The Digital Miasma: Detection and Monitoring of Emerging Infections in the 21<sup>st</sup> Century

David H Persing, MD, PhD

Chief Medical and Technology Officer Cepheid, Sunnyvale, CA, USA

Consulting Professor of Pathology Stanford University, Stanford, CA, USA

## The Ghost Map: A fascinating story about one of the first epidemiologic investigations



 Cholera epidemic waves in London, starting in the 1850s. Unfathomable sanitation conditions •The "Miasma" ... bad air....was the cause of human illness •50 years before the recognition of the importance of germ theory

## The Ghost Map: A fascinating story about one of the first epidemiologic investigations



"The Queen's Anesthesiologist", John Snow takes an interest in investigating the etiology of Cholera
High mortality due to dehydration, especially in young children
Assisted by a local minister in active case finding....mapping

the locations of the deceased

# Geopositioning of cholera cases points to an intervention





- Cases were clustered in the now-fashionable SOHO district
- Highest case loads were found in proximity to the Broad Street pump
- Contamination of the pump casing by leaking contents of an adjacent household septic tank
- Major uproar over closing down the pump, since cholera was caused by miasma, not something transmissible in water

# "The Machine that will help end TB"



Cohen, J. MIT Technology Review, Dec 2012 In November 2011, Jabu Ngcobo, 25, felt a pain in her side and went to the KwaMsane clinic, which resembles a trailer park.

"I was all along thinking I had MDR TB because my two brothers and my sister had it," says Ngcobo.

# "The Machine that will help end TB"



Ngcobo's speedy diagnosis and recovery were made possible by a machine called a <u>GeneXpert</u>, which sits atop a counter inside one of the trailers....

Cohen, J. MIT Technology Review, Dec 2012 .....and resembles a highend espresso maker.

## The Coffeemaker Analogy Taken Further

Barrista: Can I have your order please?

- Customer: I'd like a double shot decaf latte with a twist of lemon
- Barrista: I'll put your order in right away....it will be available for pickup next Wednesday
- > Why so long?

We run our decaf double shot lattes in batches three times a week, and you just missed the cutoff time for the Monday run

# Not to be mistaken for a double shot decaf lemon twist latte...



Sputum processing was the greatest technical challenge to Xpert test development Often bloody and full of inflammatory cells Cell-free DNA content makes it viscous and gravity-defying Variable number of bacilli requires large sample volume

Requirement for inactivation

# (Paradigm) Shift Happens: Xpert MTB/Rif



#### Workflow

- fully automated with 1-step external sample prep.
- time-to-result < 2 h (walk away test)</li>
- throughput: up to 1-48 tests / run
- no bio-safety cabinet
- closed system (no contamination risk)

A technology platform for

- TB & Rif Resistance
- TB Quinolone resistance
- Potential for HIV viral load

# Xpert<sup>®</sup> MTB/RIF

#### **Rapid Molecular Detection of Tuberculosis** and Rifampin Resistance'

Catharina Boehme, et al. New England Journal of Medicine, 1 Sept, 2010

#### The NEW ENGLAND JOURNAL of MEDICINE

#### Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

#### ABSTRACT

#### BACKGROUND

Global control of tuberculosis is hampered by slow, insensitive diagnostic methods, Global control of tuberculosis is hampered by slow, inscensitive diagnostic methods, particularly for the detection of dynamics dama (in patients with human im munodeficiency virus infection. Early detection is essential to reduce the death rata and interrupt transmission, but the complexity and infrastructure needs of sensitiv enchods limit their accessibility and effect. methods limit their accessibility and effect.

METHODS

ratory Service, Cape Town (M.P.N., A.M.) and the Unit for Clinical and Biomedica TB Research, South African Medical Re Micolattrium tuberulosis (MTB) and resistance to rifampin (RIF), with fully integrated in South Africa; PD. Hinduja National sample procession in 1720 accession in 1720 acces sample processing in 1730 patients with suspected drug-sensitive or multidrug-resisaja), Mumbai, India (S.S., C.R.); Ir de Medicina Tropical Alexander vo tant pulmonary tuberculosis. Eligible patients in Peru, Azerbaijan, South Africa, and

#### RESULTS

CONCLUSIONS

copy and the MTB/RIF test.

Among culture-positive patients, a single, direct MTB/RIF test identified 551 of 561 patients with smear-positive tuberculosis (98.2%) and 124 of 171 with smear-negative tuberculosis (72.5%). The test was specific in 604 of 609 patients without tuberculosis (99.2%). Among patients with smear-negative, culture-positive tuberculosis, the addition of a second MTB/RIF test increased sensitivity by 12.6 percentage points and a third by 5.1 percentage points, to a total of 90.2%. As compared with at car phenotypic drug-susceptibility testing, MTB/RIF testing correctly identified 200 of 205 patients (97.6%) with rifampin-resistant bacteria and 504 of 514 (98.1%) with rifampin-sensitive bacteria. Sequencing resolved all but two cases in favor of the org. MTB/RIF assay.

India provided three sputum specimens each. Two specimens were processed with

N-acetyl-L-cysteine and sodium hydroxide before microscopy, solid and liquid culture,

and the MTB/RIF test, and one specimen was used for direct testing with micros-

nyvale, CA (M.I., D.H.P.); and the De nent of Biostatistics and Bioinfo . Duke Univ rsity Medical Cente matics, Duke University Medical Center, Durham, NC (S.M.O.), Address reprint requests to Dr. Boehme at the Founda-tion for Innovative New Diagnostics, Ave. de Budé IS. 1202 Geneva, Switzerland, or at catharina.boehme@finddiagnostics.org. This article (10.1056/NEJMoa0907847) wa published on September 1, 2010, at NEIM

oldt, Universidad Peruana Cayeta edia, Lima, Peru (F.K., E.G.); Spe

cial Treatment Institution, Baku, Azer-baijan (R.T.); the Division of Infectious

Diseases, New Jersey Medical School iversity of Medicine and Dentistry of

New Jersey, Newark (R.B., D.A.): Cepheid

N Engl J Med 2010.

