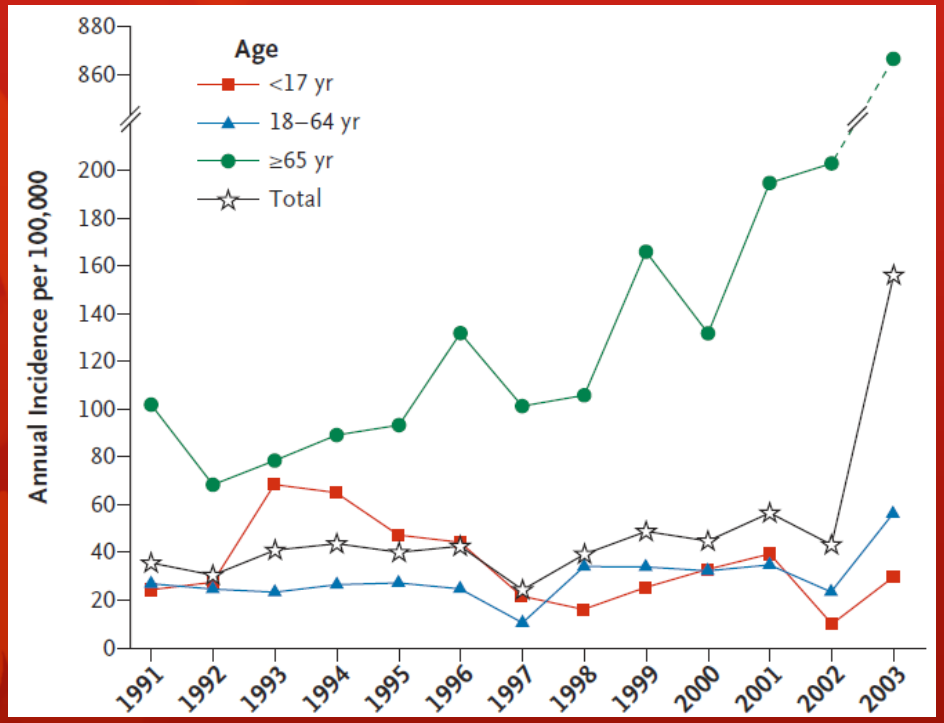
CDI Prevalence & Mortality are Increasing



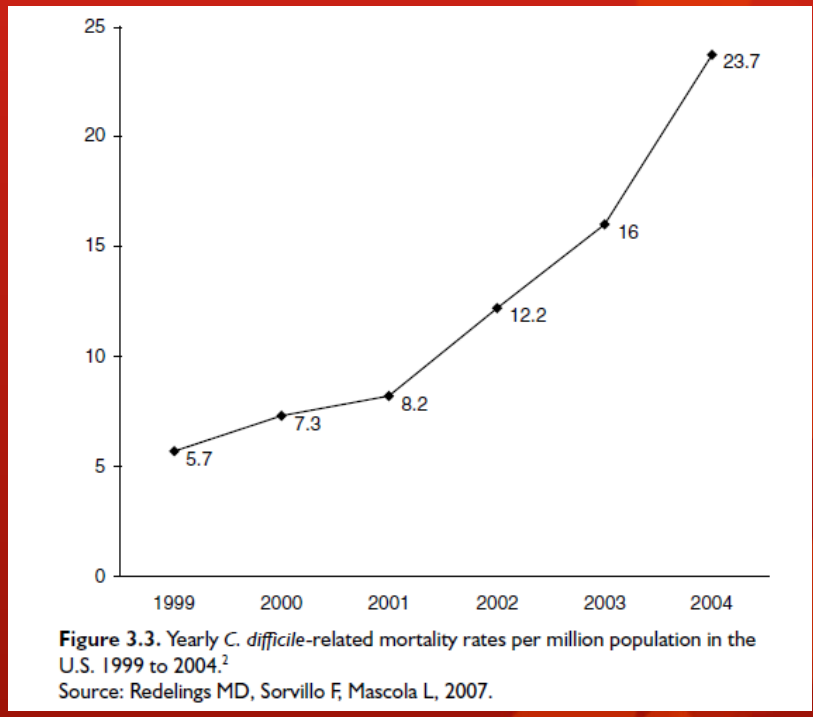


Figure 3.3. Yearly *C. difficile*-related mortality rates per million population in the U.S. 1999 to 2004.[2]
Source: Redelings MD, Sorvillo F, Mascola L, 2007.

