# Celebrating 35 Years of Innovation and Impact

## A Cytel Interview Series

Featuring Joshua Schultz, Nitin Patel, and Cyrus Mehta

For 35 years, Cytel's scientific rigor and operational excellence have enabled biotech and pharmaceutical companies to navigate uncertainty, prove value, and make evidence-based decisions with confidence. What follows is a series of interviews with Cytel's CEO, Joshua Schultz, and Co-Founders, Nitin Patel and Cyrus Mehta, celebrating this milestone with reflections on Cytel's beginnings, its innovations in technology and statistical strategy over nearly four decades, and predictions for the future of the industry.

## AN INTERVIEW WITH JOSHUA SCHULTZ, CEO

Joshua Schultz is an accomplished leader with a twenty-year track record of success in life sciences and clinical research organizations. He is known for building service-oriented teams for services spanning the development life cycle, including study start-up, late-phase trials, and market access. His achievements include the development of novel approaches to building high-value strategic partnerships with life sciences companies and creating innovative operational models that leverage real-world data and related technologies.

Cytel

# Joshua Schultz on the Evolution of Cytel and the Transformation of the Industry

On the occasion of Cytel's 35th anniversary, CEO Joshua Schultz sits down with Dr. Esha Senchaudhuri to discuss the transformation of the industry and the evolution of Cytel.

### Cytel is celebrating its 35th anniversary this year. How would you say the industry has transformed in that time?

Let me start with what I believe has stayed the same in the past thirty-five years: we are still bringing cutting-edge science to develop innovative treatments that help people live better lives. That is a great place to start and is a big part of why many of us chose to be in this industry.

And a lot has changed. Modern treatments tend to be far more complex than traditional treatments – think mRNA vaccines and monoclonal antibodies compared to small molecules like Lipitor. Data sources have also become far more complex. In previous eras, data was collected on paper case report forms at a doctor's office, and those forms were a few pages long. We now have wearables, patient-reported outcomes, lengthy follow-ups, electronic medical records, and long case report forms, all of which requires integration, management, and statistical methods to extract full value.

Third, the industry is now very global. It used to be centered in U.S. and European academic medical centers and now there is so much work happening in countries like China and Korea, which were not even really a part of the conversation thirty-five years ago.

On one hand, things are very much the same. But on the other hand, they look very, very different.

### What are some ways Cytel has been a part of that transformation you just talked about? What would you say are Cytel's main contributions to the industry?

Well, the number one impact that Cytel has had is the creation, championing, and eventual widespread adoption of adaptive designs. Thirty-five years ago, they were an oddity and largely theoretical – now, our whole industry is more efficient and effective because of them. We are making better decisions, sparing patients and costs, and getting treatments to market faster because of adaptive designs. Cytel has been a pioneer and we continue to be on the cutting edge of innovation as we invest heavily in new methods and approaches.

That said, while this is our legacy and we will continue to invest heavily in adaptive methodologies, we have also expanded our focus, recognizing that there is so much more that advanced analytic methods can do for our industry. At Cytel, this includes the application of advanced analytics to the use of real-world data, both for value evidence and registrational studies as well as leveraging vast amounts of cloud compute to power sophisticated simulations to solve many formerly intractable problems.

Value evidence is a good example of an area that we traditionally didn't support but where the power of innovative quantitative thinking can play an important role. Historically, the need for robust value evidence was relatively modest

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compared to getting regulatory approval. However, payers across the globe are now asking more complex questions, leveraging a range of data assets, and demanding a high level of scientific rigor before funding the next generation of expensive treatments. Cytel has invested heavily in innovating in this space through our Real World and Advanced Analytics group and now have industry-leading levels of peer-reviewed publications and papers/posters/presentations at industry forums like ISPOR.

Lastly, we are continuing to push boundaries in the way studies are designed and executed. This includes broadening our industry-leading statistical consulting expertise to include other domains so that we can better partner with our clients. It also means extending that design excellence into execution where we can ensure that innovative approaches are incorporated appropriately, which, in many cases, requires developing novel ways to manage wearables, real-world data, and bespoke clinical data.

