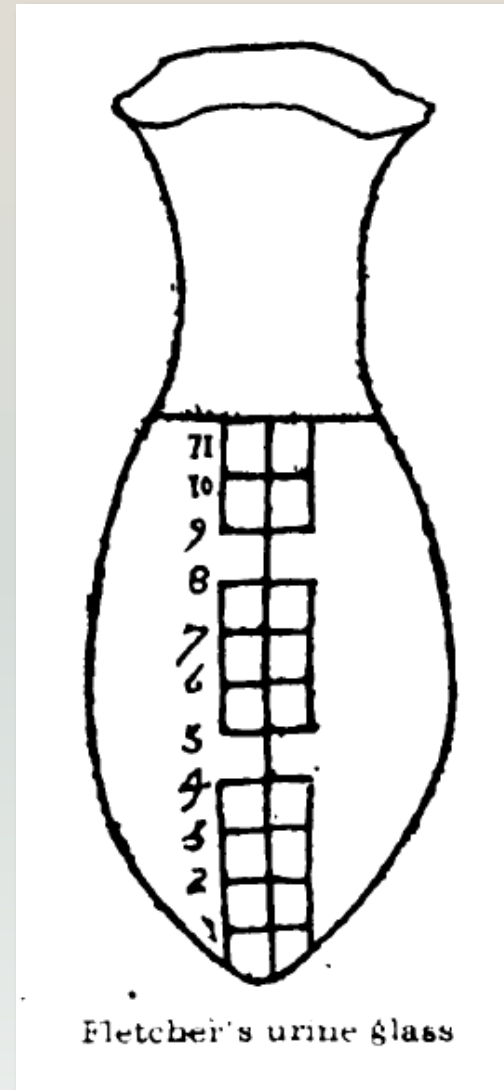
From a woodcut of the XVI century

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

Fletcher, 1541

- Advocated the use of the mixed urine passed during the entire day rather than a single sample.
 - “Take the whole urine and not the part such as is made at one time, but mingle not the urines made at severall times, but keep them severall both for quantity, color, and contents”
- Not quite a modern timed collection, but trending that way.

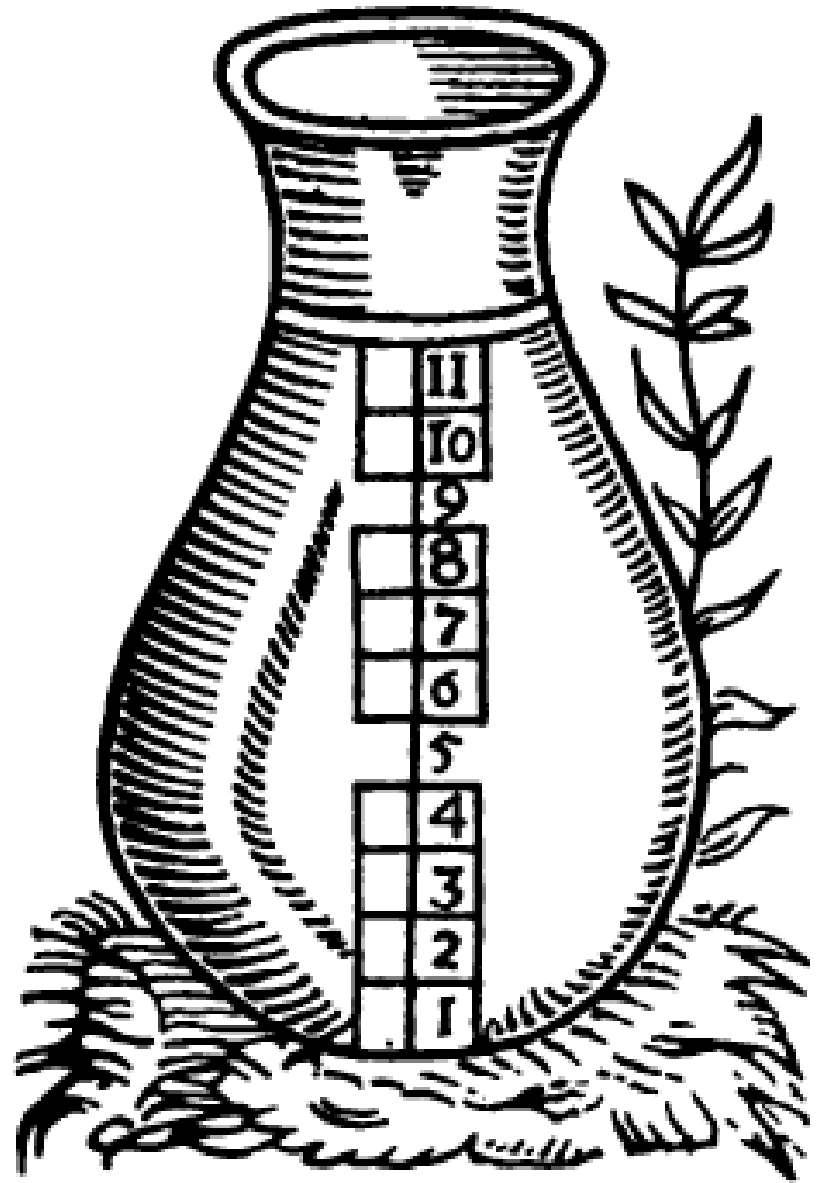


Robert Recorde, 1548

Provided another detailed set of procedures for urine examination, including:

When to examine each aspect of the urine; color and consistency while still warm, sediments and contents after cooling.

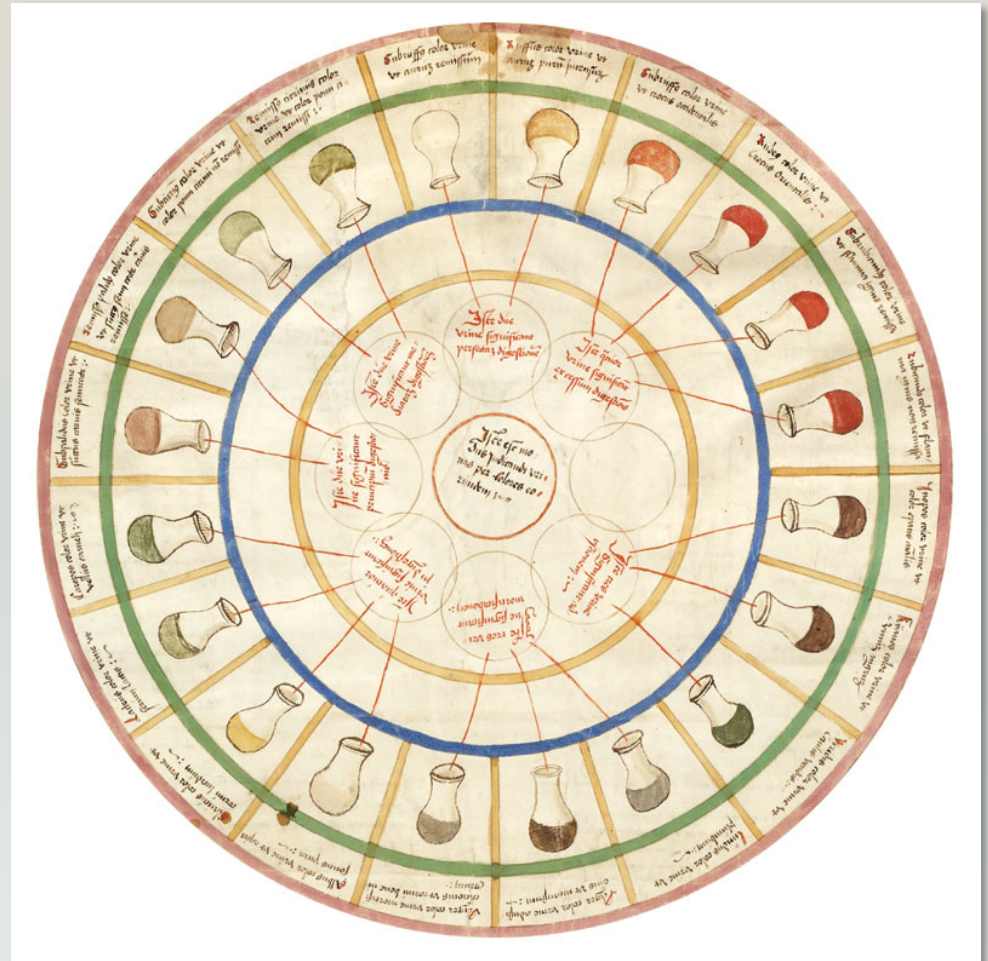
The exact nature of the viewing container (the urine-glass), and graduation of the container into segments, each used for a separate observation, e.g. the segment above the ring being used for the bubbles.



