

Truths and Falsehoods of New Clinical Lab Technology: What do Theranos and Successful Inventions have in Common?

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Answer

Theranos and successful lab inventions are both examples of the law of sowing (planting) and reaping (harvesting). The outcomes of both are predicted by principles of laboratory science, history, and management.



This is everything I know about directing a lab.

1. Avoid extreme thinking

- The sky is not falling**
- Healthcare is not ending.**
- Everything is going to be OK.**

2. Less is more in nearly all lab endeavors.

3. Innovation is manageable.



....what I know (continued)

4. Most people come to work to do a good job.
5. This is a good and honorable career.
6. Cake and pizza are both good ideas.
7. Venous blood is a very good specimen.
8. In the battle between “being right” and “being effective”, choose “being effective”.



Theranos claims

- **300 tests from a few drops of finger stick blood**
- **Breakthrough technology**
- **Very inexpensive**
- **The future of lab testing is that “more is better” meaning that more testing per patient is better in both wellness and illness settings.**



A Theranos Timeline

By THE NEW YORK TIMES, JULY 8, 2016

2003: Elizabeth Holmes drops out of Stanford to start Theranos in 2003

July 2010: Theranos raises \$45 million by selling equity. It is privately held.

May 2013: Dr. Ian Gibbons, a principle scientist at Theranos, commits suicide.

July 2013. Theranos board: Richard M. Kovacevich, CEO, Wells Fargo; Gen. James Mattis, ; Henry A. Kissinger; former Senator Samuel Nunn; former secretary of state George P. Shultz; Senator Bill Frist.

September 2013: Theranos announces a partnership with Walgreens to allow consumers to test their blood at the pharmacy's stores.

2014: Ms. Holmes profiled in national magazines and other news outlets, and starts to win awards. Fortune says the company has raised \$400 million from equity sales to investors who have effectively valued the company at more than \$9 billion.

February 2015: JAMA editorial criticizes company for operating in “stealth mode for more than a decade” in order to “change the entire health system” without publishing anything in peer-reviewed journals.



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July 2015: FDA approves Theranos's test to HSV1. No other approvals since then.

October 2015: Pulitzer Prize winning investigative journalist John Carreyrou of the The Wall Street Journal publishes pivotal piece raising questions about whether Theranos technology works.

Oct. 16, 2015: FDA raises concerns and Theranos temporarily halts its trademark practice of collecting tiny blood samples from finger pricks.

Jan. 25, 2016: CMS issues a letter saying that the company violated several clinical standards. Simultaneously, secret shoppers reveal that Theranos' patented "Edison" instrument is not in use.

March 31: An inspection report released by federal regulators says Theranos was plagued by quality control problems in its Newark, CA reference lab.

April 18: The company says that the Justice Department has requested documents and that the S.E.C. is investigating.

May: Theranos issues corrected reports for all 10,000 results (12 tests) produced by the "Edison". Dates back to results from 2013.

June 12: Walgreens terminates its relationship with the company. Closes all 40 testing centers.

July 7: Theranos announces that regulators have imposed sanctions, including banning Ms. Holmes from owning or operating a medical laboratory for at least two years. Regulators also revoke the certification of its Newark, Calif., laboratory and prohibit it from taking Medicare and Medicaid payments for its services. Theranos facing distinct lawsuits from investors and patients.



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A Theranos Timeline: continued

October 2016: Theranos closes its clinical labs, laying off 340 workers (~50% of its workforce).

January 2017 – present. Theranos faces 3 groups of lawsuits: Partners (e.g. Walgreens) investors, and patients.

January 2017: Theranos lays off another 41% of its workforce (~100 people).

April 2017: Theranos pays a \$4.65 million consumer fraud settlement with Arizona to refund 175,000 Arizona residents for all testing performed by Theranos.

August 2017: Theranos settles lawsuit with Walgreen's

September 2017: Theranos to be subject of major motion picture and HBO documentary.