## What does it mean to be a part of the Cytel community today?

When I first got to Cytel, I made a commitment to the community that the changes in ownership structure would not change who we are at our core. I am proud to say that we have lived up to that commitment with substantial increases in our investment in scientific innovation, advanced statistical methods, novel software, and accessing incredible talent on a global basis. If you looked around the first Cytel office in Cambridge, Massachusetts, thirty-five years ago, you would see exactly the same type of intelligence, curiosity, and passion for the work that made the company special then and makes it special now.

To me, that is the heart and soul of who we are, and my expectation is that we will continue to rely upon that going forward.

## How has the global nature of Cytel influenced its direction, do you think?

Well, it has not changed at all in terms of who we are and what we do. We continue to be on the cutting edge of scientific innovation, looking to hire the best and brightest individuals. We have primarily gone global to find great talent – with great effect. For example, there are thousands of fantastic statisticians and people with advanced quantitative skills in APAC more broadly that we were traditionally unable to access due to lack of footprint and focus. However, our requirements have not changed in terms of who we are looking for, what we do, and the scientific ‘DNA’ of the people.

What I think has changed quite fundamentally is the way that we work. Thirty-five years ago, we had easier and more direct access to each other, with Cyrus or Nitin literally being able to communicate with the whole company just by yelling down the hallway. But that has changed because of remote working brought on by COVID and our geographical spread. While this has made it far more challenging to have direct in-person

connection, I am also quite amazed and impressed by how people find ways to connect, collaborate, and solve tough problems despite working remotely.

**Cytel has always been committed to combining technological innovation and methodological innovation. How would you characterize how that relationship has evolved?**

I think many people know that Cytel was originally founded as a software firm, and that is still very much at the heart of what we do today. Even though most of our employees do not directly work on new software, it really informs, guides, and, in many ways, supports all the other work that we do. We are continuing to extend and modernize our flagship East® product and have extended that to new areas such as East Bayes®. Our Solara® software showcases a whole new way of bringing compute and methods to the problems of study design.

With Cytel's LiveSLR®, and soon-to-be-launched LiveHTA™, we are helping researchers stay up-to-date with literature and analyses that are constantly changing so that they can make better decisions. I am particularly pleased that this idea came from an innovative, entrepreneurial, and passionate Cytel staff person who helped us take it from concept to a fully functional and rapidly growing product. Internally, projects like Cytemation, our automation initiative, has saved us tens of thousands of hours of people's effort, in what would otherwise be relatively tedious activities, and allowed them to instead focus on high value-add work. When you think about all these different ways in which we have been bringing technology to bear, the relationship from the very early days to now is clear.

**In 1982, Professor Marvin Zelen, a pre-eminent statistician who mentored dozens of Cytel scientists and became a Cytel board member, predicted that statistics and computing would become closely aligned, particularly in the biomedical space – a view that received some vigorous criticism at the time. He was also the one to predict that the industry would shift from traditional biostatistics to a more robust data science. Has Cytel proven Marvin right?**

I think time has definitively proven Marvin right, and Cytel has both greatly benefited from and been a part of driving that shift. The idea that you could do biostatistics without robust computation and what we now call data science is not something anyone would question anymore. If you think about some of the areas where we have been on the cutting edge such as simulation and real-world data, they would have been right at the heart of Dr. Zelen's argument.

**Where do you see Cytel at its 45th anniversary celebration? In the spirit of innovation and forecasting, do you have any predictions about what the industry will look like then?**

It is dangerous to follow Dr. Zelen with my own predictions! I am sure his are far more accurate than mine. But I absolutely do have a perspective on what the industry will look like and the role we will play. Firstly, I believe it will be in many ways unrecognizable and much better. We are at the forefront of some profound changes that I believe will greatly impact the way that trials get designed and executed, with a commensurate improvement in efficiency and effectiveness that our industry desperately needs. For example, I believe that study design will go from being a lot of art and some science to being some art and a lot of science, with the help of real-world data, simulation, tools like Solara, and better integration across disciplines.

This will impact the kind of studies that get designed with a shift toward reliance on innovative data sources. This will, in turn, reduce the focus on data collection (where the majority of study budgets traditionally sat) to data sourcing, integration, and analysis.

