Molecular Diagnostics + Automation: Impacting Patient Lives through Accurate and Reliable Clinical Testing

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Hologic - Diagnostic Solutions
Presentation Outline

- My Personal Education Journey
- Hologic Nucleic Acid Amplification Technology
- Hologic Instrumentation/Engineering
- Putting it all Together: Hologic Amplification + Automation for detection of infectious disease
- STEM in Diagnostics
About Me

• Navy Family

• Born in Subic Bay, Philippines

• Father’s last station and retirement at 4 years old – San Diego, CA

• Grew up in South Bay San Diego (~ 8 minutes from the Border)
My Education Journey

**High School:** Montgomery High School
c/o 2002

**Community College:** Southwestern College

**Undergrad:**
California State University, Northridge

**Graduate School:** Johns Hopkins School of Medicine

**Post Doctoral Training:** The Scripps Research Institute
My Education Journey

• Prior to Transferring to CSUN, Applied to NIH MARC Program

• MARC Program
  – The goal of this program is to increase the nation's pool of students from underrepresented groups who have the research experience and science preparation to matriculate and succeed in biomedical Ph.D. programs.

• NIH Training Grant Awarded to Minority Serving Institutions (Certain % of student population) – CSUN, SDSU, UCLA, etc.

• MARC Program Provides:
  – Mentorship
  – Research experience (Selection of Research Laboratory and Undergraduate Thesis requirement)
  – Financial support (fees, tuition, stipend)
  – Other trainee-related experiences (Weekly seminar series, Society Conferences, Summer Program Application Prep, GRE Prep, Graduate School Application Prep)
My Education Journey

• MARC participation in Junior and Senior year of College
  – Applied as a transfer student from Southwestern College

• Activities I participated in that made my graduate application competitive:
  – Completed Undergraduate Thesis in Mutation Analysis of Inherited X-Linked Genetic Disorder: CDPX2
  – Accepted and Attended Summer Research Program at the Johns Hopkins School of Public Health: Biochemistry Department
  – Poster Presentation at ASM ABRCMS Annual Biomedical Research Conference for Minority Students
  – Competitive GRE Scores
  – Mentor Editing of Statement of Purpose
  – Strong Letters of Recommendation from PI’s
Mentorship and Opportunity

• Excitement about science at an early age due to one of my favorite teachers in high school in the courses I took; AP Biology, Human Anatomy and Physiology

• Attribute success to key figures/mentors I’ve met throughout every level of my education

• Pushed me to strive for higher and better even with a bad case of imposter’s syndrome

• Constantly searching for opportunities to get real world/hands on experience
  – Internships, lab work, summer programs, research conferences, NIH grants
Hologic Amplification Technology
Worldwide, Laboratories are Under Unprecedented Pressure

- Timely, Accurate Results
- Increased Labor Productivity
- Testing Consolidation Options
- Clinical Service & Performance
- Reliable & Hassle-Free Maintenance
- Cost-Effective

Reliable 
& Hassle-Free 
Maintenance
Hologic – The Science of Sure

**Hologic** – As a global leader in women’s health, Hologic offers options for screening, detection, and treatment that provide a continuum of healthcare solutions for women.

**Diagnostics**

- ThinPrep Pap Test + Aptima HPV Screening
- Aptima Molecular Assays & Automated Instrumentation
- 3D Mammography & Biopsy Instrumentation

[Image of medical equipment and products]

More than 650 Million Pap tests performed globally.
Molecular Diagnostics

• Develop and Validate assays for the detection of Infectious agents

A single, integrated solution

The Aptima® assay menu on the Panther system includes testing for STIs, women’s health and virology on a single, integrated instrument.