Recorde's urine glass

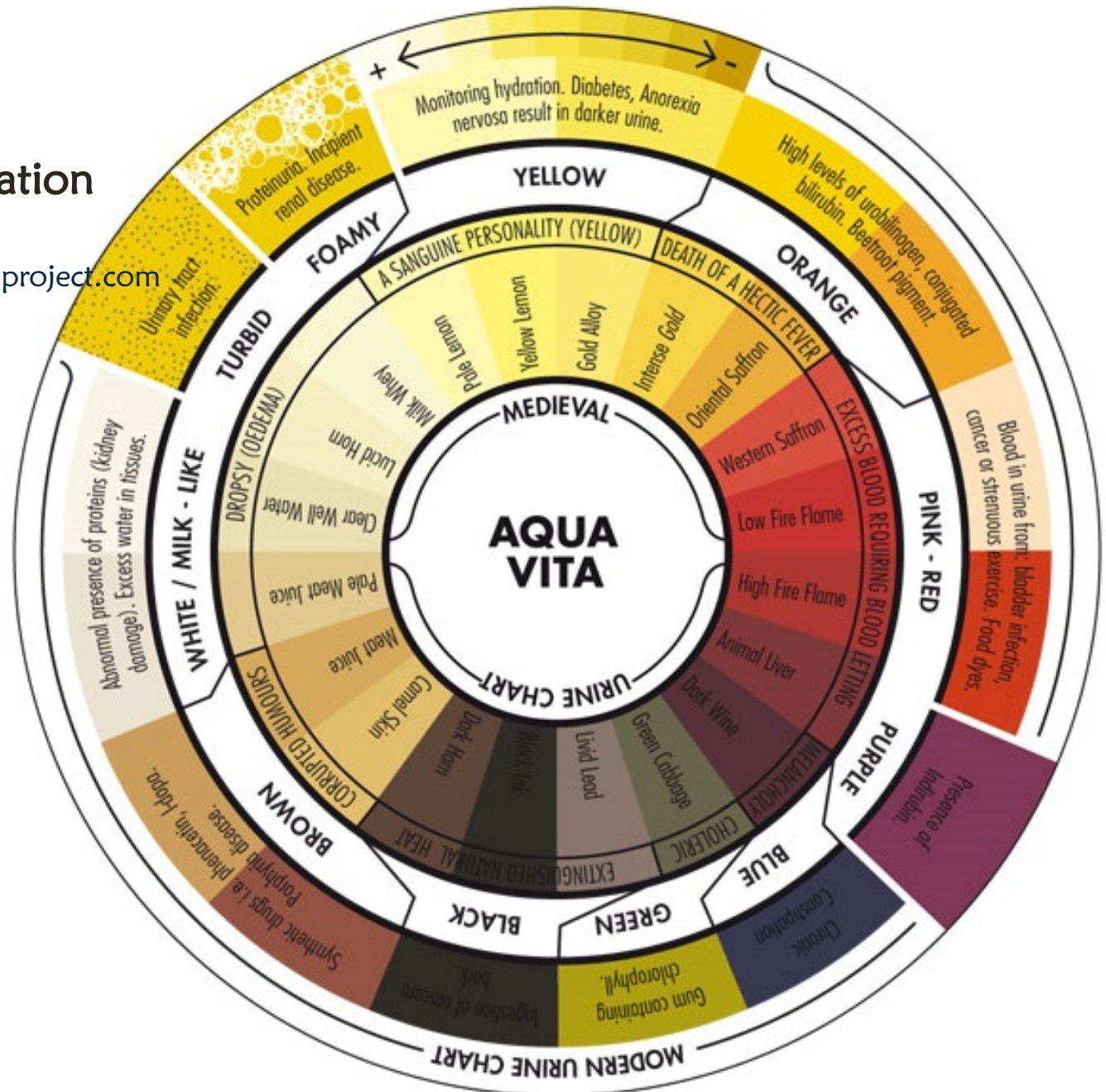
Historical Attempts to Comply with CLIA

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



A Modern Translation

From
<http://www.theaquavitaproject.com/project.php#>



Paracelsus (1493-1541) and Analytical Uroscopy



PARACELSUS

THEOPHRASTUS BOMBASTUS VON HOHENHEIM

Physician and Alchemist. 1493-1541

According to his theory, disease originated from the chemicals of which man's body was formed, which were said to be mercury, sulphur and salt. Mercury, he declared, referred to the lower limbs. To discover the cause of a disease it was necessary then to resolve or divide each of these elements by a mysterious chemical process and to endeavour to find out which degree was in excess of the others in quantity. For this purpose, the urine was taken as the diagnostic agent, and was distilled and weighed. The distillate was said to correspond to the portion of the body where the disease was located, and thus its nature was indicated. "Spagyric analysis"

As an example, it may be stated that mercury or sulphur diseases were indicated by the vapour as it rose in the upper part of the alembic, which indicated dizziness, ear troubles and delirium, while the vapour which was deposited in the alembic was thought to be less harmful than that which escaped, especially if it came forth from the left-hand side of the cucurbite, which indicated dire events, such as apoplexy and death.

Van Helmont (1578-1644): Measurement

Measured the comparative weight – what we'd identify as the specific gravity – of urine in various conditions.