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Finally, I think there are a whole bunch of relatively smaller elements that, in aggregate, will add up to a fundamental change. For example, we will keep coming up with new statistical methods. The flexible working model that was thrust upon us with COVID will remain that way. Compute will continue to become ever more ubiquitous. If you fast forward ten years and look at what Cytel is doing, it will look dramatically different because of all of these factors. But one thing that will not change is our focus on solving tough problems, leveraging quantitative tools by the brightest folks in the industry.

## Would you be willing to speak about how Cytel has responded to the COVID-19 pandemic?

I’ve had the privilege of multiple moments in my career that I look back on with fondness, but I have to say that I am most proud of Cytel’s response to COVID-19. I mean that in two very different ways.

One of them is internal. The downright heroism that was displayed by all of our 1,700 employees in March 2020, who had to start working remotely over the span of a weekend, was incredible. The disruption to many people’s lives was intense and was made worse by the general environment of intense anxiety and uncertainty generated by COVID in those early days. It was amazing to witness the whole organization step up and find new ways of working together that allowed us to not just execute, but to continue growing at a great pace, drive innovation, and push boundaries. To me, that is an unbelievable outcome and one I absolutely would not have expected.

The other area of great pride for me personally was how Cytel helped support the response to COVID externally. As we go about our work, it is easy to forget how we are positively impacting people’s lives every day. Our industry’s response to COVID was a reminder of how big an impact we have in supporting a healthy global community. More specific to Cytel were the dozens of COVID studies we supported directly, the COVID studies that we designed (including the TOGETHER Trial, which was awarded Trial of the Year), and the many non-COVID studies that needed rescuing due to recruitment and data collection delays.

COVID, and our response to it, truly demonstrated what Cytel looks like at our very, very best.

## Any messages you want to send to the Cytel community on this occasion?

It has been an honor and privilege to work with this team on the cutting edge of science to make a real difference. I look forward to the future with excitement as we build upon a great foundation to make even bigger contributions to human health.

## AN INTERVIEW WITH NITIN PATEL, CO-FOUNDER

Nitin Patel, a distinguished management scientist and Fellow of the American Statistical Association, co-founded Cytel in 1987 with Cyrus Mehta. They hoped to make modern methods in statistics and operations research accessible to clinical researchers by creating quality software for statistical analyses. A widely respected expert in the development of fast and accurate computer algorithms for the implementation of computationally intensive statistical methods, Nitin played a leading role in pioneering Cytel's StatXact® and LogXact® software.

Cytel

# Nitin Patel on 35 Years of Technological Innovation

On the occasion of Cytel's 35th anniversary, co-founder Professor Nitin Patel sits down with Dr. Esha Senchaudhuri to discuss the founding of Cytel, its evolution over the last 35 years, and his vision for the future of the field.

## Tell us a little bit about the founding of Cytel. What led to the need for a software company that paved the way for innovative designs?

Well, it all began from the research that Cyrus and I were conducting, and we came across problems that were of common interest to both of us. He was very interested in applications and biostatistics, and I really enjoy working on algorithms. Together, we managed to get funding and grants that enabled us to begin the production of our first product at Cytel. We also felt there was a big change in the 1980s in computer technology in what was called the microcomputer revolution, and there was an opportunity for small companies to produce software using Federal Research grants and to put them on the market.

Before Cytel was launched, I was in India and there was no internet, so we had to mail drafts to each other describing our research ideas. But it all eventually worked out. It looked like it was possible to do some work that centered on new problems, that could be solved with sophisticated algorithms on inexpensive desktop computers. The rapid growth in these computers in the United States meant that there would be a market if we developed a software product based on these algorithms. Marvin Zelen, who was the chair of the biostatistics department at Harvard, gave us a couple of statistical problems he thought were very important and unsolved. We realized that solving these problems would require constructing algorithms that combined ideas from the fields of statistics and scientific computing, with optimization methods we had learned in operations research. That is what got us started on the journey of building Cytel.

## The combination of statistics with operations research (OR) and computer science, was it new in the 1980s?

Yes, it was. It turns out statistics and OR are closely related, but they started in different applications. Modern statistics started essentially in agriculture, while OR started in mathematical modeling for military applications. Use of mathematical models was common and there were many overlapping methodologies. I have always found it difficult to draw a line between the two.