N. Engl. J. Med, 2008

- CDI prevalence have more than quadrupled in the past two decades and remain at historically high levels while most types of hospital-associated infections (HAIs) are declining
- Deaths related to CDI increased 400% between 2000 and 2007, due in part to a stronger germ strain

CDI Transmission / Financial Burden

- 3 million CDI cases annually in the US
- Accounts for 20-30% of hospital-associated diarrhea
- Causes 14,000 annual deaths in the US
- Cost > $3B to treat in the US annually
- ~50% CDI occur in people younger than 65, but >90% of deaths occur in people 65 and older
- CDI risk generally increases with age; children are at lower risk
- About 25% of CDI first show symptoms in hospital patients; 75% first show in nursing home patients or in people recently cared for in doctors' offices and clinics

Treatment / Patient management

Treatment

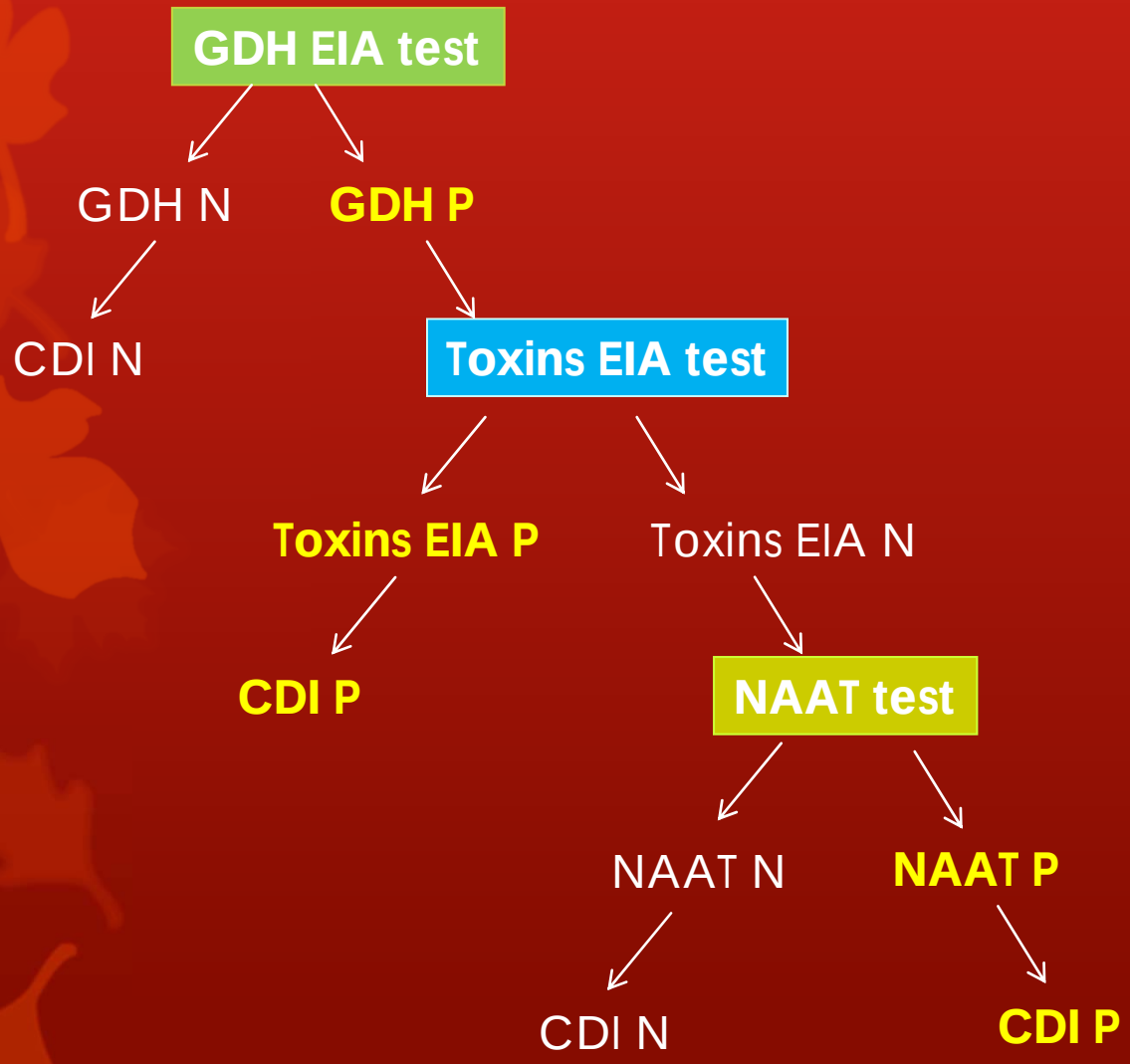
- First step is discontinuation of antibiotic therapy
- Mild diseases are treated with oral Metronidazole
- Severe diseases are treated with Vancomycin
- In rare cases, surgery may be needed
- Relapse or reinfections occurs in 12-24% of patients