Reasons to be skeptical initially about claims:

- **The initial pronouncements from Theranos violated, right away, some basic principles of:**
 - **Laboratory science**
 - **Laboratory Management and History of Lab**
 - **Laboratory Economics**
 - **Common sense**



Seattle Mama Doc

From: Astion, Michael
Sent: Wednesday, December 17, 2014 3:24 PM
To: Swanson, Wendy Sue
Subject: follow-up

Wendy,
You mentioned Theranos. I wanted you to know my opinion based on the common sense the lord gave me and 25 years of hanging around some of the best minds, business people, and inventors in lab medicine.

I do not believe Theranos has a breakthrough technical advance. At best it is incremental improvement, and it is likely they have nothing at all of significance. We have been measuring 25-100 things from small drops of blood for a very long time. Capillary blood is not venous blood, and it is much more variable and subject to collection problems. Patients don't like venous blood draw and they do not like finger sticks either.

Theranos is likely to be a small part of the incremental advance of the consumer movement in healthcare. They have purchased –and will continue to purchase--market share from Quest and LabCorp with the help of celebrity board members and a huge amount of investment and publicity. Much of the publicity appears to be around the cult of personality of their scientific director. They are likely to end up a conventional commercial lab, perhaps even bought by one of the large commercial labs. That is what they look like. No different than hugely financed tech firms out of silicon valley that get sold for a lot, but really amount to very little.

That is my current belief.
Mike



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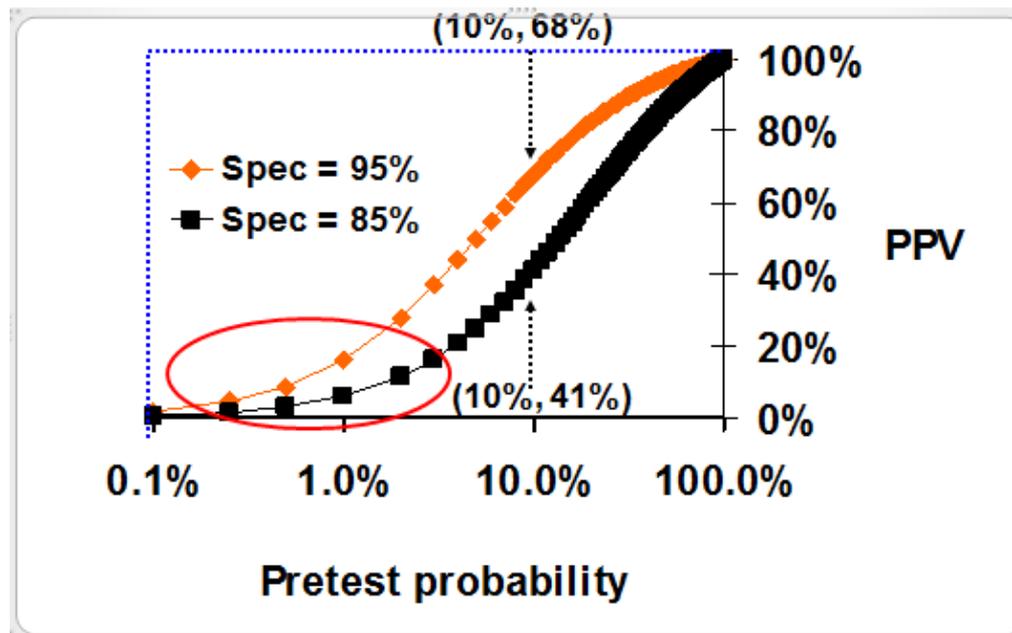
Reasons to be skeptical about these claims: Laboratory Science

- Much is known about finger stick blood.
 - Difficult to obtain accurately.
 - Not the same as venous blood. Venous blood is a very good specimen.
 - Patients don't like getting their fingers pricked.
 - The accuracy and precision of testing with finger stick blood tends to be worse than venous blood
- Thus, basing a DISRUPTION, on finger prick blood is a tenuous foundation for disruption.