Performing calculations rapidly on mechanical calculators was essential to apply statistics and OR methods in practice. Computers were an obvious upgrade from calculators. However, computer science grew alongside both fields and developed far more sophisticated methods than were common practice with calculators. We had to use some of these sophisticated methods to enable the massive calculations required to be done within acceptable time limits. These methods were not common knowledge in the field of statistics and OR in the 1980s.

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### What was the technological landscape like at Cytel’s founding? What were biomedical experts expecting to achieve with such new technological tools?

The most important aspect of the technological landscape at Cytel’s founding was that the IBM PC had established itself as a fast-growing presence in companies and universities, and the DOS operating system provided a stable platform for software development. Our earlier research programs had migrated from using minicomputers at Harvard and at the Indian Institute of Management in Ahmedabad to a personal computer made by DEC owned by Cyrus. It became obvious to us at this time that we needed to move to the IBM PC. It was clear that biostatisticians in academia and industry would be interested in statistical software that ran on the IBM PC. There was a worry in companies and regulatory authorities in the biopharm industry that many of the commonly used methods made large sample approximations. There were questions about how reliable these methods were in cases where you had, for instance, rare events occurring in a large sample or had a small sample. Some statisticians were looking for ways to avoid making those assumptions. That is what gave us a start, and we got a number of statisticians from industry and academia to write supporting letters for our grant proposals. This was extremely helpful.

At the same time, we found that selling to big pharmaceutical companies was much more difficult and took longer than we had expected. Fortunately, since we had grant funding, we could continue to operate through long sales cycles. Change is also always hard, and it’s especially hard in larger companies. The pharmaceutical industry is known to be quite conservative, and rightly so as they are dealing with life and death matters. However, things have been changing recently, largely due to the various environmental factors. The industry was way more conservative back then than it is today.

### As Cytel celebrates its 35th anniversary, tell us a little bit about what you see as Cytel’s greatest technological and methodological achievements?

I think it was our algorithms to solve problems related to analysis of small samples and rare events in large samples. It was exciting to solve difficult problems in computational statistics with novel tools that involve integrating ideas across disciplines, a founding strength of Cytel. The greatest strength of Cytel in terms of innovation is being able to create solutions that bridge theory and practice in applications using methods that integrate statistics, operations research, and computer science.

**Professor Marvin Zelen, who sat on Cytel's Board of Directors, argued in 1982 that statistics and computing would someday become inseparable fields. A number of statisticians criticized the view at the time. What was the debate about and how has Cytel navigated it throughout the year?**

I agree with Marvin that statistics and computing are tightly coupled. Computing enables many methods in statistics to be useful in practice, and statistics plays a big role in solving important problems in computer science (for example, Monte Carlo simulation). Also, today, a vast amount of data that is collected by computers has to be organized, sampled, and cleaned. These methods are modern versions of the kind of data cleaning that has been done for census data for many years but require algorithms that work at scale.

We were speaking to several statisticians who were not very comfortable with recently developed optimization methods and computer science techniques. But they understood the techniques at a high level, and we were able to convince them of the usefulness of these methods through collaborative research projects, papers, and seminars.

**New innovations in operations research also played a key role in early software development for clinical trial design. What is operations research and what was its contribution to design?**

INFORMS, the professional society of OR in the United States, defines OR as "the scientific process of transforming data into insights to make better decisions." Many statisticians would feel that transforming data into insights is the core of what they do. You can see why I have trouble drawing a line between the two disciples conceptually!

I like to think OR focuses more on optimization, heuristics, and systems thinking. OR and statistics often use very similar models. Differences in terminology and emphasis often mask a common underlying mathematical structure. East uses recursive methods for analysis of group sequential designs that follow the paradigm of dynamic programming in OR. Maximum likelihood estimation in statistics involves optimization.

**Recent work you have done argues about the importance of aligning statistics and analytics with business strategy. Would it be possi ble to highlight some of the main ideas that you are now positing?**

I am working on extending statistical models to include analytics that incorporate commercial and financial components in clinical trial designs and sequences of clinical trials. I have also been using a systems perspective to include analytics on drug supply that enable integration of decisions in execution of trials with trial design. In the past, I have also worked on designing trials from program and portfolio perspectives.

I've been working on developing visualization methods that enable statisticians and clinicians to interactively inject judgmental considerations in finding the best trial designs in a dataset of thousands of designs using a decision support framework.

