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EDITOR'S PAGE

Fake It Till You Make It

What Every Translational Investigator Can Learn From the Rise and Fall of Theranos

Douglas L. Mann, MD, *Editor-in-Chief, JACC: Basic to Translational Science*

Fake it till you make it refers to the idea of projecting self-confidence in order to convince yourself that you can attain a goal that you feel as though you do not *yet* have the skills to achieve. The Silicon Valley adaptation of this aphorism has led to the notion that, in an effort to attract investors, it is okay to talk the talk, even if you don't quite yet know how to walk the walk. The trial of Elizabeth Holmes, who was the founder and former chief executive officer of Theranos Technology in Silicon Valley and was once heralded by the news media as the next Steve Jobs,[1] represents a chilling example of how the self-confidence that undergirds the fake it till you make it ethos can lead to self-delusion and ultimately to self-downfall.

At age 19, Elizabeth Holmes dropped out of Stanford University in order to form the Silicon Valley startup company Theranos (a mashup of therapy and diagnosis), which promised to disrupt the blood-testing industry with novel technology that would make blood tests cheaper, more convenient, and more accessible to the consumer.[2] Because Theranos was a small private startup tech company, it was able to operate in stealth mode from 2003 to 2013. However, in 2013, Theranos began publicizing its technology, which purported to screen for more than 200 health conditions with a few drops of blood that were extracted from a single finger stick. The company's valuation swelled and eventually reached more than $9 billion.[2] As detailed in the book *Bad Blood*,[3] medical authorities along with investigative reporting in *The Wall Street Journal* by John Carreyrou, began to question the actual effectiveness of Theranos' technology. From 2015 to 2018, the company faced a series of uphill legal and commercial challenges from investors, the U.S. Securities and Exchange Commission, Centers for Medicare & Medicaid Services, and patients, which culminated in the collapse of Theranos and the indictment of Holmes and Ramesh Balwini (former Theranos president) by a federal grand jury on 11 counts of wire fraud and conspiracy to commit wire fraud for distributing blood tests with falsified results to consumers.[2]

Although Ms Holmes is not the first Silicon Valley executive to sell investors on an ethereal version of reality, what is different about the Elizabeth Holmes case is that she was placing people's lives at risk by knowingly using a blood testing technology that did not work. In an effort to move new ideas from the laboratory bench into the clinical arena, translational investigators are often required to sell their ideas to study sections, to investors, and to regulatory agencies (eg, the Food and Drug Administration) in order to be able to move into the clinic with the hope that they will see a glimmer of efficacy in early phase clinical studies that will allow them to attract additional funding to advance their ideas into phase III clinical trials. I believe that there are a number of parallels between what happened with Theranos and what can happen to translational investigators who seek to move their ideas from the basic laboratory into early phase clinical trials.

Are there lessons that translational scientists can learn from the rise and fall of Theranos? First and foremost, the Theranos saga clearly demonstrates the limits of the fake it till you make it strategy. Translational research that is not grounded in science and that has no clear mechanism of action, or that is based on early-phase clinical data that appears promising based on an overinterpretation of marginal *P* values for non-prespecified exploratory end points is doomed to fail in phase III clinical trials. As I have stated previously in this Editor's Page, "you cannot fool phase III (clinical trials)."[4] Second, although Elizabeth Holmes believed in the concept of being able to diagnose a myriad of

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diseases with a single drop of blood, her self-confidence slipped into self-delusion as she continued to hype a technology that was not working. Because there are no formal statistical guidelines for how investigators should handle secondary end points in phase Ib and phase II clinical trials, investigators often search for statistical significance in post hoc analyses by combining, or splitting treatment groups, or alternatively retrofitting new mechanisms of action to explain efficacy signals observed in exploratory end points derived from small sizes. Although this is not exactly the same as self-delusion, it is fraught nonetheless, and is ultimately self-defeating. Small exploratory clinical trials are susceptible to asymmetric sampling errors that can lure even the most well-intentioned investigators into believing that effect sizes that are too good to be true are actually true. Unfortunately, these types of studies are unlikely to be replicated in phase III clinical trials. The third lesson is that scientific journals need to learn how to not overhype the results of small clinical trials, no matter how amazing the technology or therapy appears. Witness the retraction of the interim results of the SCIPIO (Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy) trial (n = 16 treated patients and 7 control patients), which showed ~40% relative increase in left ventricular ejection fraction and a ~30% decrease in infarct size 1 year after a single infusion of $cKit^+$ lineage-negative stem cells isolated from the heart.[5] The SCIPIO trial was ultimately retracted over concerns about data fabrication with regard to the self-regenerating capability of $cKit^+$ stem cells.[6] Thomas Lüscher, the former editor-in-chief for the *European Heart Journal*, commenting on the issue of scientific misconduct in the field of cardiac regeneration, remarked that "As an editor, we have to be careful. There is fashion in science and we want to be the first. This is something that has been a lesson. When things look too good, we need to be more critical in the future."[7] What was lost in the entire discussion with respect to scientific misconduct is that we recruited patients into clinical trials that required potentially harmful intramyocardial injections that were unlikely to repair their heart. Fake it till you make it violates the 2 principal rules of beneficence: first, do no harm; and second, maximize possible benefits and minimize possible harms.

Our mission at *JACC: Basic to Translational Science* is to publish novel and innovative science that has the potential to help patients afflicted with, and suffering from cardiovascular disease. This means that as a journal, we may take some risks on new ideas and early-phase discoveries. As editors, we recognize the epistemic limitations of this quest and recognize that we may occasionally over-reach in our enthusiasm to advance new therapies. One of the take-home messages from the rise and fall of Theranos is the ever-present need to remain editorially balanced in all of our efforts, and to openly discuss the strengths and the limitations of the science we publish, so that we always provide our readership with the proper context. As always, I would like to hear your thoughts on this topic, either through social media (*#JACC:BTS*) or by email (JACC@acc.org).

ADDRESS FOR CORRESPONDENCE: Dr Douglas L. Mann, Editor-in-Chief, *JACC: Basic to Translational Science*, American College of Cardiology, Heart House, 2400 N Street Northwest, Washington, DC 20037, USA. E-mail: JACCBTS@acc.org.

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