WHERE WE BEGIN

Every seat was taken in the auditorium when Don Berwick took the podium in front of the 11th annual forum on quality improvements in health care. Looking down at his notes, the affable fifty-three-year-old former pediatrician, Dr. Berwick collected his thoughts before rehearsing his speech to himself. His posture and gaze suggested that nothing less than the auditorium's total acceptance would lead him to break his focus and determination. Clearing his throat, he began to tell the story of Wag Dodge.

In 1941 a storm sparked a forest fire that spread across acres of Montana’s pristine mountain forests. To stave off disaster, a team of forest-fire-fighters parachuted in to try and stop it. Landing on a hillside, the team's foreman, Wag Dodge, led his fifteen fellow smokejumpers down the hills steep gradient, of almost seventy-five degrees, towards the river which lay in the valley below and separated the men from the fire raging on it's other side. Then, just as Dodge and his men were in eye shot of the river bank, the river's turbulent winds gusted up the flames and ash from across the river allowing the fire to cross over to the other side. Suddenly, the reassurance and protection of the river were gone, and instead the smokejumpers were facing the ferocious flames and tremendous heat of the raging fire. Dodge ordered his men to retreat.

Realizing the peril in their efforts the men attempted to outprint the fire, frantically dropping their gear and fleeing uphill. Dodge, however, recognizing the fire’s speed and the hill’s steep incline, dropped to his knees, and lit a match while calling for his men to stop. On his knees he lit the brushes and shrubbery at his feet.

The fire engulfed the mountainside, killing thirteen of the smokejumpers and leaving two others badly burned. Dodge, meanwhile, had remained virtually unharmed, laying inside his little sliver of scorched Earth while the fire sped had past.

Dodge's innovative survival is now referred to as an Escape Fire. By acknowledging his failures, and embracing the opportunity as the framework to innovate a solution, Dodge avoided catastrophe; and in doing so Dodge not only revolutionized smokejumper training, but also set president for the critical steps to sensing making through uncertainty, and providing us with instruction on overcoming failure.
and adversity.

Dr. Berwick, recognizing healthcare’s unsustainable condition, used the story of Wag Dodge and his escape fire to articulate the importance of innovating solutions to the American healthcare system’s current failures, in hopes of staving off catastrophe and enabling a platform of betterment.

**HOW-TO: PROBLEM SOLVING**

Years later, equally important lessons were delivered from Gregory Treverton, who eloquently differentiated puzzles and mysteries. Solving puzzles required us to put pieces of information together. One solved a mystery by determining the relevant and valuable pieces of information to connect together and form a pattern. The data and information of mysteries cannot be jumbled together into any discernable or accurate picture. Mysteries, after all, are problems of too much information and thus require more tasking and sense-making.

Solving a mystery requires us to make judgments but be flexible with our perspectives. When solving a puzzle, we are afforded the luxury of a holistic perspective, where we can look down see all the pieces scattered in front of us and leaving it up to us to discern how they all fit together.

**ADDRESSING CANCER**

In the decades since the initial notion that of the somatic mutation theory, which has become the central dogma of cancer biology for which much of cancer research is based off of, we have investigated cancer as if were a puzzle—as if we were trying to find a needle in a haystack. The problem is cancer is not a puzzle, it is a mystery.

To date, the cancer research community has viewed cancer as a puzzle, not as a mystery.

Like all mysteries, the problem is that we are overwhelmed with information. Consider, for instance, the human genome project clearly shows the massive amounts of data, and yet few actionable results.

To make sense of the chaotic, unconnected, and uncertain data that composes our knowledge of cancer, we must start anew and by acknowledging our shortcomings and failures, as well as looking for positive deviants to baseline our demonstrable success. In order to do better we must ask ourselves: why after decades of research why are the same drugs found to be successful over 70 years ago, still the most effective? Why, when we take into account that improved and earlier diagnostics are responsible for reducing cancer mortality, have the merely marginal gains in cancer patient survival not demanded that researchers attempt to rework their hypotheses? Why are we so risk averse in funding? Why do we use funding to select again any idea that is unconventional when we are so desperately in need of a paradigm shifting discovery? Why after decades of well-intended research and effort do we still not know the difference between the cancer that will kill you and the one that will not?

