



LABORATORY FOR  
FINANCIAL ENGINEERING



Event Summary — April 11-12, 2023

# New Approaches to Accelerating Biomedical Innovation

*Case Study on Appendiceal Cancer*

# Welcome Dinner: Fireside Chat

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**Christopher Austin**, Vesalius Therapeutics  
**Greg Simon**, Simonovation, LLC

## OVERVIEW

Developing treatments and cures for rare diseases such as appendiceal cancer has been hard and slow. Rare diseases receive less attention and research funding than more common diseases. But change is possible, there are examples of success, and rare diseases are receiving increasing attention and funding, resulting in increased FDA approvals for drugs to treat rare diseases.

Keys to success include leadership of a passionate, business-savvy patient; formation of an engaged, motivated, diverse team that develops and executes a research plan; and identification of specific milestones. Patient and team engagement is necessary to secure funding and for advocacy.

## CONTEXT

Greg Simon, who started FasterCures, ran the initial Cancer Moonshot for then-Vice President Biden and subsequently led the Biden Cancer Initiative, and Christopher Austin, who is currently CEO of Vesalius Therapeutics and CEO-partner at Flagship Pioneering, and was previously director at the NIH's National Center for Advancing Translational Sciences (NCATS) and director of the NIH Center for Translational Therapeutics, shared their thoughts on the keys to accelerating treatments and cures for appendiceal cancer and other rare diseases.

## KEY TAKEAWAYS

**Those involved in rare disease research are attracted to the human side of research.**

The question was raised, “Why do people get involved in rare disease research, when there are so many other things they can do?”

Dr. Austin answered that researchers are attracted to the human side of medical research—rare disease research is very personal, and the stories of patients are very compelling. These aren't stories about statistics or healthcare costs; they're human stories. “I have found that the community of rare disease researchers and patients and scientists and doctors are a real special breed,” Dr. Austin said.

**The pace of play in rare disease research is improving but is still too slow.**

Prior to the late 1990s and early 2000s, very few researchers and very few companies worked on rare diseases; almost everyone worked on common diseases. With anywhere from 7,000 to 10,000 or even 13,000 rare diseases—and with about two rare diseases per year going from untreatable to treatable—it would be approximately 2,000 years before there's a treatment for every rare disease.

This focus on what's more common has also occurred in cancer, where institutions such as the NIH, the NCI, and others have mainly focused on those disorders that numerically cause the most suffering and death. While there are 3,000 to 4,000 rare cancers, said Dr. Austin, research funding has traditionally focused on a few major cancers, including prostate, lung, colon, and breast.

However, the situation is changing. Over the last 20 years, the focus on rare diseases has increased. As a result, Dr. Austin said that over the past five years, the majority of new FDA approvals are for rare diseases or orphan drugs.

**Catalyzing change requires a team and must include patients.**

There are now many stakeholders focused on specific rare diseases, including rare cancers. Stakeholders include government agencies, researchers, biotech and pharma companies, investors, disease-focused nonprofits, and more. An important concept is that every research team should include patients with the disease. Patients bring deep knowledge of their disease and know what aspects of the disease are most relevant to them. Patients bring urgency and focus, and patients are resourceful and can help bring funding—they can be considered one of the major disruptive technologies in rare disease research.

**Siloed rare disease communities can benefit by coming together and focusing on commonalities.**

Often, the community focused on a particular disease views their disease and their situation as a special case. “Each of those 10,000 rare diseases view themselves as a snowflake,” Dr. Austin said. Each disease community essentially works independently to try to

secure funding from the government and from various institutions. But each disease community acting alone “just turns into white noise; they just don’t even hear it,” Dr. Austin observed.

He said that rare diseases and rare disease communities have more in common than they realize. Organizations can benefit from aligning and collaborating for funding purposes and for science purposes. Examples of common interests include policies about sharing data, conducting adaptive clinical trials, and getting more patients involved in trials.