**What is different about how sponsors now approach clinical development strategy compared to how it was being done 35 years ago, 25 years ago, or 10 years ago? Today, we have all of this computing technology, dynamic visuals are coming up with Solara, but has there been a shift according to you?**

Yes, there has been a major shift. The most obvious one is the vast increase in use of simulation approaches in trial design compared to earlier.

In the past 10 years, the acceptance of adaptive designs has also increased. Back in the day, when Cyrus started talking

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about adaptive designs to people, they did not understand the need for it. Moreover, in some places, the old methods worked very well, while in others, they did not. So, it is important to know when adaptive designs should be selected over traditional designs.

One of the biggest criticisms of clinical trials is that they work with a very narrow segment of the potential population and then show promising results. But in medical practice, frequently, the promise does not materialize. Earlier, one made assumptions to select a design and did some sensitivity analysis around it. Now, there is a much larger effort in trying to look at various scenarios that reflect what might happen. We look for robust solutions rather than making strong assumptions to develop designs that are optimal using tenuous assumptions. Sponsors are looking for designs that will stand up to a lot of uncertainty.

**Given all these changes, what do you think the field will look like 35 years from now? Do you predict any paradigm shifts? You said that Cytel was prepared for computing because we could understand, even in the 1980s, 1990s, and early 2000s, the synergy between statistics and operations research. Based on your position now, what do you see coming downstream toward us?**

Today, in software development at Cytel, statisticians develop prototypes for functions in products in R. These are too slow to deploy as engines in industrial-strength products. Software engineers code the logic in C and C++ to provide the necessary speed. This transfer is time-consuming and often requires rework when the production engines are tested. One of the biggest developments I can see coming up in the next few years is a language called Julia, which solves this two-language problem. Julia has largely been used in physics and engineering domains, but it has begun to be deployed in products in the life sciences. I believe Julia has the potential to greatly reduce development costs as well as time to market for our software products.

Julia’s syntax is designed to be similar to Python, thus reducing the learning time for statisticians and engineers, and it automatically constructs parallel programming code that today requires a large amount of customization work.

Another major advantage is that programs in Julia smoothly interface with programs in R and C++ so we can make a smooth transition to deploying Julia in our products using earlier programs written in these languages. We have a small research project in the Innovation Center to explore the promise of Julia.

## Would you say we are heading toward a universal computer language?

I don't think there will be one universal language ever. There will always be specialized languages. Especially now, when computing is getting into so many different fields; each discipline will want to find a language that best captures constructs that are most meaningful to it.

## Do you predict a specialist model or a generalist model in 2050?

I think it will be a combination of both. We need specialists because of the accelerated pace of learning in so many fields. But we also need generalists to provide the connective tissue that is essential for effective cross-disciplinary teams.

## Are there any bits of wisdom you would share with young people in the field today about how to push the boundaries of science forward?

In my opinion, there is room for play in work. In other words, there should be some elements of your work that seem like just plain fun. One needs to be ready to experiment and be open to change to avoid becoming obsolete. It is good to have some breadth along with depth in your specialization. I always say, try to be at least a T-shaped person, if not a π-shaped person. That is, you should try to have breadth and know one or two areas of depth in your skill set.

## AN INTERVIEW WITH CYRUS MEHTA, CO-FOUNDER

Cyrus Mehta, a prominent biostatistician and Fellow of the American Statistical Association, co-founded Cytel in 1987 with Nitin Patel. They hoped to make modern methods in statistics and operations research accessible to clinical researchers by creating quality software for statistical analyses. Cyrus's efforts helped establish Cytel as an industry leader in exact statistics as well as in adaptive and group sequential methods. He remains a driving force behind Cytel's East®, the industry standard software for trial design, simulation, and monitoring.

Cytel

# Cyrus Mehta on the Founding of Cytel and Innovations in Statistical Strategy

On the occasion of Cytel's 35th anniversary, co-founder Professor Cyrus Mehta sits down with Dr. Esha Senchaudhuri to discuss the founding of Cytel, the evolution of the industry over the last 35 years, and the ongoing innovations in software and statistical strategy.

### Cytel was founded after an extensive collaboration between you and Nitin Patel in places like the Dana Farber Cancer Research Institute. What were the problems you were collaborating on that led to the founding of Cytel?