Reasons to be skeptical about these claims: Laboratory Science

- “Less is more” is a good rule in lab testing. “More is better” is not.
 - Less is more has a strong theoretical foundation.
 - In the era of evidence based medicine, we’ve never had more tests and never have so few been recommended for screening.



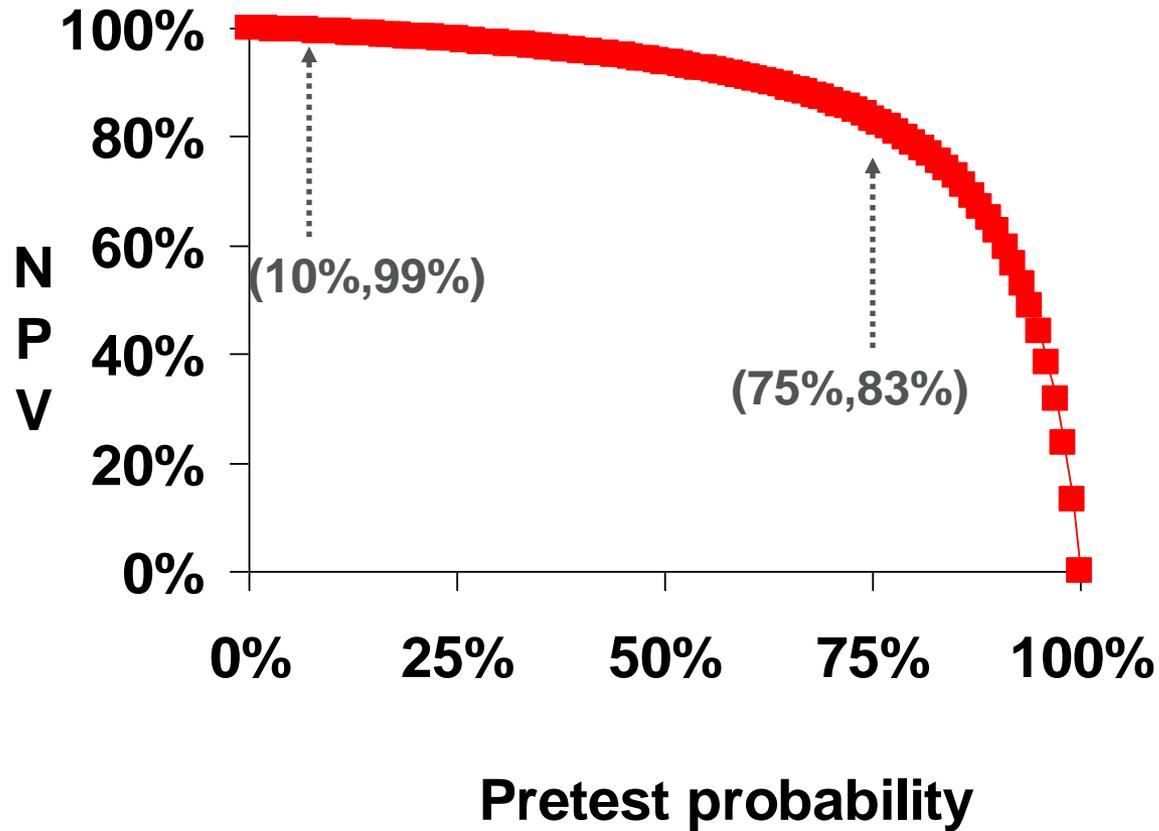
2017 Evidence-based recommendations for screening tests in asymptomatic adults with no family history

(www.ahrq.gov/clinic/pocketgd1011/gcp10s1.htm)