### **It’s possible to pursue a model for developing treatments for appendiceal cancer outside of traditional institutions.**

Mr. Simon observed that petitioning the government to allocate funding to a particular rare disease is “the slow way to get it done.” Key questions include how to make progress more quickly, and how do we self-organize to accelerate development of treatments for appendiceal cancer.

Dr. Austin said, “It’s been done before,” and suggested, “Look at examples where it’s worked.” The critical ingredients for success in accelerating progress to develop treatments for a rare disease include:

- **A passionate leader.** The most effective leader is a patient who’s well organized, passionate, and business savvy. A business orientation is important because businesspeople are good at identifying what’s most critical and focus on deliverables. They’re persistent and undeterred.
- **A motivated team.** A passionate leader can’t do it alone. Progress requires a diverse and committed team with the right expertise and motivation. The work of this team is to develop a research plan that identifies who will do what, with specific time frames. Effective teams are aligned, with everyone pulling in the same direction, driven by helping patients.
- **Milestones to get to a product.** It was noted that scientists and researchers can, at times, become distracted, due to scientific curiosity. But developing treatments requires an obsessive entrepreneurial focus on milestones, driven by a goal of getting to a product.

### **This meeting can serve as a starting point for initiating meaningful progress on appendiceal cancer.**

Mr. Simon reflected that when he started the Melanoma Research Alliance, it seemed that nothing in the space was working. So, he brought together a group, similar to this meeting focused on appendiceal cancer. The melanoma group worked together to fundamentally change how funding was allocated in the melanoma world so that about one third of funding would go to new researchers; one third would go to inter-institutional collaborations; and one third went to the old guard. Within a few years, enormous change and progress occurred.

In previous roles, such as at the Cancer Moonshot, Mr. Simon was frequently asked, “What can you really get done in just a few months?” The answer is “not much.” But the more appropriate question is: What can we start in just a few months, or even a few weeks? The same logic applies to appendiceal cancer: What can be started right now that will make an enormous difference in the life expectancy of the people with this disease? Let this gathering be a call to action to collaborate and start activities that will make a profound difference.

# Welcome, Introductions, and Background

**Andrew W. Lo**, Laboratory for Financial Engineering, MIT  
**Steven Wallman**, Former Commissioner, SEC

## OVERVIEW

Despite amazing scientific breakthroughs, too few scientific discoveries are translated into treatments that get to patients. A key reason is that investors withhold funding due to too much perceived risk and uncertainty. Solutions to this problem lie in continuing to develop scientific breakthroughs with high returns while developing financial structures and business models that can reduce financial risks. These structures and models require multi-stakeholder collaboration, must be centered around patients, and must be pursued with urgency, to save lives.

## CONTEXT

Professor Andrew W. Lo described challenges to developing and getting new treatments to patients, and expressed optimism that stakeholders collaborating on new business models and financing structures can reduce risks. Steve Wallman described his wife's unexpected diagnosis of appendiceal cancer and called for urgency and collaboration in addressing this and other rare cancers and diseases.

## KEY TAKEAWAYS

**Almost everyone has been personally touched by cancer and is motivated to cure cancer.**

Previously, Professor Lo had little knowledge of or connection to cancer, healthcare, or the biopharma industry. He was an outsider to this world, as it wasn't relevant to him as a finance professor at MIT's Sloan School. But that changed when several relatives and friends died of cancer within a few years.

Like so many other people, this unexpected personal connection led him to learn more about cancer, the biotech world, and the healthcare system. He's since worked to make a difference by bringing together key stakeholders to change the system, beginning with a gathering called CanceRx in 2013.

Mr. Wallman, a lawyer, finance expert, entrepreneur, and former commissioner of the US Securities and Exchange Commission, also had no personal connection to cancer or healthcare. That is until his wife, Kathy—who

seemed completely healthy—was diagnosed with stage 4 appendiceal cancer following a routine physical exam. This has motivated Mr. Wallman to act with urgency in asking questions, seeking answers, and bringing together key stakeholders to work in collaboration in pursuit of treatments and a cure for this deadly disease.