Patient management

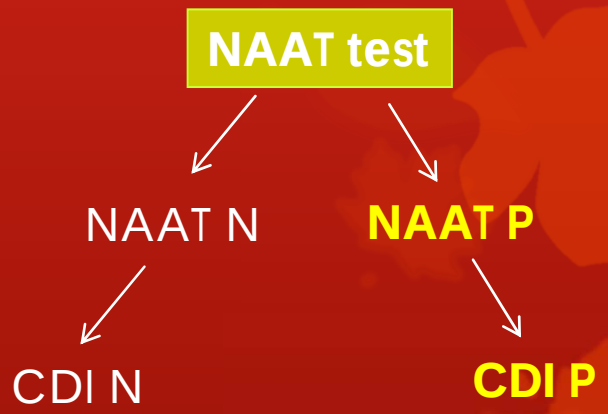
- CDI patients are isolated in a single room or cohorted with other CDI patients
- All healthcare workers and visitors must wear gloves and gowns when entering the room of CDI patients

Current CDI Diagnosis

(A) Combination of EIA and NAAT



(B) NAAT stand alone test



NAAT: Nuceic Acid Amplification Test (of toxin genes)

EIA: Enzyme enhanced ImmunAassay

GDH: surface antigen

Emerging Epidemic Hyper-virulent Strains

- Since 2005, hyper-virulent strains such as BI/NAP1/027 are emerging
- Hyper-virulent strains possess a third toxin, **binary toxin gene**

- CDI 30-day mortality rate
  - 17% without binary toxin gene
  - **28% with binary toxin gene**

- CDI recurrence rate
  - 17% without binary toxin gene
  - **28% with binary toxin gene**

- **Early detection and correct treatment is critical to reduce severe outcomes**
- **Detection of the binary toxin gene in addition to the toxins genes is important to combat CDI**

Unmet Need

Accurate, Affordable, multiplexed, Rapid and Point-of-Care test

NAAT

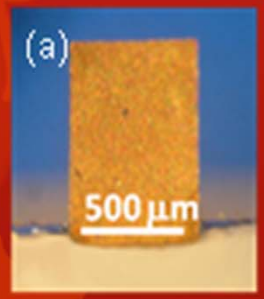
Meridian, Cepheid, Nanosphere, BD, Prodesse

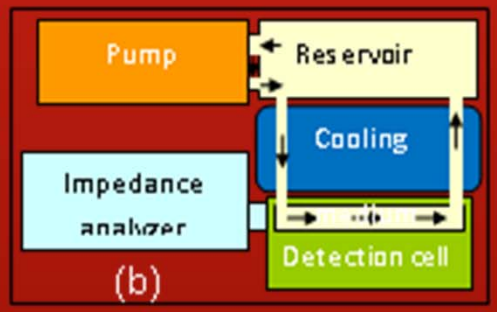
$35-$58/gene

Sensitive (>90%) but expensive
Does not multiplex, adding binary toxin gene would further increase the cost