<u>Test</u>	<u>Perform screening?</u>
Chemistry panel	No
Urinalysis	No
CBC	No
TSH	No
Fe / Ferritin	Pregnant woman only
CA-125	No
PSA	Insufficient Evidence
Glucose	Yes, if > 45 yrs, but controversial
Cholesterol	Yes, if male > 35 yrs or female > 45yrs
C-Reactive Prot	No
Chlamydia /GC	Yes, if female < 25 yrs, sexually active
HIV	Pregnant woman; high risk behavior

NPV increases with decreasing pretest probability

(sensitivity = 95%, specificity = 75%)



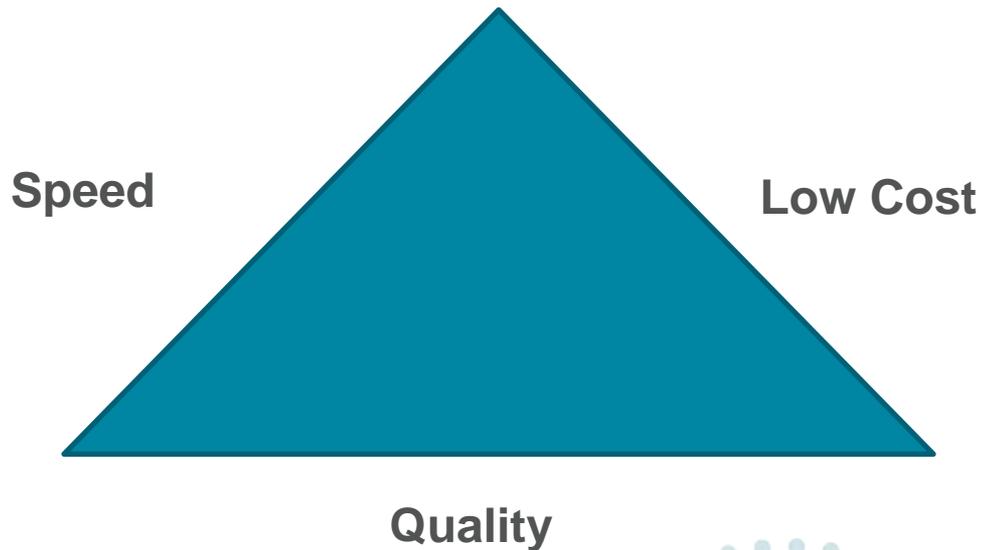
For those willing to listen, predictive value theory (“Less is More”) accurate predictions regarding...

- The limited success of population screening programs.
- The success of targeted screening programs.
- Direct to Consumer Testing of all kinds, including genetics.
- What types of clinics and labs will succeed in grocery stores, pharmacies, and mini-malls.
- Wearables
- Increase in misdiagnosis and story telling in the age of consumerism and social media.
 - Allergy
 - Celiac Disease
 - Genetic testing



Reasons to be skeptical about Theranos: History

In the history of lab medicine, there is a holy lab testing triangle of very fast TAT, very low cost, and high quality. Usually, only 2 of 3 are possible. Why aren't lab tests more like cell phones?



Reasons to be skeptical about Theranos:

- **Lab Management:** Defer to expertise is a great rule of thumb in management.
 - Expertise in lab medicine is real and deep, and often innovative and profit-driven.
 - Most lab entrepreneurs have invested of thousands of hours before their big invention. The big lab inventions including the Coulter principle, total lab automation, the Luminex principle, Kodak dry chemistry, automated core chemistry of all sorts; the major successes in point of care testing; rate nephelometry; sanger sequencing, next generation sequencing, PCR all were invented by people or teams with tremendous expertise.
 - Major inventions tend to be from teams that are highly innovative, educated and experienced and often involves collaborations between academics and industry that occur over very long periods of time.