Van Helmont gives the result of his researches as follows: "One ounce of urine weigheth 600 grains, but I had a glassen vessel of a narrow neck weighing 1,354 grains, but it was filled with rain-water weighing besides 4,670 grains. The urine of an old man was found to weigh in the same vessel 4,729 grains, or to exceed the weight of the rain-water 50 grains. But the urine of a healthy woman 55 years old weighed 4,745 grains. The urine of a healthy man of 19 years old weighed 4,766 grains. But that of another young man of a like age being abstemious from drink weighed 4,800 grains. The urine of a young man 36 years old, undergoing a tertian ague with a cough weighed 4,763 grains. But the aforesaid youth of 19 years old with a double tertian had drunk little in the night aforegoing, but his urine weighed 4,848 grains, which was 82 grains more than while he was healthy.

Van Helmont urges the importance of weight in the judgment of urine

Further Advances

- In 1620, De Peiresc described rhomboidal crystals in urine; later shown to be uric acid.
- Thomas Willis (1674) distilled urine and described the components derived; also described the sweetness of urine in diabetes mellitus.
- Lorenzo Bellini (1643-1704) evaporated urine and concluded that urine was composed of 'water, salt, and tasteless earth'.
- Boerhave (1668-1738) directly measured specific gravity; also discovered urea.
- Urea more completely described in 1771 by Rouelle the Younger.

Matthew Dobson (1772) and Diabetes

- Evaporated diabetic urine to dryness; discovered that the residue was indistinguishable from common sugar by taste, smell, or chemical treatments.

In the following year, Matthew Dobson, of Liverpool, published the results of his epoch-making experiments which he had carried out with the urine of diabetic patients. He noted that the urine of such was very transparent, of pale straw colour and sweet, and, upon placing it on one side in an open vessel, separation began to take place, and woolly clouds appeared which gradually subsided and covered the bottom of the vessel with a loose white precipitate. He observed that with longer keeping, the urine underwent vinous and then acetous fermentation. He experimented also by heating the urine to boiling point, and noted that he got no coagulation. He further tried, although without result, the addition of the mineral acids, thereby inaugurating the era of the chemical testing of urine.

Dobson's
important
investi-
gations

His final experiment was that of evaporating two quarts of the diabetic urine to dryness, from which he observed that the residue he obtained was in the form of a white cake, which weighed four ounces, two drachms and two scruples. This, he states, could not be distinguished from ordinary sugar, by the taste or smell. On the addition of acid elixir of vitriol no effervescence was caused, but on the addition of a more concentrated vitriolic acid an effervescence ensued and some pungent fumes were given off.

He
introduces
chemical
tests

Judging from Dobson's original experiments, and especially of his use of the mineral acids as tests, he may be regarded as one of the most important pioneers in the scientific era of urine analysis.

Further Analysis of Urine

- Tests for sugar, bile, and albumen were developed during the 1800s, and their use in diagnosis of disease developed.
- Use of the microscope in examination of urine sediment also developed in 1800s.

In 1847, Markwick wrote a guide to the examination of the urine which was practically the first handbook to its scientific analysis. He mentions the use of blue and red litmus paper, and calls attention to the importance of taking the specific gravity of the liquid. He estimates albumen by boiling a given quantity and weighing the residue, bile, by the addition of hydrochloric acid, and sugar, by the yeast test, or the copper test of Trommer, in which a solution of copper was added to the urine, followed by an excess of liquor potassæ, the whole of the liquid being then boiled. From this time the copper test for grape sugar became universally employed.

Markwick
on exam-
ination of
urine

Creatures in the Urine

CHAPTER IV

ANIMALCULA IN UROSCOPY

The earliest record of living animals voided with urine is that mentioned by Plutarch, who observes that a friend of his, an Athenian *ephebus*, passed by way of the urethra "a pilous and many legged beast." The medical works of the Middle Ages abound with curious allusions to animalcula, fabulous and otherwise, that were observed in the urinary excretion. Bartolinus relates that a Pole passed "with gravelly urine many small, blackish, scorpion-like worms." Scalliger also mentions the voiding of "smooth, white worms, with sharp beaks, and eyes of fire," while Rondelet describes what he calls "a small dragon the size of the middle finger, provided with tail and wings," which Argentarius saw *per urinam excretum*, in 1535, at Lyons. Levin gives a description of a terrible dragon, which was passed by a woman, "with long, curved, and sharp beak, vibrating eyes, and a pointed tail." It moved very rapidly on its feet, and filled the room with its rage and hissings. Fortunately, according to the author, the patient succeeded in smothering it with her pillow.