The MTB/RIF test provided sensitive detection of tuberculosis and rifampin resistance directly from untreated sputum in less than 2 hours with minimal hands-on time. (Funded by the Foundation for Innovative New Diagnostics.)

#### The New England Journal of Medicine

who add from www.nejm.org on September 2, 2010. For personal use only. No other uses without permission From the NEJM Archive Copyright © 2010 Massachusetts Medical Society.

Studied >1,700 Patients

 Peru, Azerbaijan, South Africa and India

#### Smear Positive Patients

- 98.2% Sensitivity, 99.2% Specificity
- Smear Negative, Culture Positive Patients
  - 90.2% Sensitivity with Three Samples •
  - 72.5% Sensitivity with One Sample

Patients with Rifampin Resistance

97.6% Sensitivity, 98.1% Specificity •

# GeneXpert Cartridge

- Critical interface between macrofluidic requirements of sample processing with microfluidics of PCR
- Universal sample prep
  - Sputum, stool, blood, BAL, CSF, urine, swabs
- Room-temp stability of reagents within lyophilized beads
- Contamination Control via enclosed, real-time PCR
- Nested PCR capability
- Multiplexing capability
- Built-in assay controls

PCR Reaction Tube

> Cartridge Body with Multiple Reagent Reservoirs

**Rotary Valve** 

Ultrasonic Interface

# **GeneXpert Systems**



#### **GeneXpert Module**

GX-I GX-II GX-IV GX-XVI GeneXpert Infinity-80 Sys



Common features: 1) Any module can run any test in any order

- 2) Always on, always Stat Capable
- 5) All systems are electronically interface-able
- 6) Systems fromGV4 to Infinity havebeen implementedunder the HBDCprogram

# Demonstration Studies: Impact of Rapid Testing



- Decentralized testing: Significantly more results reported same day
- Decentralized testing: Significantly more results reported overall
- Significantly fewer MDR TB patients on ineffective Rx
- Potential for significant impact on transmission dynamics
- "Rapid molecular testing" can be slow and inefficient when done in central labs in these settings

# WHO Endorsment Leads to Rapid Uptake

### Policy impact (1)



99 GeneXperts (524 modules) in the public sector in 23 countries

898 GeneXperts (4,660 modules) in the public sector in 73 countries



# GeneXpert Placement Map More than 17.000 systems



Question from WHO in 2010: Can we get the data?

No ready answer at the time

- > Lunch meeting at Stanford with faculty candidate Jeff Klausner
- Led to collaboration with Dennis Israelski, Eduardo Jerezinski and Wendy Schultz of InSTEDD

Culminated in development of C360 cloud-based Dx monitoring software, released in 2017



### South Africa's Experience with Xpert<sup>®</sup> MTB/RIF



- 0.30

0.28 0.26 - 0.24

- 0.22 - 0.20

- 0.18

- 0.16

- 0.14

- 0.12

- 0.10

- 0.08

- 0.06

- 0.04

- 0.02 - 0.00

0.0

Number of positive tests ---- Number of RIF-resistant tests --- Proportion RIF-resistant

Jul

#### **Xpert Distribution (March 2011–March 2016)** National Health Laboratory Service: All Gx Instruments Connected to a Central Data Warehouse

314 GeneXpert instruments: 4180 modules



- 207 sites servicing
- ~4710 facilities from previous microscopy centres

### 6.4 Million Xpert<sup>®</sup> MTB/RIF Results: Centrally Collected and Displayed

Xpert positive tests 2015





### 6.4 Million Xpert® MTB/RIF Results

Xpert Rif R tests 2015





### Correlation of Probe Data to Rif Resistance



22 © Cepheid. Confidential – For Internal Use Only.

### 100 years ago: the 1918 Flu Pandemic













23

### What do we do with the Flu/RSV data?

- Xpress Flu/RSV design predicts ca.100% coverage for the 1918 pandemic flu strain recovered from corpses preserved in permafrost
- Same predicted performance for avian and swine flu strains because of redundant design



24



A CLIA waived test designed for worst-case scenarios

# C360 as a Predictor of Influenza Severity?

- Predict Flu severity earlier in the season
  - -Better anticipation of antivirals, Dx supplies, HC burden
- Leverage Cloud-based data aggregation
  - Real time flu results, sorted according to HIPAA compliant parameters like age range (available now)
  - -Add vaccination status to C360 (new feature)
  - Viral load (CT values) across the sorted populations might give an indication of transmission pressure and relative vaccine effectiveness
  - -Early indicator of seasonal flu severity?
  - -Early indicator of novel pandemic strain?

Out of Sputum, Snot, and Spittle-Precision Medicine and actionable Public Health information



From the respiratory cloud....to the digital cloud....the digital miasma

# THANK YOU

**InSTEDD** team **Jan Steuperart David Alland Bob Kwiatkowski Martin Jones Fred Tenover Ellen Jo Baron** Marika Kleman **Russ Higuchi** 

Reuel Van Atta Per Grufman Wendy Stevens Leslie Scott Jeff Klausner

FIND/BMGF, NIAID, Unitaid, PEPFAR