These uneasy questions we find that they all seem to share a commonality: that the foundational premise, where all today’s theories and therapies are derived from, is flawed. Acknowledging this, we can begin to revise the prevailing dogma to cancer biology: that cancer is *simply* the accumulation of small genetic changes overtime.

**A NEW-OLD WAY**

Over 100 years ago, Theodor Boveri first proposed that abnormal alterations, gains/losses, in chromosomes (humans have 23 pairs of chromosomes, responsible for carrying nearly 22,500 human genes and defining the unique expression patterns resulting in a cell’s specific phenotype or identity) underlie carcinogenesis. For decades much of cancer research has failed to fully appreciate the magnitude of this research. To be fair, this was at times due to technical limitations, but once these technologies arose researches biases entrenched them in their beliefs and blinded them to alternative perspectives. This in large part helped shape the widely (and I should note thus endorsed and
incentivized by funding) gene centric view of cancer.

All the while researchers seemingly ignored the significance of two astonishing observations in cancer: first, people with down-syndrome whose cells have three copies of chromosome 21 have a 20-fold increase in leukemias and are resistant to solid-mass tumors; second, while patients with acute myelogenous leukemia (AML) recognized to have a chromosome translocation this aberration was only appreciated through the lens of its gene-product consequence and not the underlying mechanism of true significance.

While technological advances were enabling researchers to examine cancer genomic in finer more specific detail, the encouragement in our technological gains similarly fueled encouragement in the validity of the gene centric research. This is not to say findings in gene centric research is not of significance, but that their significance is shortsighted in relation to understanding the underlying mechanisms driving cancer.

Consider for example, how certain genes are said to be up-regulated in one context and down-regulated in another. Now, gene centric enthusiasts will argue that “context” matters. They will say that a gene’s role is relative to a cancer’s type, cancer’s stage, an anatomical site of a biopsy, number of biopsies performed, etc. The real question they fail to ask is, is there another mechanism at play that may more readily explain this phenomenon and also fit with our understanding that cancer is an evolutionary processes selection for mutations conferring the most robust fitness potential?

One answer is, if you can or lose a part or a whole chromosome it deregulates large amounts of gene expression, as well as promote genomic instability and under certain conditions also benefit a cancer cell’s fitness. What makes such a theory more attractive is its ability to consider the value in gene centric research as well as take into account the very contradictions that make gene centric view of cancer so sort-sighted.

However, because we have been looking at cancer as a puzzle, and only saw the trees amidst the forest.

Even in times of success, we shaped evidence in agreement with our biases, failing to rescue our failed dogma. When researchers discovered the drug Gleevec to reliably keep a previously terminal cancer in remission for unprecedented amounts of time, we shaped the evidence. Gleevec, which targets the protein bcr-abl, the gene product of the fusion of chromosomes 22 and 9 in AML.

While a chromosome based theory of cancer is not likely to provide the end-all understanding of cancer’s biology, the story of how we got from here to there, how we began to unravel the mystery and find evidence of greater utility serves as a testimony to how our current system for cancer research is not sustainable. But for cancer researchers to embrace cancer as a mystery, and not a puzzle, they have to be able to admit their failures. Only first by acknowledging, our shortcomings and failures in cancer research can we begin to redesign strategies and therapies that will make a meaningful impact. We must have courage to do so, once we do we will be able to rescue success from failure.

The problem is, as Max Planck points out, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it”.

And with the heads of cancer research are leaders, brilliant minds, who are famous for their work in addressing the gene mutation theory. Allowing these people to also have stake in the pharmaceutical industry, is not only alarming as a conflict of interest placing their ideas and theories over other peoples lives, but it only further embeds and reinforces the public in the status quo.

So how do we find solutions to make the needed improvements and do better?

Cue Don Berwick.