Living
animals
in urine

A terrible
dragon
passed
in urine

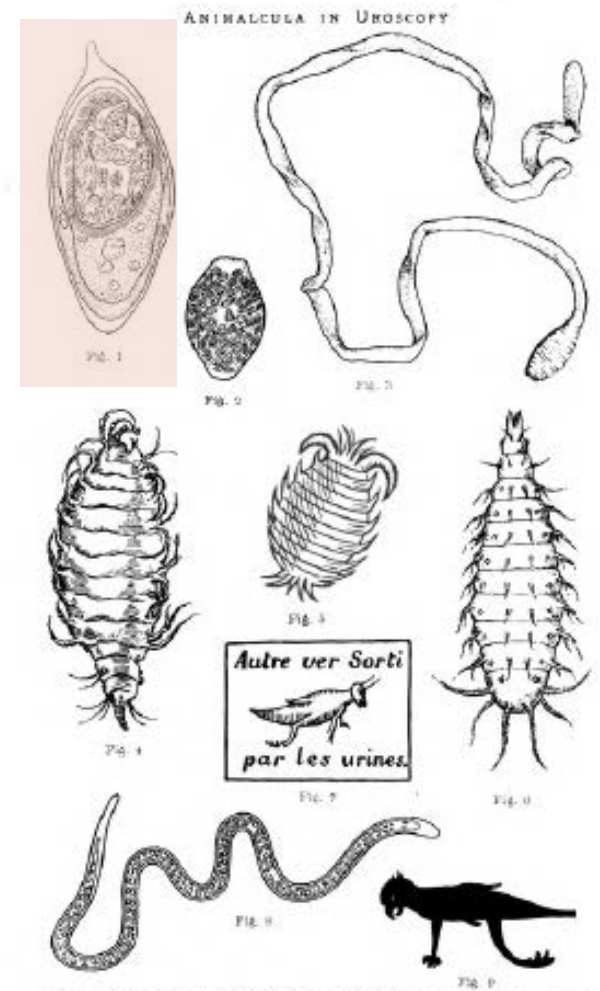


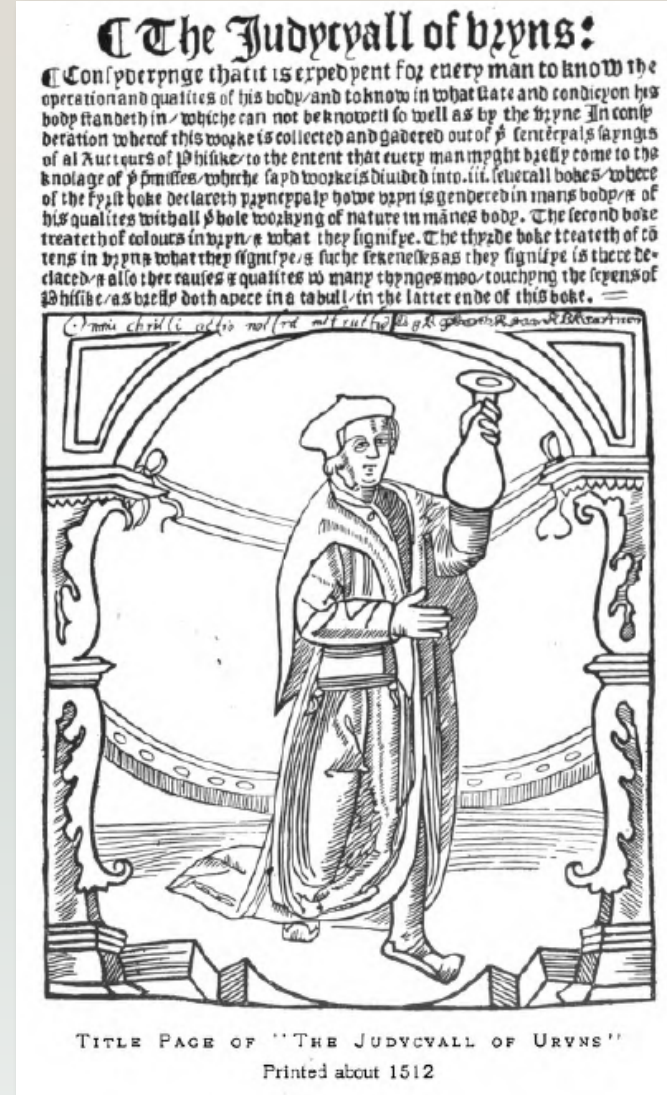
FIG. 1. Egg of *Schistosoma haematobium*, cause of *schistosomiasis* (after Leach). FIG. 2. Egg of *Clonorchis sinensis* (*Clonorchis sinensis*) (after Ward). FIG. 3. *Spermatozoa* *monstrum*, a parasite occasionally voided through the urethra (after Sambon). FIG. 4. Larva of *Anthelmia canicularis* (after Tulpius, 1641). FIG. 5. Larva of *Anthelmia canicularis* (after Park, 1863). FIG. 6. Larva of *Anthelmia canicularis* (after Chevrol, 1800). FIG. 7. Andry's reproduction of Park's drawing (fig. 6). Note the transformation into a locust-like organism, 1780. FIG. 8. Larva of *Filaria bancrofti* (after Nansen). FIG. 9. Drawing of animal-like body, possibly a *confusum*, voided with urine (after Park, 1865).

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

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

Ecclesiastes 1:9



An Image of Uroscopy

17th Century print by Isaac Sarabat, from the NLM History of Medicine collection.



The Modern Era of POC: 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.

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 decades¹; 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 pharyngitis⁴; 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

Evolution of Rapid Tests

- Methodology
 - Flow-through cartridge EIA succeeded latex.
 - And was succeeded by lateral-flow tests.
- Regulation: CLIA
- Analytes (waived)
 - Antibody Tests: *Helicobacter pylori*, Hepatitis C, HIV 1&2, EBV, Lyme, RSV
 - Antigen Tests: Adenovirus, Influenza A&B, RSV, group A Strep, *Trichomonas*.

Limits of Antigen Testing

Influenza A Rapid Test Performance¶

Rapid Test¶	Sens%¶	Spec%¶	Compared With¶	Comments¶	Reference¶
Directigen ¶	58.8¶	99.2¶	Molecular¶	A&B performance combined¶	Liao et al JCM 47(3):527-32, 2009 Mar¶
3M- QuickVue ¶ BinaxNow¶	75¶ 73¶ 55¶	98¶ 99.5¶ 100¶	Culture¶	Archived specimens¶	Dale et al JCM 46(11):3804-7, 2008 Nov¶
BinaxNow¶	53¶	¶	RT-PCR¶	2 of 237 samples were flu B pos by RT-PCR but flu A by NOW. ¶	Landry et al JCV. 43(2):148-51, 2008 Oct¶
BinaxNow¶	61¶	100¶	RT-PCR¶	DFA was 81% sensitive¶	Rahman et al Diag Micro Infect Dis 62(2):162-6, 2008 Oct¶
RemelXpect- BinaxNow¶	47.7¶ 78.3¶	98.7¶ 98¶	Culture¶	20.3/99.8 Flu B- 35.9/99.9 Flu B¶	Cruz et al JCV 41(2):143-7, 2008 Feb¶
BinaxNow¶	52¶	¶	RT-PCR¶	70% in days 1-3 of disease¶	Nilsson et al Inf Cont & Hosp Epi 29(2):177-9, 2008 Feb¶
Directigen ¶	42¶	96¶	Culture¶	¶	Rahman et al Diag Micro Infect Dis 58(4):413-8, 2007 Aug¶
BinaxNow- Directigen- QuickVue¶	73¶ 69¶ 67¶	99¶ 100¶ 100¶	RT-PCR¶	Sensitivity only 30% vs flu B for all¶	Hurt et al JCV 39(2):132-5, 2007 Jun¶
Quickvue¶	85¶	97¶	RT-PCR¶	¶	Mehlmann et al JCM 45(4):1234-7, 2007 Apr.¶
Directigen + Quickvue + BinaxNOW¶	63¶	97¶	RT-PCR¶	Data pooled from all rapids; ¶	Grijvala et al Pediatrics. 119(1):e6-11, 2007 Jan¶

Convenience sample of recent literature; selected by Medline search + fit to single page

1826 Image

- **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.



Molecular Testing for Influenza

- Real-time methods can provide result in ~1h or so.
- Molecular methods as a class exceed culture in sensitivity (probably due to viral loss in transport)
- Detection properties do vary from system to system – do your homework!
- Moderately to very expensive equipment
- Moderate to high complexity (no CLIA-waived tests yet).
- Now clearly the ‘gold standard’
- Information sources:
 - <http://www.cdc.gov/flu/pdf/professionals/diagnosis/table1-molecular-assays.pdf>
 - CAP Website for some price information
 - Manufacturer’s web sites and PubMed for pictures, workflow and other information.

FDA-approved Molecular Influenza Tests

- Cepheid Xpert Flu Assay
- eSensor Respiratory Viral Panel
- FilmArray Respiratory Panel
- Ibis PLEX-ID Flu (seems to be off the market)
- Prodesse PROFLU and PROFAST
- Quidel Molecular Influenza A+B Assay
- Qiagen Artus Influenza A/B Rotor-gene RT-PCR kit
- Simplexa Flu A/B & RSV and Flu A/B & RSV Direct and Influenza A H1N1 (2009)
- Verigene Respiratory Virus Nucleic Acid Test and RV+ Test
- X-TAG Respiratory Viral Panel and RVP-FAST
- Iqum LIAT Influenza A/B Assay
- Alere i Influenza A/B

More on the way!!