Reasons to be skeptical about these claims:

- **Lab Management.** Our field is highly regulated, requires huge amounts of scientific evidence to justify a change, and its history tends toward the incremental (not disruptive) even for significant improvements.
 - Even the very biggest inventions, like automated chematology, and total lab automation took a decade or more to penetrate the field. NGS, touted as the biggest disruptor ever, has already taken 10 years, and will take another 15 to make a large scale difference for patients.
 - True analytic disruption would be a waived test with the ability to measure 150 analytes by bouncing light off of the skin and reading the reflection, all in the privacy of your own home. Still, this would mainly benefit the ill.



Reasons to be skeptical about these claims: Lab Economics

- **Lab Economics: Basic Lab testing does not cost much ANALYTICALLY.**
 - In the USA, the average test requisition in a primary care office reimburses as \$44 (for 2.7- 3.0 tests), and has a profit of 2 to 8\$. Patients in the USA get, on average about 5 tests per year.
 - The marginal cost of the next automated, common chemistry test in your lab is several cents. For esoteric tests, that might be a few dollars.
 - Much of the cost of testing comes from legal (accreditation, HIPAA, compliance) requirements, the cost of IT, transport, customer service (including troubleshooting and test interpretation). In the USA, there is also the cost of billing.
- So dramatically lowering the cost of common testing through only a better technology is hard to believe. Theranos would have to dramatically lower the cost of healthcare delivery, not just lower the cost of a technology.



The current structure of lab economics makes predictions regarding...

- The actual decrease in the cost of medical exome testing.
 - While the analytic cost of sequencing is decreasing relatively rapidly, the cost of medical exome interpretation by highly educated staff is dropping slowly or maybe not at all.