Inexpensive, Rapid, Multiplexed, and Accurate CDI Test Solution…

Piezoelectric Plate Sensor (PEPS) Array



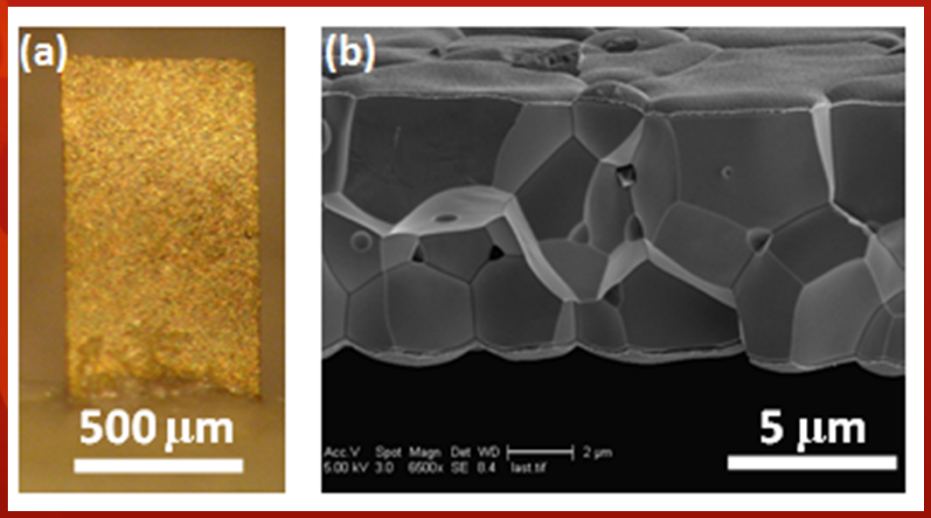


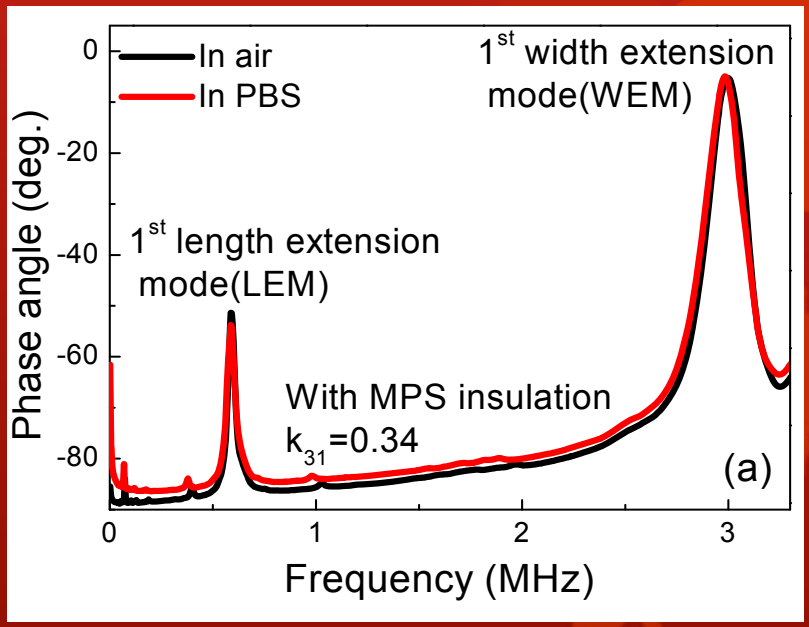
- Rapid, sensitive, and yet low-cost detection using PEPS with
  - *in situ* bacteria lysing,
  - *in situ* DNA release,
  - *in situ* DNA denaturing,
  - *in situ* DNA detection All in 40 min

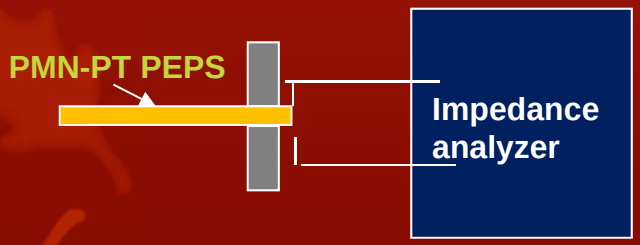
- With PCR-like sensitivity but no DNA extraction, concentration, and amplification
- Real-time genetic detection using array piezoelectric plate sensors (PEPS) with a $500 impedance analyzer