Cepheid Xpert Flu Assay

- From Cepheid
- Detects Flu A and B; discriminates 2009 H1N1.
- Approved for nasopharyngeal swabs, nasal aspirates, and nasal washes.
- Moderately complex
- List price ~\$50/cartridge, instruments \$24,900–\$174,400 depending on capacity
- Sample to answer ~1h



Xpert Flu Workflow

①

Transfer 300µl of prepared sample into the large hole



②

Dispense binding reagent into small hole



③

Insert cartridge and start assay

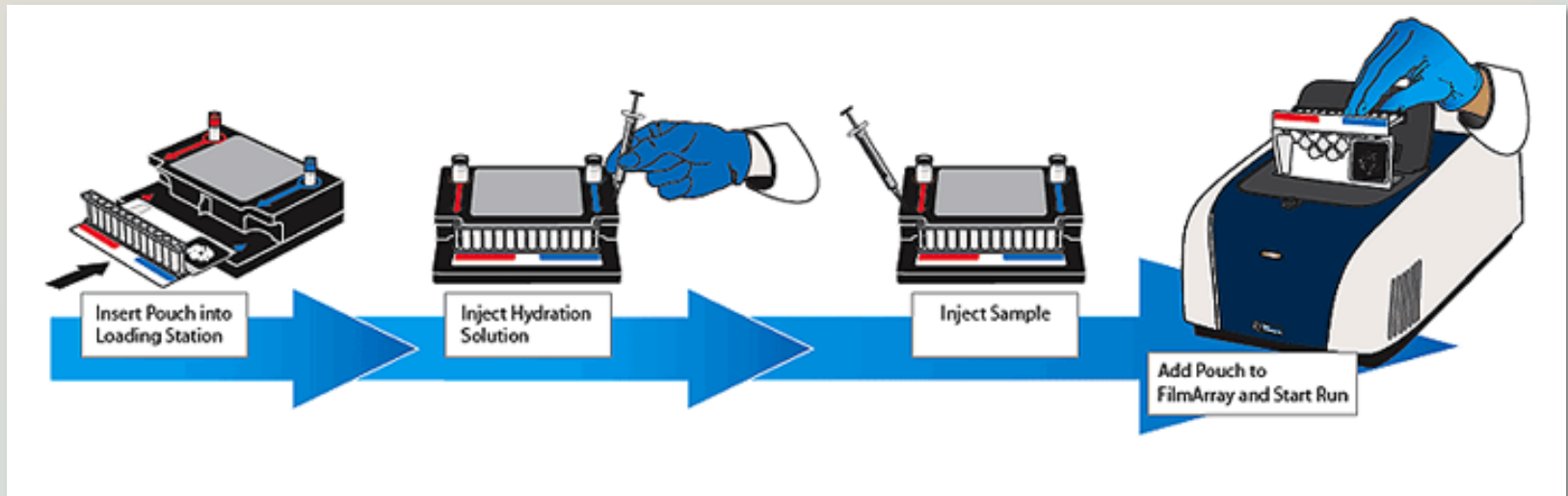


FilmArray Respiratory Panel

- From: Biofire, in the process of being acquired by BioMerieux
- Detects: Influenza A and B (discriminates H1, H3, 2009 H1) Respiratory Syncytial Virus, Parainfluenza 1, 2, 3 and 4 virus, Human Metapneumovirus, Rhinovirus/Enterovirus, Adenovirus, 4 Coronavirus variants, *Bordetella pertussis*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*
- Approved for NP swabs
- Moderately complex
- List price: \$129/sample; instruments \$39,500 each
- Sample to answer ~1h



Filmarray Workflow



Simplexa Flu A/B & RSV and Flu A/B & RSV Direct and Influenza A H1N1 (2009)

- From Focus Diagnostics / 3M
- Detects Influenza A&B and RSV; a separate test discriminates 2009 H1N1
- Approved for NP Swabs
- Highly complex (Direct version is Moderately complex)
- List price: \$49 reagents, requires Focus/3M Cycler
- Sample to answer ~4h, ~2h for Direct



Verigene Respiratory Virus Nucleic Acid Test and RV+ Test

- From Nanosphere
- Detects Influenza A & B, RSV A&B, Plus version discriminates H1, H3, and 2009 H1N1
- Approved for NP swabs
- Moderately complex
- List price \$70 reagents, instruments N/A
- Sample to answer 3.5h



Reader and Processor SP⁺



Verigene RV / RV+ Workflow

STEP 1

Load Test Cartridge, test consumables, and sample into Processor *SP*



STEP 2

Automated sample preparation and test processing on Processor *SP*



STEP 3

Place slide from Test Cartridge in Verigene Reader for results



Alere i Influenza A and B

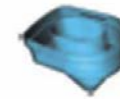
- CLIA Waived; 15 min to result



Alere I Workflow

- Bring supplies to room temperature.
- Put test base and sample receiver on instrument; allow to warm.
- Place swab in sample receiver, mix.
- Apply transfer cartridge to sample receiver.
- Move transfer cartridge to test base.
- Close lid; test runs 10 minutes.

Consumables:



Sample Receiver



Test Base

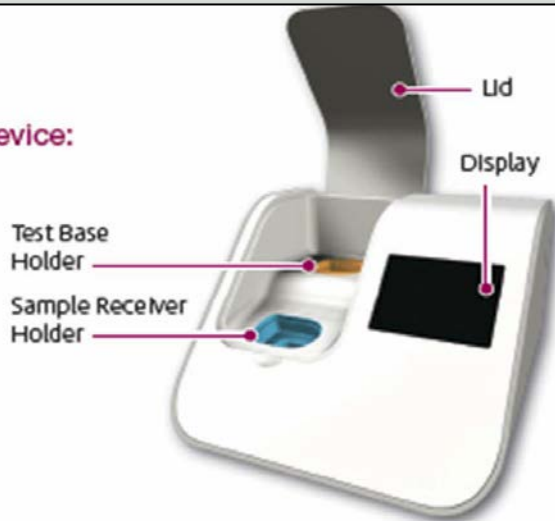


Transfer Cartridge



Cotton Swab

Device:



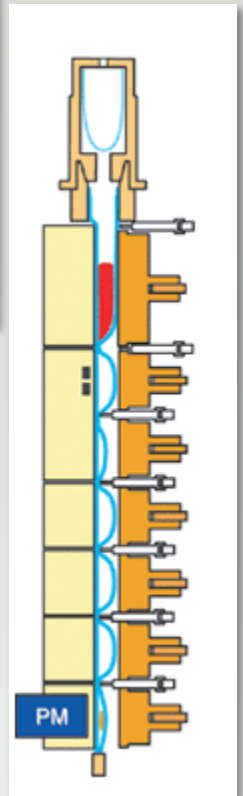
RESULT INTERPRETATION

When the test is complete, the results are clearly displayed on the instrument screen. An individual result for both influenza A and influenza B will be provided.

Instrument Display	Interpretation of Results and Follow-up Actions
	Flu A Viral RNA Detected; Flu B Viral RNA Not Detected. This result does not rule out co-infections with other pathogens or identify any specific influenza A virus subtype.
	Flu A Viral RNA Detected; The presence or absence of Flu B Viral RNA cannot be determined. This result does not rule out co-infections with other pathogens or identify any specific influenza A virus subtype.
	Flu B Viral RNA Detected; Flu A Viral RNA Not Detected. This result does not rule out co-infections with other pathogens or identify any specific influenza B virus lineage.