We were primarily collaborating on developing computational methods to perform inferences on small categorical data sets, that is, exact tests for categorical data. These problems arose from my work at the Dana Farber Cancer Institute, where we had to make decisions on whether a new drug was safe relative to the controlled drug. The data was classified in terms of the levels of toxicity that were obtained from these clinical trials, and the categories were no toxicity, mild toxicity, moderate toxicity, severe toxicity, and drug death, in that order. There were very few drugs in the high categories, and more in the lower categories. Analyzing that data where you had zeroes and small numbers in higher categories could not be done using the traditional large sample methods. These problems led us to tackle categorical data differently, primarily by using permutation tests.

### What was the statistical landscape like in the pharmaceutical industry at Cytel's founding? How does it compare to the landscape now?

It is completely different now. In the 1980s, and part of the 1990s, too, clinical trials were outsourced by pharmaceutical companies to the National Institutes of Health. The National Institutes of Health funded cooperative groups that were academic centers, especially in oncology, and they grouped together and pulled their patients into these clinical trials. Multiple institutions formed one cooperative group, such as the Eastern Cooperative Oncology Group, the Radiotherapy Oncology Group, or the Children's Leukemia Group A. These groups had a coordination center, an operations office, and a statistical center, and these different institutions ran the trials, funneled all the data through them, and developed reports.

This model gradually changed over time as the pharmaceutical companies began to conduct clinical trials themselves, with their own data. Today, I believe, there is very little work done by the cooperative groups, and almost all the trials are sponsored by pharmaceutical companies.

### How did Cytel move from small sample to group sequential to adaptive design expertise?

It started as a business opportunity where we had to expand our offerings as it was not sufficient to just provide statistical software for small sample problems. There was not enough scope for consulting and no design component to it. We were

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providing tools for analyzing small, sparse, and incomplete data. Hence, pharmaceutical companies could use our software StatXact® and LogXact® to analyze the data on their own. The only consulting opportunity we had was in training them. On the other hand, group sequential problems had a larger impact on the business of the sponsoring organization, because with group sequential design you could get your products to the market faster with fewer patients. So, it was a bigger opportunity for us.

The methodology for these group sequential methods was developed by some of the statisticians at Harvard, where I am a faculty member. That allowed me to collaborate with some of those statisticians and persuade them to act as consultants to Cytel in the early days when we were developing the East® software. Later, these group sequential methods evolved further into adaptive methods. Again, we sensed this as an opportunity for Cytel, and our East software evolved further into providing solutions not just for group sequential designs, but for adaptive group sequential designs.

## How was East created and how did it become the flagship product that it is today?

In those days, we used to conduct an annual seminar with the pharmaceutical industry. There was a pharmaceutical company called Schering-Plough Corporation, which is now a part of Merck. The biostatistics departments at Harvard and Schering-Plough used to have an annual, two-day symposium at Harvard on different important topics. One of the early ones was on group sequential designs and, subsequently, there were other such workshops on missing data, multiple comparisons problems, and numerous other important statistical issues that needed solutions. The workshop on designing group sequential clinical trials inspired me to develop a software based on the methods that were being presented at that symposium, which was perhaps in the early or mid-1990s. I was able to gain support from the National Cancer Institute through their program called the Small Business Innovation Research Program. We were able to apply for a grant to develop the East software through this program.

During this process, we collaborated with Anastasios (Butch) Tsiatis, Kyungmann Kim, and Sandro Pampallona, outstanding experts on group sequential methods, who were at Harvard at that time. We also received a lot of advice from David DeMets, who developed the famous Lan and DeMets error spending function. Chris Jennison and Bruce Turnbull, who have written the standard textbook on this topic, also extended their support, engaged in technical discussions with us, and offered joint workshops with us to industry statisticians.

## One of Cytel's greatest innovations is undoubtedly within the realm of sample size re-estimation. What was the innovation of the promising zone?

Around the turn of the century, some papers were being published on adaptive methods. Adaptive methods were the next evolution of group sequential methods, in the sense that one was now able to look at the interim data and adapt the sample size of the study, the number of looks that were needed or the spacing of the looks. All of this could be done unblinded because there was a model already set up for doing unblinded interim analysis in group sequential designs. An independent data monitoring committee could look at the data, without revealing anything to the pharmaceutical sponsor. That made it possible to develop more innovative designs than simply stopping a trial early for overwhelming efficacy or futility.