<table>
<thead>
<tr>
<th>FDA Approved/Cleared/EUA</th>
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<tbody>
<tr>
<td>Aptima Combo 2® assay for CT/NG</td>
<td>Aptima® HPV assay</td>
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<td>Aptima® Mycoplasma genitalium assay</td>
<td>Aptima® HPV 16 18/45 genotype assay</td>
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<td>Aptima® Trichomonas vaginalis assay</td>
<td>Aptima® HIV-1 Quant assay</td>
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<td>Aptima® HSV 1 &amp; 2 assay</td>
<td>Aptima® HCV Quant Dx assay</td>
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<td>Aptima® Zika Virus assay</td>
<td>Aptima® HBV Quant assay</td>
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<tr>
<th>In Development</th>
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<td>Bacterial vaginosis</td>
<td>Candida vaginitis</td>
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Hologic Nucleic Acid Testing Technology

A suite of technologies for nucleic acid isolation, amplification, and detection

- **Target Capture**
  - Sequence-specific, non-specific

- **Amplification Chemistries**
  - Transcription-mediated amplification (TMA)
    - End-point TMA, real time TMA; both RNA and DNA targets
  - Real time PCR, RT-PCR

- **Detection Chemistries**
  - Acridinium ester-labeled probes
  - Molecular torches
  - Invader Chemistry
Targeting rRNA yields clinical accuracy and Enhances Sampling Efficiency

- Abundance of rRNA target enhances sensitivity of amplification technology
  - Drives kinetics when low numbers of organisms are present
  - Target nucleic acid distributed throughout sample reducing false negatives due to sampling error
- If organism is lysed prior to sampling, there will be 2,000-10,000 rRNA molecules in the sample tube (~3mL of lysis media)
Hologic Nucleic Acid Testing Technology

one tube, 4 technologies

Sample preparation
1. Target Capture Assay (TCA): release mRNA and Internal Control mRNA and capture both on magnetic bead.

Target Amplification
2. Transcription-mediated Amplification (TMA): add primers and enzymes and generate billions of RNA amplicons via double-stranded DNA intermediates containing T7-promoter sequence.

Amplicon Detection
Target Capture – Isolation of Assay Targets

Poly-T oligomer bound to magnetic particle

Capture oligomer

Target sequence
Benefits of Target Capture

- Simplifies sample processing
- Allows for use of large sample volumes
- Accommodates numerous specimen types
- Virtually eliminates false negatives by removing inhibitors, resulting in improved sensitivity
- Improves specificity by eliminating false positives due to cross-reactivity
Transcription-Mediated Amplification

• RNA transcription amplification system using two enzymes: RNA polymerase and Reverse Transcriptase

• Isothermal amplification of nucleic acid target producing RNA product amplification
  – In comparison to PCR, rapid thermocycling not required for amplification simplifying automation process

• Rapid kinetics results in excess of ten billion-fold amplification within 15-30 minutes

• Combined with probe detection chemistries in a single tube format
Transcription Mediated Amplification

https://youtu.be/qQQtq1LaGL8
• 10 billion-fold amplification in less than 1 hour
• Isothermal amplification
• Maximizes sensitivity and specificity
Detection Methods: Hybridization Protection Assay (HPA)

- Specific DNA probe labeled with chemiluminescent molecule (acridinium ester)
- Probe hybridizes with RNA specific to organism
- Separation of hybridized from unhybridized probe is achieved by addition of selection reagent which hydrolyses the AE on the unhybridized probe (in solution, no washing steps)
- AE on the hybridized probe is protected within the double helix and is not hydrolyzed by the selection reagent. Light is emitted and detected by the luminometer
Detection Methods: Real Time TMA

- Simultaneous fluorescence detection by molecular torch binding
- One reaction tube
- Real-time detection during 42°C amplification
Benefits of Real-Time Fluorescence Detection over End-Point HPA Detection

- Increased throughput/turnaround time
- Improved precision (+/- 0.1 log copy CV’s)
- Significantly increased quantitative dynamic range (5-8 logs vs. 3).
- Increased Detection Multiplexing
- Closed format
Hologic Instrumentation
The Panther System is the ONLY…..

- Fully automated instrument on the market that combines STIs, Women’s Health and Viral load testing
- Run assays simultaneously
- Proven Flexibility, Reliability and Performance
- Serves as a foundation for future capabilities and content
Sample Loading and Access

Flexible Sample Loading

• Load samples at any time while instrument is processing, no waiting to batch.
• Controls valid for 24 hours.
• Ability to prioritize urgent samples.