Iquum LIAT Influenza A/B Assay

- From Iquum (recently acquired by Roche); LIAT stands for Lab-In-A-Tube
- Detects Influenza A&B
- Approved for NP swabs
- Moderately complex; platform is **CLIA-waived** for group A strep
- List price N/A
- Sample to answer .5h



LIAT Workflow



STEP 1.
Add sample



STEP 2.
Scan barcode



STEP 3.
Insert tube



Done!
Results in 20 minutes

Not All Molecular Tests Are The Same

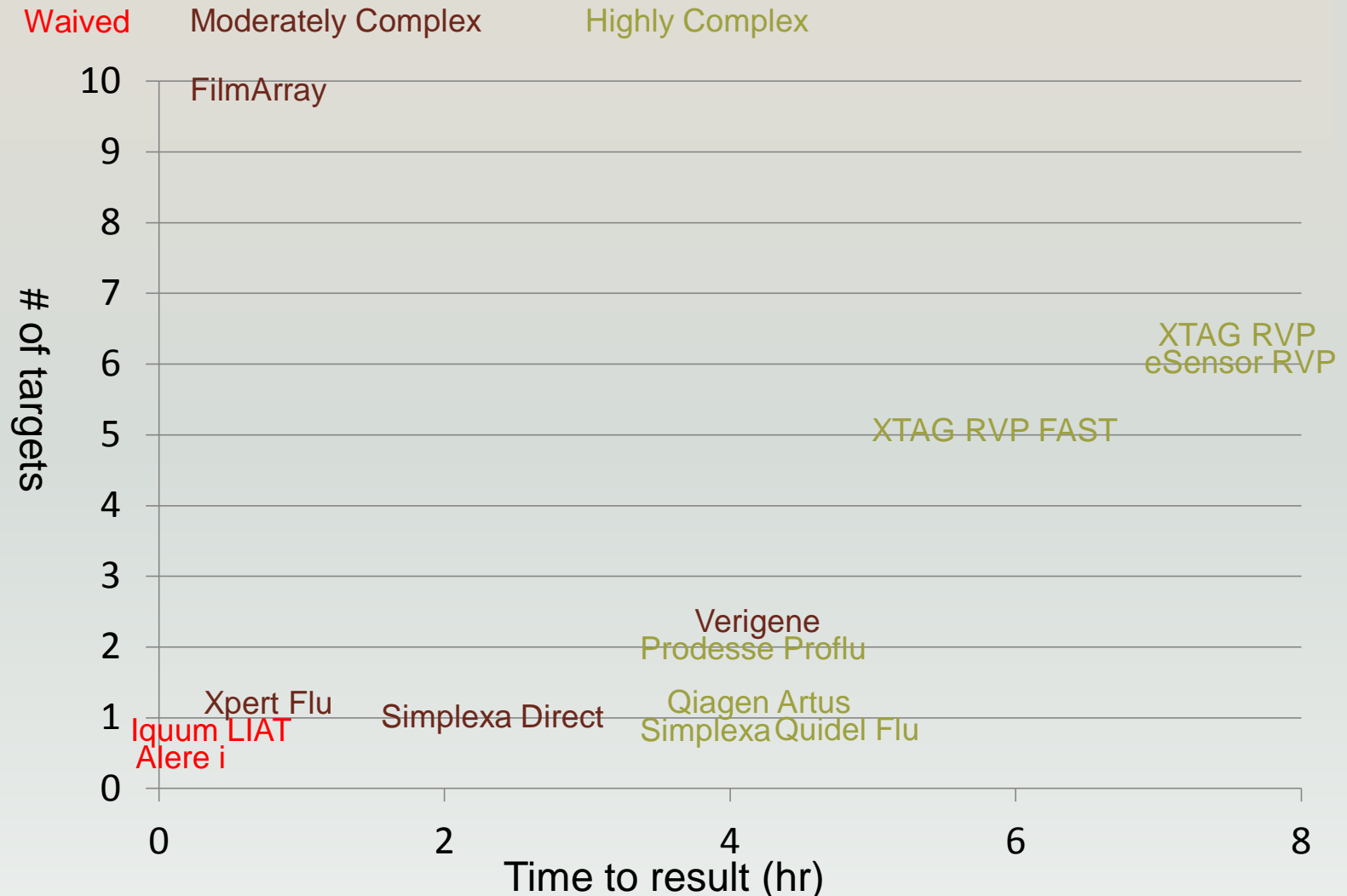
- Numerous, rather confusing studies; I picked one simple example.
- Don't take this as a comprehensive assessment of both assays; neither performed as well as the authors' homebrew RT-PCR.

TABLE 1

Sensitivity of the Verigene RV+ test and the Simplexa Flu A/B & RSV kit by virus ($n = 350$)

Test	% Sensitivity for ^a .		
	Influenza A virus	Influenza B virus	RSV
Verigene RV+	96.6 (56/58)	100 (21/21)	100 (93/93)
Simplexa	82.8 (48/58)	76.2 (16/21)	94.6 (88/93)

Speed and Multiplexing and Complexity



Parsing Cost

- Cost per test depends on reagent + instrumentation + labor.
 - How many single-test modules do you need?
- Make sure to count in instrumentation for extraction, if needed.
- Reimbursement is a moving target; ask an expert.
- Potential for savings elsewhere in the system, if your bean-counters are sophisticated.

Cost of Waivers

- 1,200 hours per waiver application
- FDA expects each manufacturer will spend 2,800 hours creating and maintaining the record of the application
- \$350,000 = total operating and maintenance cost associated with a waiver application (specimen collection, lab supplies, reference testing, shipping, instructional materials, study oversight)

Future Developments

- Technological advances
 - - performance
 - - speed
 - - footprint
- Expanded test menus
 - - quantitative assays
- Resource limited settings

What to think about as POCC

- All the usual QC and QA, plus:
- Interferences
 - Extraction efficiency
 - **Inhibition** by:
 - Blood
 - DNA
 - Internal amplification / extraction controls
- Contamination
 - Extraordinarily sensitive methods
 - **Specimen** cross-contamination
 - Native material transferred from a positive to a negative specimen
 - Collection devices
 - Ports, racks, hands
 - **Amplicon** contamination
 - From amplified material
 - How well is the product contained?
 - Waste disposal
 - Carry-over studies



From an Oil Painting by Teniers

Where are we going?

- I've thought about this a lot.
- Derived Campbell's Laws of POCT
- Two Laws, with inpatient and outpatient corollaries
 - Feedback encouraged.

Campbell's First Law of POCT

- Nobody ever went into Nursing because they wanted to do lab tests.
 - I can't document this with a literature citation, but it has high face-validity.
 - Anecdotally, our nurses/docs have hated glucose monitoring (still done but loathed), ER troponins (tried, failed), and rapid HIV (tried, failed).

Campbell's Second Law of POCT

- No POC test is easier than checking one more box on the laboratory order form.
 - Waived tests are easy, but much, much harder than checking one more box on a form you already filled out.
 - A lot of simple, rapid tests end up being *done in the lab*.