There was now an operational process for looking at interim data, while at the same time many papers were published on statistical methodology for making adaptive changes based on the interim looks, without inflating the type one error. These papers made it clear that this was a good opportunity for East. Hence, we started putting these methods into East, and the word Promising Zone was coined by my colleague, Stuart Pocock. We wrote a paper on sample size re-estimation, and we called it the Promising Zone Method. We proposed that the best way to implement sample size re-estimation was to partition the interim data into zones. So, if the interim data were excellent, you need not make any change in the sample size. Also, if the interim data were quite bad, you need not make any change in the sample size. In the first case, you could stop early for efficacy or just continue unchanged. In the second case, you might stop early for futility or continue unchanged.

There would be a sweet spot in the middle where it might be advantageous to increase the sample size, because having seen the interim data, it may appear that you could increase power. In this case, it would be called conditional power, that is, conditional on what you would have already seen. So, there would be a good opportunity to increase the sample size and boost the conditional power back to the desired 90% that the sponsor would be interested in. The Promising Zone was defined as the zone in which we could boost the conditional power. Outside of this zone, it would not boost the power high enough, be too expensive, or the conditional power might already be super high, and it would not be necessary to increase the sample size.

## Some people don't realize that there are still innovations being added to the promising zone and to sample size re-estimation methods in general, and that these will create ripples across the industry. Would you be able to highlight some of what we will see in the next few years?

There has been a lot of research parallel to Adaptive Designs, on testing of multiple end points, or multiple treatment arms. It has been observed that in a clinical trial, you will gain a lot of efficiency if you ask more than one question about what is it that you want to discover about the new treatment, relative to the standard of care. At the same time, preserving the integrity of the family-wise error rate, which is the equivalent in multiple testing of the type one error in a two-arm simple trial. This methodology has been developed, but what is needed now is to combine this methodology with the interim analysis.

Group sequential and adaptive methods focus on taking interim looks at the data and using them to make modifications. Multiple testing has been developed for no interim analysis, it allows single look at the data and asking multiple questions at the end of the study, such as, which of many sub-groups is doing better, or if you know that the treatment is already good for overall survival, is it also good for progression free survival? Or the other way around. Does the presence or absence of a genetic mutation make a difference to the patient's response compared to the population at large? A number of such multiple questions can be asked. If you combine this opportunity with the interim analysis, you can refine the

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questions and focus the sample size only on those questions that look interesting from the interim analysis point of view. Hence, the promise is that you combine the methods of adaptive design with the available statistical research that has already emerged on multiple testing, but for which there has been no interim analysis.

### How do you think software and statistical strategy will shape clinical trials in the next few years?

There is already a huge community building open-source software, but that software, which is useful for research and to explore new ideas, is probably not ready for regulatory submissions. For regulatory submissions, one needs software that has been vetted and seen to be valid from a regulatory perspective. That is where we have been very successful with East. We are moving forward with our latest software at Cytel called Solara, which makes it possible to efficiently, intuitively, and quickly explore all the different multiple testing and group sequential options that are available under different scenarios of treatment effects, enrollment rates, and other unknown co-variants.

With Solara, you can have a possible design space of thousands of trials and use technology to explore all of them very quickly and find the ones that are worth pursuing further. This is an example of how software can combine with statistical methodology. We are developing many different statistical methods that give us lots of options for design parameters, and we are developing software that allows you to quickly generate all these different statistical models, and then explore them quickly with a nice visualization. In the end, you can have the best possible design for any given situation.

### In the past few years, you have occasionally argued that private sector companies, even smaller biotechs, could evolve to make use of the advantages of multi-arm and platform trials. How would this work and how would Cytel help?

At present, I think they need a neutral party to set up the infrastructure for a platform trial. If it is a pharmaceutical company that sets up the platform, then they will only be testing their own drugs on it, and it will not be a collaboration with different industry partners. An academic center can probably be the neutral partner. A good model is the STAMPEDE Trial where the Medical Research Council in England had set up the infrastructure. In this trial different molecules from different companies were tested over a twenty-year period for prostate cancer.