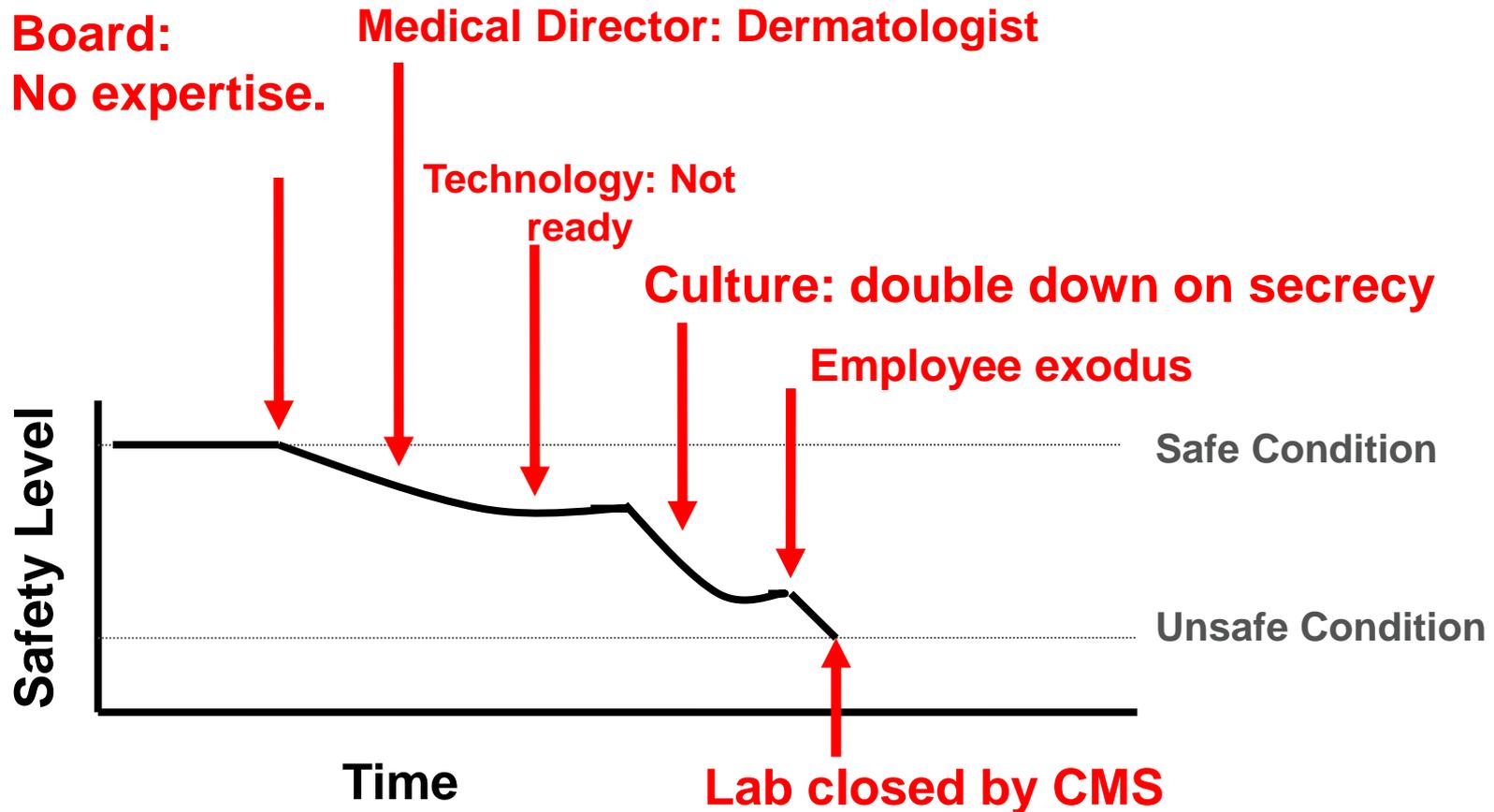


Reasons to be skeptical about Theranos:

- **Common Sense: Extreme thinking tends to be erroneous.**
 - “Avoid extreme thinking” is a great rule in the lab, and in life.
 - So if a college dropout tells us that he or she is going to do 300 tests for a low cost and driven by patient desire, and is going to make sense of those tests medically, and is going to disrupt a highly incremental industry, that is extreme thinking.
- **Common Sense: “You are only as sick as your secrets”.**
 - Lab science without peer review is not good science.
 - Since the invention of the pH meter by Arnold Beckman, and probably before that, lab scientists have made significant profits off their inventions while subjecting them to peer and customer review. There are many paths to protecting and licensing inventions that allow them to be scrutinized.



How organizations drift into failure: incremental decisions seem safe at the time, but they are unsafe.



Dekker S. Field Guide to Human Error Investigations. Ashgate Publishing. Aldershot, United Kingdom, 2002.

Technology and the Lab: Lessons learned

- Stay in school
- Develop expertise, defer to expertise, surround yourself with expertise.
- Avoid extreme thinking
- Inventions take time
- Ready, aim, fire is a good rule of thumb. Theranos was not ready, then they fired, and now they are trying to aim and become ready at the same time.
- There is no avoiding the law of sowing and reaping. Planting a lack of expertise in fertile soil, can lead to a harvest of failure, scandal and shame.

***“From \$4.5 Billion To Nothing:
Forbes Revises Estimated Net
Worth Of Theranos Founder
Elizabeth Holmes”***

Forbes headline, June 21, 2016

Conclusions

- **Technology changes in laboratory testing are slow and steady and important for patient care.**
- **Be cautious when claims of laboratory disruption are made, especially if they violate basic rules of math, science, and common sense.**
- **The future of laboratory medicine is bright.**



Inventions I would like to see.....

- **Something that makes it impossible to lose a specimen**
- **Something that makes it impossible to mislabel a specimen.**
- **Something that dramatically increases the chances of:**
 - **Ordering the right test**
 - **Retrieving the result**
 - **Interpreting it correctly**
 - **Increasing the transparency of cost to the patient (for USA patients).**
- **Point of care that could be used at home for more analytes (e.g. much better than a glucometer; TDM for transplant patients as 1 example).**