Campbell's Laws Example: Primary Care HIV Testing

- **June 8, 2010: Provider A:** “Sheldon, has rapid testing been considered to prevent this problem? Would this be feasible? Might allow us to expand testing to highest yield sites (i.e. the ER)...”
- **July-October 2010:** Set up program, created templated progress notes, ordered kits, trained 20+ Primary Care providers to do rapid HIV tests.
- **October 2010-January 2011:** Number of rapid HIV tests performed: **1**
- **January 2011: Provider B:** “Even though I am one of the biggest proponents, I have only done one, and that was for another provider who didn't know how to do it. I don't see people clamoring to do the test. I'm interested in Provider A's thoughts.”
- **Response, Provider A:** “We have had very little use in <our clinic>. I think that it's so easy to send the pt for bloodwork that there is not much demand.”
- **January 7, 2011, POCC:** “Next week I will be coming around to the Primary Care areas to collect the HIV kits. Please have them easily accessible. **Thank you and have a pleasant weekend.**”

Campbell's Laws: Inpatient Corollaries

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

Campbell's Laws: Outpatient Corollaries

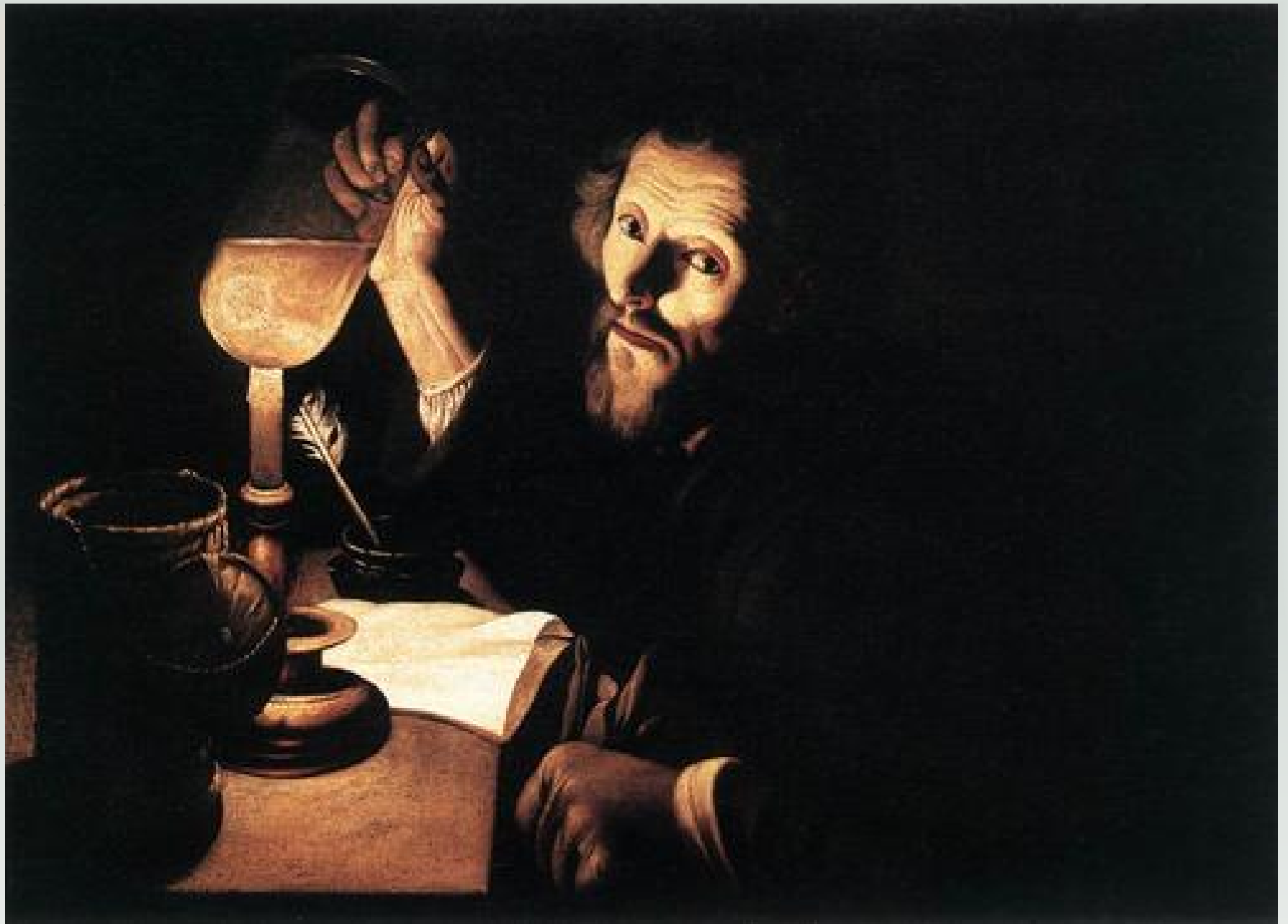
- An outpatient POC test is useful only if:
 - The test result is available during the patient visit AND a decision can be made or action taken on the basis of it without waiting for other lab results, OR
 - If you can make money doing it.

Campbell's Outreach / Developing-World Corollaries

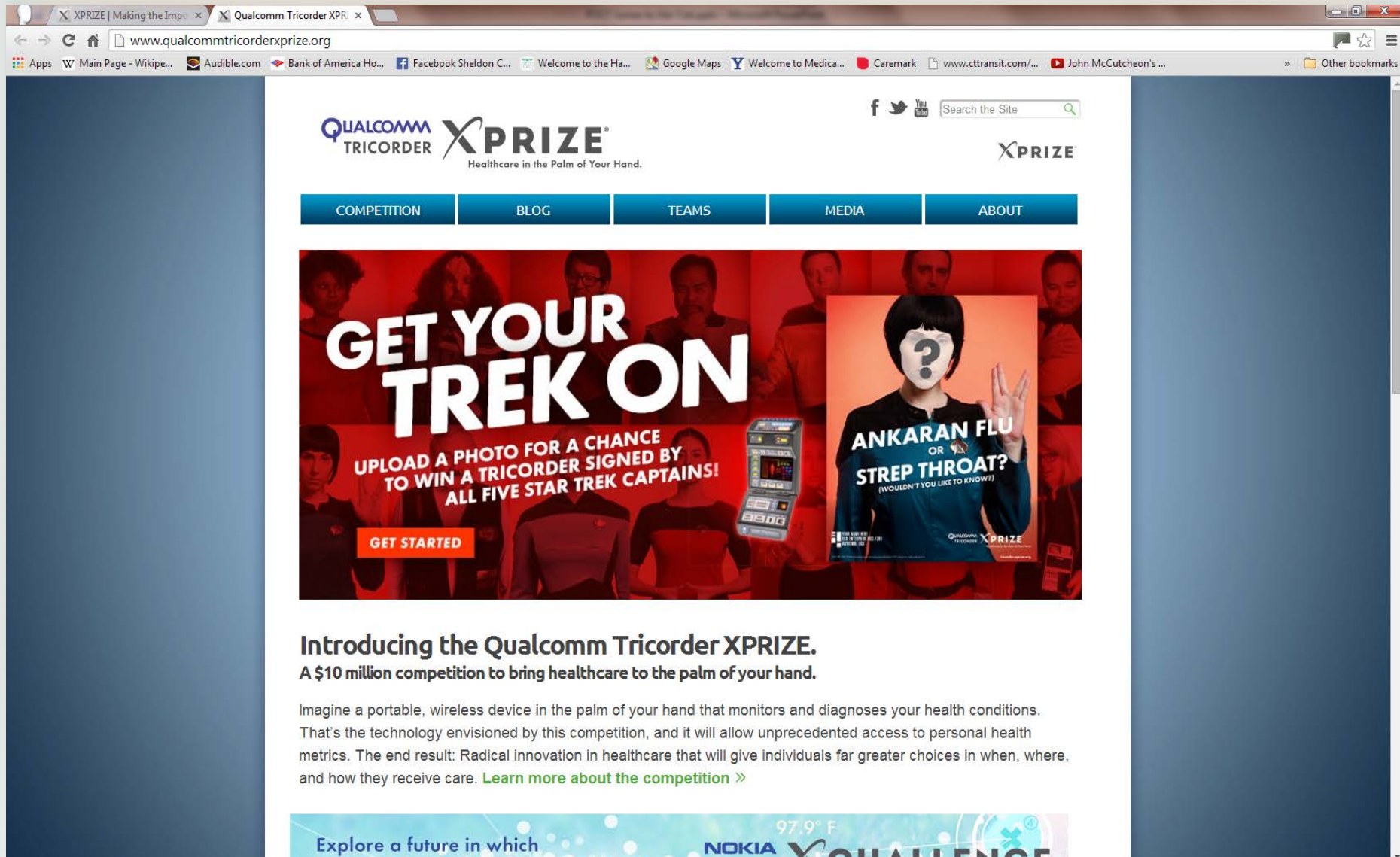
- Sometime's there's no lab-order form.
- Sometimes there's no nurse.
- Sometimes there's no refrigeration, power, or lights.
- Campbell's Laws should not be applied outside of a healthcare environment where the basic terms apply.