Many successful drugs were discovered in this manner as it did not require going through the Phase II and Phase III set-

tings. You can have many patients right up front, and you can test the new molecules with large sample sizes against the standard control arm. These molecules did not have to be tested in sequence. Instead, you could test several at a time against a common control arm. The winners would be taken off the trial, and then be available to the patients, and new molecules could take their place.

When we attended the ASCO meetings every year, we would find that very often there would be a new discovery from the STAMPEDE Trial, and it would be announced at ASCO. The reason this works is because there are plenty of new molecules coming out from small biotech companies and large pharmaceutical companies. Hence, when you have a plethora of molecules, you can test them simultaneously against standard of care, rather than testing sequentially. These are exciting new molecules and there is no shortage of physicians who want to put their patients on these trials. Consequently, there is no difficulty in recruiting patients and finding new molecules. In fact, in the Medical Research Council, they have very strict criteria for which new molecules they will accept for testing because they get requests from several companies.

## Within therapeutic areas, Cytel's greatest contributions have arguably been in oncology and cardiovascular. How have these areas developed in the past 35 years and how has Cytel contributed?

Cardiovascular trials have advanced in a very specific way. The clinicians who work in the cardiovascular area have become more sophisticated about statistical methods. They love partnering and working with statisticians. They also understand the data really well, and I would say, much more than the oncologists. They have used group sequential methods a lot and have no difficulties with it. But they have not looked at biomarkers yet and are now looking to start designing trials where they can look at biomarkers and reduce the size of their trials. Typically, their trials have been quite large because they have been so successful with their treatments.
There is a group called the Heart Failure Collaboratory, which is a public-private partnership between statisticians and cardiologists. They meet once a year, and they are now starting to look at more sophisticated problems. Typically, they have been looking at time-to-event trials and the standard has always been to make the assumption that the hazard ratio of the treatment to the control arm is constant. They have discovered in recent trials that this assumption does not always hold, and are starting to look at new methods, in partnership with experts on these questions. How will you analyze these data if the proportional hazard assumption is not valid? I think there is a good opportunity here for Cytel to work one step earlier. How will you design trials where you do not know whether the proportional hazards assumption will hold or not? If you can design such trials, where the design is so good that if the proportional hazard assumption holds, you have the right sample size, and if it does not hold, you still have the right sample size, that will be a holy grail. Some of us have been working on that question.

In Oncology, they have moved further ahead than cardiology, in terms of looking at biomarkers. They recognized long ago that large oncology trials are not successful. The population is too heterogeneous, so they are looking at starting with smaller subgroups and trying to develop methods where the molecule is targeted at specific biomarkers only. Here, there are opportunities for adaptive designs, which we have been involved with, but only with the smaller biotech companies. Large pharmaceutical companies are generally more cautious about using new methods.

## As it is a 35-year anniversary celebration, where do you think the industry will be in 2050 (about 35 years from now)?

That is a very difficult question. Technology advances at an exponential pace. This acceleration is something that my friend, Ray Kurzweil, has been demonstrating over the years with specific examples from different fields. If you look at how we have moved, for instance, from doing computations on a slide rule to 50 years later doing computations in the Cloud, then the kind of computing power that will be available in 30 or 50 years from now is unimaginable. How the biopharmaceutical industry will exploit this power is another question.

My guess is that they will be able to use predictive models very successfully. But again, this will be combined with medical advances, which are also accelerating. The new therapies are developed much more rapidly now. Hence, it is very hard to predict what will happen 50 years from now.

## Are there any words of wisdom you would like to share with young people in the field now?

I think young people should follow their passion and pursue their interests in research, and not think of it as just a job. If they're interested in something and find it promising, even if it is not fashionable, then they should pursue it and not worry about whether it is going to be popular. They should believe in it themselves and follow their instinct.

Cytel

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## About Cytel

For over thirty years, Cytel has enabled the world's biotech and pharmaceutical companies to make confident, evidence-based decisions to ensure successful outcomes. As industry leaders in delivering advanced data analytics solutions, we continually invest in deepening our expertise.

Powered by the unique experience and expertise of our researchers and consultants around the world, we conceptualize and execute HEOR and RWE studies, using advanced quantitative techniques to prepare sponsors for regulatory submission and to support their product's clinical and economic value proposition.

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