Multiple Tests from a Single Sample

• CT/NG, *Trichomonas vaginalis* and HPV from the same sample tube.
• Primary tube sampling with penetrable cap eliminates uncapping/recapping.
• Primary tube ensures sample integrity while ensuring multiple aliquots from each specimen.
Increase Productivity and Optimize Lab Space with a Small Footprint

- **CAP/CTM 96**
  - 146 in x 30 in
  - 72 tests/8 hr
  - 30 SQ. FT
  - 2 tests/sq ft

- **Cobas 4800**
  - 112.15 in x 30.5 in
  - 192 tests/8 hr
  - 23 SQ. FT
  - 8 tests/sq ft

- **m2000 rt & sp**
  - 109 in x 31.3 in
  - 96 tests/8 hr
  - 23 SQ. FT
  - 4 tests/sq ft

- **Panther System**
  - 48 in x 32 in
  - 320 tests/8 hr
  - 10 SQ. FT
  - 30 tests/sq ft

- **Cobas 6800**
  - 115 in x 50.75 in
  - 384 tests/8 hr
  - 40 SQ. FT
  - 9 tests/sq ft
**Panther Fusion: Expanding Menu Capabilities, Amplifying Productivity and Enhancing Flexibility**

Panther Fusion Side Care Adds Fully Automated Real Time PCR Capability to Panther instrument

### Productivity and Scalability
- Continuous access of samples and reagents.
- On-demand processing for a wide range of volumes.
- Expanding menu enables testing consolidation.

### Reducing Labor and Laboratory Resources
- Minimal set-up for extended testing intervals.
- Up to 32 assays anytime; multiple tests from one sample extraction.
- Space efficient, self-contained design.

### Foundation for the future
- In-lab, 1-day upgrade leverages existing investment.
- Multiple assay chemistry options.
Putting it all Together: Hologic Amplification + Automation for detection of infectious disease
Hologic Assays utilizing Amplification + Automation for detection of infectious disease

**Women’s Health & STI**
- Aptima Combo 2: Chlamydia and gonorrhea detection
- Aptima *Trichomonas Vaginalis*
- Aptima HSV 1 & 2
- Aptima *Mycoplasma genitalium*
- Aptima Bacterial Vaginosis and Candida Vaginitis (in development)

**Virology**
- Aptima HPV
- Aptima HPV 16 18/45 Genotyping
- Aptima HIV 1 Quant
- Aptima HBV Quant
- Aptima HCV Quant
- HIV Dry Blood Spot (Europe & Africa)

**Respiratory**
- Panther Fusion Flu A/B/RSV assay
- Panther Fusion AdV/hMPV/RV assay
- Panther Fusion Paraflu assay
Current State of Infectious Disease

• STDs at record high, indicating urgent need for prevention
  – CDC, Sexually Transmitted Disease Surveillance Report, 2017
  – Increases in new diagnoses of chlamydia, gonorrhea and syphilis
  – Increase seen in multiple population; women, infants, young adults 20-24yr, and MSM

• Antibiotic Resistant Bacteria on the rise
  – Need of Diagnostic tests to distinguish rapidly between bacterial and viral infections as well as identify bacterial drug susceptibilities
  – New antibiotics and other therapies for those infected with resistant bacterial strains
  – Implementation of evidence-based infection control practices can prevent the spread of resistant pathogens
Current State of Infectious Disease

Consequences of STIs are particularly severe for young women

Undiagnosed STIs cause 24,000 women to become infertile each year

Unique factors place youth at risk for STIs

**Insufficient Screening**
Many young women don't receive the chlamydia screening CDC recommends

**Confidentiality Concerns**
Many are reluctant to disclose risk behaviors to doctors

**Biology**
Young women's bodies are biologically more susceptible to STIs

**Lack of Access to Healthcare**
Youth often lack insurance or transportation needed to access prevention services

**Multiple Sex Partners**
Many young people have multiple partners, which increases STI risk

The STATE of STDs in the United States

- **1.7 million**
  - CASES OF CHLAMYDIA
  - 22% increase since 2013

- **555,608**
  - CASES OF GONORRHEA
  - 67% increase since 2013

- **30,644**
  - CASES OF SYPHILIS
  - 76% increase since 2013

Anyone who has sex is at risk, but some groups are more affected

- YOUNG PEOPLE AGED 15-24
- GAY & BISEXUAL MEN
- PREGNANT WOMEN

Left untreated, STDs can cause:

- INCREASED RISK OF GIVING OR GETTING HIV
- LONG-TERM PELVIC/ABDOMINAL PAIN
- INABILITY TO GET PREGNANT OR PREGNANCY COMPLICATIONS

Help interrupt the steady climb in STDs with these three steps:

**TALK**
Talk openly about STDs with your partners & healthcare providers.

**TEST**
Get tested. It's the only way to know if you have an STD.

**TREAT**
If you have an STD, work with your provider to get the right medicine.
Antibiotic Resistance

- *N. gonorrhoea*
  - CDC estimates 30% of cases are resistance to at least 1 drug
  - SNPs in multiple genes involved in resistance mechanisms

**Antibiotic-Resistant Gonorrhea**

Gonorrhea is developing resistance to the antibiotics we use to treat it.

- There are about 820,000 new gonorrhea infections each year in the U.S.
- Gonorrhea is the 2nd most commonly reported infectious disease
- We are down to 1 recommended effective class of antibiotics to treat it

The public health and medical communities must work together to:

- Monitor antibiotic resistance
- Develop new treatment options

With only one recommended treatment option remaining, it's time to take action.

Learn more at www.cdc.gov/std/gonorrhea/arg
**M. genitalium** – The Other STD you (probably) never heard of

- M. genitalium – small and pathogenic bacterium that lives on skin cells of the urinary and genital tracts of humans that is sexually transmitted
  - Recently listed by CDC as “emerging issue” in its Sexually Transmitted Diseases Treatment Guide in 2015
  - Causes urethritis and cervicitis with symptoms similar to gonorrhea and chlamydia
  - Resistance to azithromycin (highly effective against M. gen) seen in 50% of infections
  - Hologic is first Company with FDA approved diagnostic assay to detect Mgen (2019)
Hologic Response

• Initiatives to develop molecular tests for antibiotic resistance underway

• Barriers to Development of Testing
  – SNPs occurring in multiple genes/proteins conferring antibiotic resistance present in the population of bacteria
  – Technology allows for SNP detection but is limited to number of targets
  – As Bacteria evolve to overcome replication in our current antibiotic regimen, SNPs that confer antibiotic resistance will change over time
    • Molecular assays will need the flexibility to be updated depending on disease trends
STEM in Diagnostics
STEM Career Options in Diagnostics

- **Lab Scientist** - Research and Develop Assays, new detection methods
- **Engineering** – Developing New Instrumentation for Automation, Improving Existing Instrumentation, Repair
- **Bioinformatics Scientists** – Data analysis, Data mining, Algorithm Development
- **Clinical Scientists** – Clinical Trial Setup, Management, Data management
- **Regulatory and Quality Control** – Oversee regulatory submissions and production of reagents
Hologic Resources for students

- **Summer Internship Programs**
  - College Level internships in Engineering, Software Development, R&D
  - Search Internships - [https://www.hologic.com/careers](https://www.hologic.com/careers)

- **San Diego Festival of Science and Engineering (March 2, 2019 @ Petco Park)**
  - Hologic Booth with Hands on Activity for Students
    [https://www.lovestemsd.org/](https://www.lovestemsd.org/)

- **Hologic Supports the Ocean Discovery Institute**
  - Ocean Discovery Institute uses ocean science to empower young people from underserved urban communities to transform their lives, their community, and our world as science and conservation leaders
    [https://oceandiscoveryinstitute.org/](https://oceandiscoveryinstitute.org/)
This is what we're here for.

IMPROVING LIVES.

We care about these things:

Great science.
Meaningful innovation.
Early detection.
Accurate diagnoses.
Compassionate technologies.
Every product we deliver.
Every customer we serve.
Every patient whose life we touch.

EACH OTHER.

We are passionate about the work we do.
We research tirelessly. Design thoughtfully.

Innovate fearlessly.
Listen carefully. Improve continuously.

Create success by

doing the right thing.

At Hologic we believe
every life is extraordinary.

And that defines our lives.