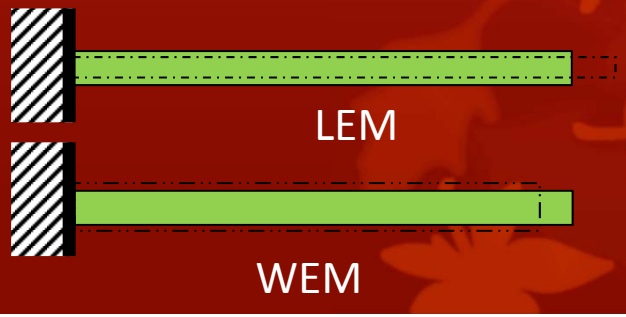
PMN-PT piezoelectric plate sensor (PEPS)

PMN-PT PEPS: (1) 1 mm x 0.5 mm made
(2) made of PMN-PT freestanding film 8 μm thick
(3) operated at length extension mode (LEM)
or width extension mode (WEM)



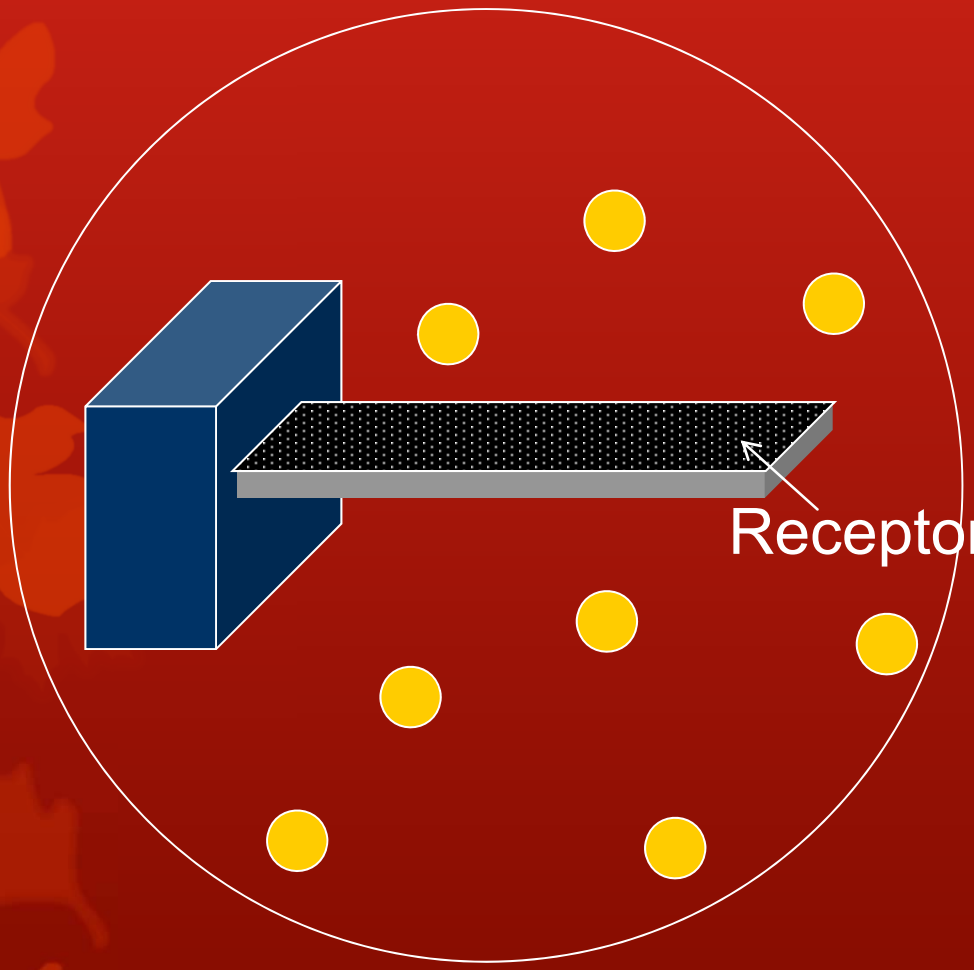


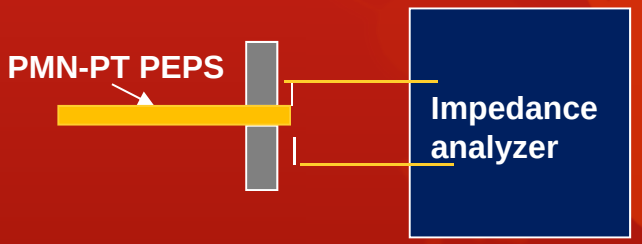


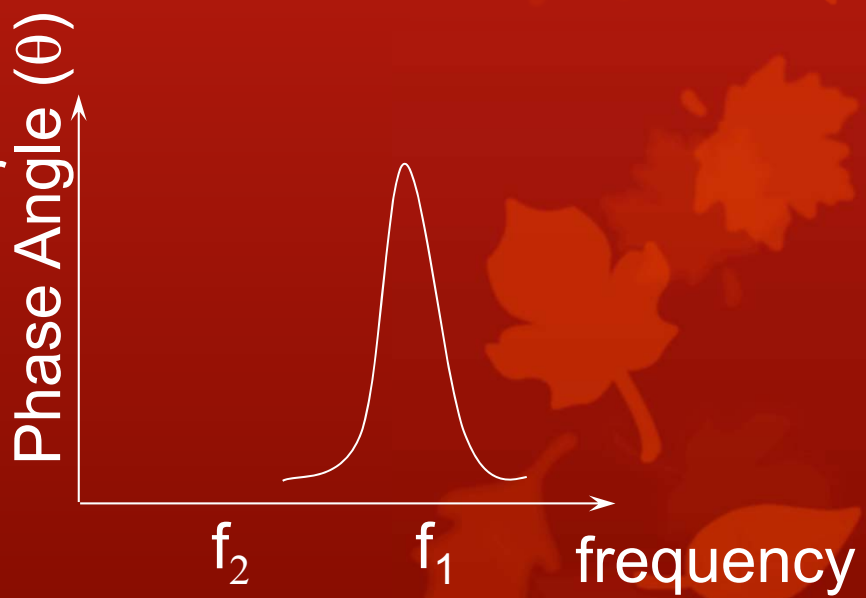


PMN-PT Piezoelectric Plate Sensor (PEPS)