Recommendation

- “Point-of-care testing, especially those analyses that are conducted at the patient’s bedside, in a physician’s office, or in a clinic, is a growing trend in health care, and clinical microbiology professionals should prepare for this future reality. Clinical microbiologists must ensure that the individuals who perform point-of-care testing understand how to interpret the results. Clinical microbiologists should be called upon to help select the assay targets, advise on test formats, and participate in clinical trials.”
- From “Clinical Microbiology in the 21st Century: Keeping the Pace”. American Academy of Microbiology, 2008.
Available on-line at:
<http://www.asm.org/academy/index.asp?bid=58445>



The Future, Perhaps



The screenshot shows a web browser window with the URL www.qualcommtricorderxprize.org. The page features the Qualcomm Tricorder XPRIZE logo with the tagline "Healthcare in the Palm of Your Hand." and a navigation bar with links to COMPETITION, BLOG, TEAMS, MEDIA, and ABOUT. A large red banner promotes a contest to win a Tricorder by uploading a photo, with a "GET STARTED" button. Below the banner, the text "Introducing the Qualcomm Tricorder XPRIZE. A \$10 million competition to bring healthcare to the palm of your hand." is displayed. The main body of text describes the competition's goal of creating a portable, wireless health device. At the bottom, a blue banner for the "Nokia X Challenge" is partially visible.

QUALCOMM TRICORDER XPRIZE®
Healthcare in the Palm of Your Hand.

COMPETITION BLOG TEAMS MEDIA ABOUT

GET YOUR TREK ON
UPLOAD A PHOTO FOR A CHANCE TO WIN A TRICORDER SIGNED BY ALL FIVE STAR TREK CAPTAINS!
[GET STARTED](#)

ANKARAN FLU OR STREP THROAT?
(WOULDN'T YOU LIKE TO KNOW?)

Introducing the Qualcomm Tricorder XPRIZE.
A \$10 million competition to bring healthcare to the palm of your hand.

Imagine a portable, wireless device in the palm of your hand that monitors and diagnoses your health conditions. That's the technology envisioned by this competition, and it will allow unprecedented access to personal health metrics. The end result: Radical innovation in healthcare that will give individuals far greater choices in when, where, and how they receive care. [Learn more about the competition >>](#)

Explore a future in which 97.9° F NOKIA X CHALLENGE

Overview

Competition Guidelines

Competition Schedule

FAQs

Stay In Touch

Sign up to receive occasional news alerts on this competition.

Enter Email Address

Subscribe

Overview

The Prize: Empowering Personal Healthcare

The Qualcomm Tricorder XPRIZE is a \$10 million global competition to stimulate innovation and integration of precision diagnostic technologies, helping consumers make their own reliable health diagnoses anywhere, anytime.

The dire need for improvements in health and healthcare in the U.S. has captured the attention of government, industry, and private citizens for years. But a viable solution has yet evaded one of the most technologically advanced, educated and prosperous nations on the globe. Integrated diagnostic technology, once available on a consumer mobile device that is easy to use, will allow individuals to incorporate health knowledge and decision-making into their daily lives.

Advances in fields such as artificial intelligence, wireless sensing, imaging diagnostics, lab-on-a-chip, and molecular biology will enable better choices in when, where, and how individuals receive care, thus making healthcare more convenient, affordable, and accessible. The winner will be the team whose technology most accurately diagnoses a set of diseases independent of a healthcare professional or facility, and that provides the best consumer user experience with their device.

The Instrument Itself



As envisioned for this competition, the device will be a tool capable of capturing key health metrics and diagnosing a set of 15 diseases. Metrics for health could include such elements as blood pressure,

The Instrument Itself



As envisioned for this competition, the device will be a tool capable of capturing key health metrics and diagnosing a set of 15 diseases. Metrics for health could include such elements as blood pressure, respiratory rate, and temperature. Ultimately, this tool will collect large volumes of data from ongoing measurement of health states through a combination of wireless sensors, imaging technologies, and portable, non-invasive laboratory replacements.

LONGITUDE PRIZE 2014

Got an idea?
Register your interest and we'll let
you know when submissions open.

Home The Challenge ▾ Got an idea? Case studies Blog Schools About us ▾

Other challenges

ANTIBIOTICS

How can we prevent the rise of resistance to antibiotics?

Summer 2014

Autumn 2014

Autumn 2014 – 2020

Development of winning criteria, timeline and prize rules

The challenge opens for submissions

Reviewing submissions and judging

\$17.1 million Longitude prize for
POCT for bacterial infections

Challenge

The challenge for Longitude Prize 2014 will be set to create a cheap, accurate, rapid and easy-to-use point of care test kit for bacterial infections.

Impact

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.

an average of 20 years to
crise of antibiotics has
f untreatable superbugs

se doctors have to act
microbes to evolve

icrobial resistance, to
ns.

f applied with current
ion involves a long-term
effective prevention,

Acknowledgements

- 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.
- FDA waiver requirements from a slide provided by Dr. Barbara Robinson-Dunn.

During the fifteenth century quack uroscopists abounded in every land. These charlatans, who travelled the country on a pony or nag, with the urine basket slung on the arm, preyed on the credulity and ignorance of the people. With a glib tongue they made them believe that they could diagnose every disease known under the sun, as well as prognosticate all kinds of events, from a glance at the urine.