Rapid, Label-Free Sensing





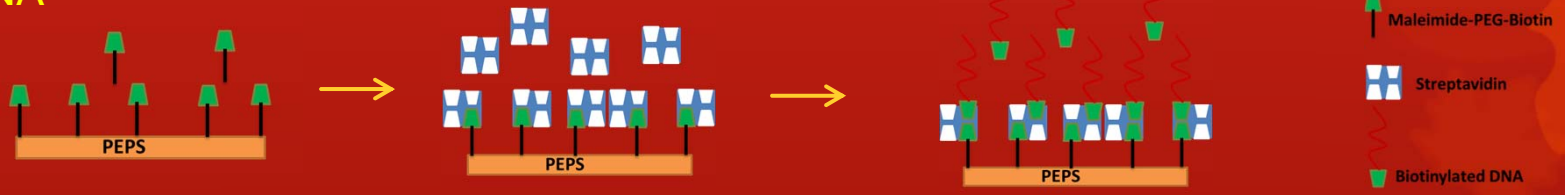


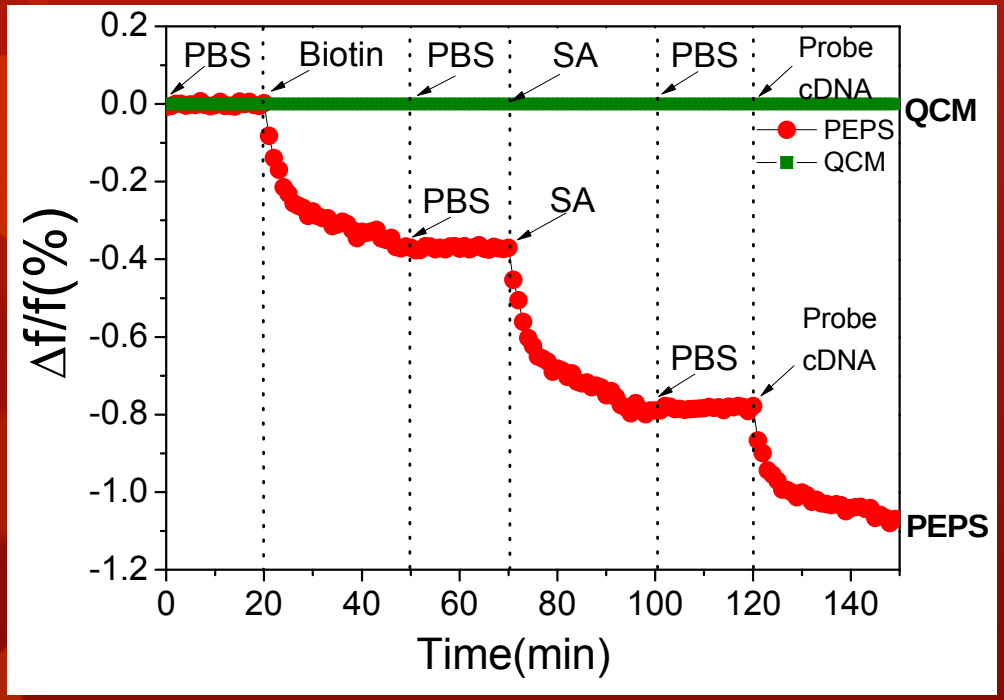
Target antigen/analyte

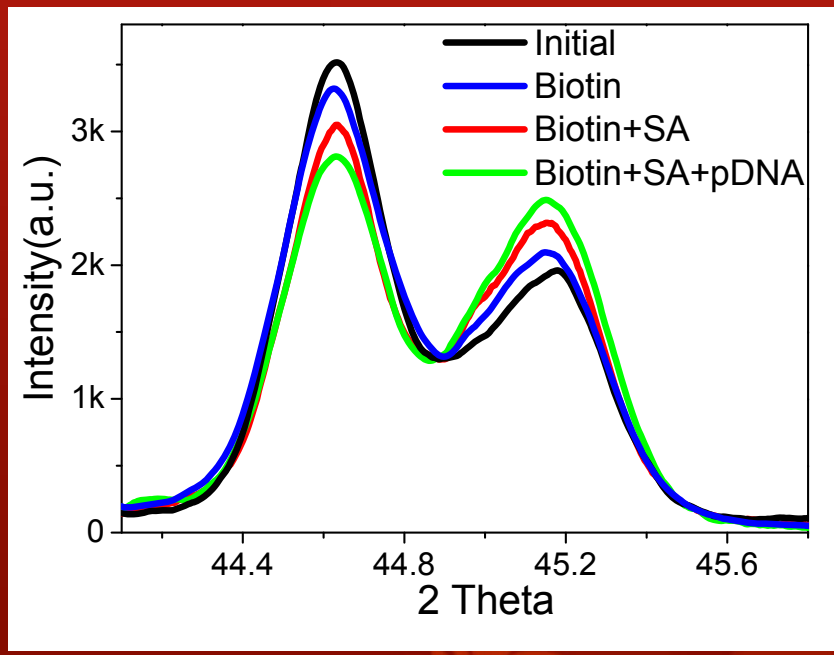
- WYS and WHS have worked on PEPS and its predecessor, PEMS
  - For more than 15 years
  - with more than $4M federal/state funding
  - more than 10 PhD theses
  - 10 patents/patent applications
  - more than 40 published journal papers
- The piezoelectric-material and sensor development is ripe

1000 times Self Enhancement of Detection Δf/f

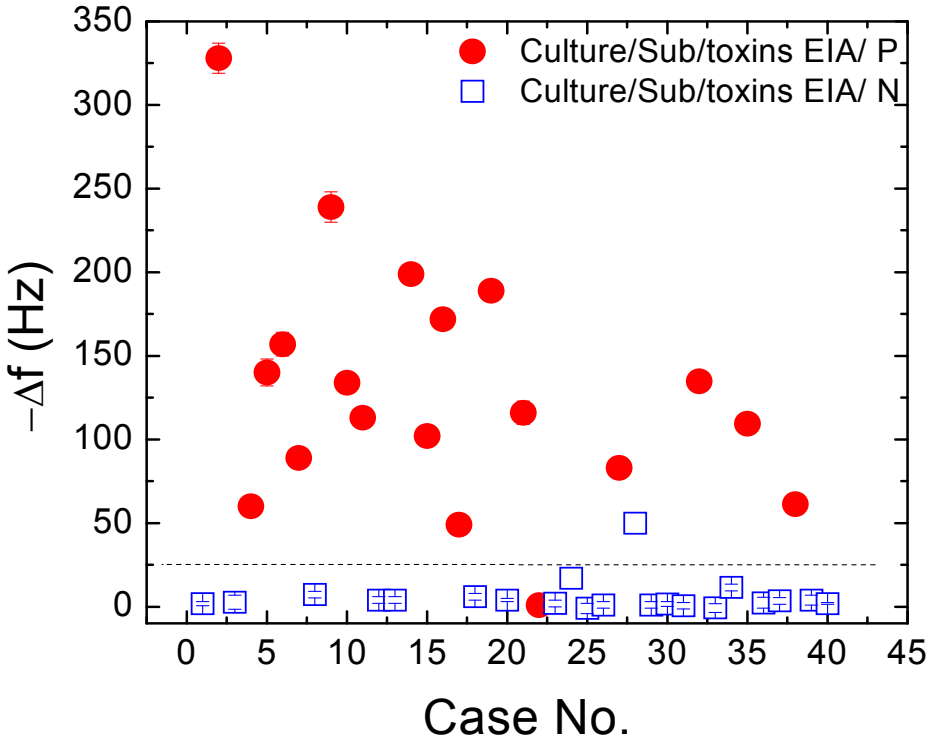
- Due to crystalline orientation switching in “thin” PMN-PT layer induced by binding stress---No such enhancement in other piezoelectric sensor (QCM, SAW…)
- The enhancement increases inversely with a decreasing thickness
- Enhancement is further amplified in DNA detection due to the highly negatively charged nature of DNA







Testing on 40 Blinded Patient Stools



40 stool samples:
20 CDI positive
20 CDI negative
According to stool culture/sub/toxins EIA

PEPS exhibited

- **95% sensitivity--** positive 19/20 CDI positive stools
- **95% specificity--** negative 19/20 CDI negative stools

—The same as Cepheid Xpert (the best genetic test)

Comparison with Current Technologies

Table 2.1 Competitive Comparison between PEPS and commercially-available CD diagnosis alternatives							
	Equipment	Detection time	CDI diagnosis	Sensitivity	Specificity	severity test	Cost/test
GDH+toxins EIA	$20 – 50k	Hours	No	50-60%	95%	No	$17.5
Genetic test	Free to $150 – 180K	1 hour	Yes	95%	95%	No	$30-$58
GDH/toxin/ Genetic test	$150 – 180K	Hours	Yes	87%	>90%	No	$40
PEPS	**Free to $3K**	**40 min**	**Yes**	**95%**	**95%**	**Yes**	**$20**

Reimbursement from the Centers for Medicare and Medicaid Services

$17.5 for GDH test

$50.27 for bacterial detection using amplification

Hospital Revenue Potential

# of hospitals		Bed size	Avg Estimated CDI tests*	Total Estimated CDI tests*	Revenue Potential	% of Revenue potential
XL-size	75	>800	3,000	225,000	$4,500,000	4%
L-size	430	400-799	2,250	967,500	$19,350,000	17%
M-size	1500	150-399	1,032	1,547932	$30,958,640	27%
S-size	3400	<149	891	3,029,323	$60,586,460	53%
Total	5405		6,282	5,769,756	$115,395,120	100%

*Estimate is based on Hahnemann, a 400-bed hospital that performed 1,500 tests last year.

- $20/test makes it a +$100 million opportunity
- Cepheid Xpert penetrates only 30% and 10% of mid-size and small hospitals, respectively due to its costs.
- Even large hospitals like Temple University Hospital moved away from using Cepheid Xpert and is trying to develop their own PCR method
- Small and mid-size hospitals accounts for 53% and 27% (together 80%) of the market, or *$92MM a year based on $20/test*