## KATHY WALLMAN'S JOURNEY

Joining via a video that was recorded prior to the workshop, Kathy Wallman recounted her personal journey and offered thanks to all who have helped her along the way as well as to those attending the workshop for their participation.

While feeling completely healthy and fit, a routine ultrasound during a normal physical exam revealed the presence of appendiceal



cancer. After four surgeries, about thirty rounds of chemotherapy, and one recurrence, Kathy described the disease as “sneaky,” noting that “it’s hard to track, it’s hard to measure progress.” Further confounding the situation is that the appendix is considered a vestigial organ, but even after having her appendix removed, Kathy said “it left a mess, and it’s been the task of the last several years to try to clean up that mess.”

She expressed hope in this age of breakthrough research, and encouraged participants to collaborate and share information about what has and hasn't worked, highlighting that it's important not to leave false trails for other researchers.

**Development of cancer treatments is limited by “the valley of death.”**

In exploring what was preventing great science from getting to patients, Professor Lo kept hearing about “the valley of death.” This valley occurs between basic science and phase 1 clinical trials, where it's extremely difficult to get funding for translational medicine.

The reason for this valley of death is high levels of risk and uncertainty, making it hard to raise money for early-stage ideas.

## The key to addressing the valley of death is improving the Sharpe ratio.

To think about how to address the valley of death, it's important to understand what investors want. Ultimately, investors want high-yield, low-risk assets. The returns and risks of an investment are measured by the Sharpe ratio; it's essentially the ratio of the expected return of an investment per unit of risk.

$$\text{Sharpe Ratio} = \frac{\text{Reward} \uparrow}{\text{Risk} \downarrow}$$

Over the last several years, biomedicine has actually had a declining Sharpe ratio.

- In the aggregate, the **returns have been good** from biomedicine investments; that's not the issue.
- But the problem is that despite good aggregate returns, any individual biotech investment is **enormously risky**—and these risks have been going up.

The key to improving the Sharpe ratio is quite simple: either increase the numerator (the returns) or decrease the denominator (the risks).

## There's optimism that it's possible to make progress in developing treatments for appendiceal cancer.

Through previous efforts spearheaded by the MIT Laboratory for Financial Engineering, progress has already been made in treating cancer. A number of papers have been published, several companies have been started, and an adaptive platform trial has been launched focused on ovarian cancer.

Professor Lo believes it's possible to create a multi-center adaptive platform trial for appendiceal cancer, financed by the private sector, that will be the right thing for patients and will be profitable for investors.

In addition to serving as a catalyst for an adaptive platform trial, goals for this meeting focused on appendiceal cancer included:

- Breaking down barriers and bridging cultural differences between science, regulatory, and finance.
- Developing sustainable models for dealing with rare cancers and going from rare to common.
- Focusing at all times on the patients.
- Acting with urgency.
- Using the meeting as a springboard and continuing structured, focused, collaborative efforts after the meeting concludes.

# State of the Union in Appendiceal Cancer

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## Facilitator:

**Jane Wilkinson**, Koch Institute for Integrative Cancer Research at MIT

## Panelists:

**Andrew Blakely**, National Cancer Institute

**Andreana Holowatyj**, Vanderbilt University

**David Ryan**, Massachusetts General Hospital

**John Paul Shen**, MD Anderson

**Konstantinos Votanopoulos**, Wake Forest

**Michael Yaffe**, MIT

## OVERVIEW

While appendiceal cancer is extremely rare, and there are only 10 clinical trials underway, there's already a great deal of scientific knowledge about appendiceal cancer: what it is, what it's not (it's not colon cancer), which treatments show promise and which don't work, and many areas where further research activity is needed. The panelists concur that appendiceal cancer is multiple diseases, with different symptoms, prognoses, and treatments. They see a host of opportunities for research in areas such as genetics, personalized medicine, organoids, biomarkers, and much more.

## CONTEXT

Each of the panelists provided a short presentation about their work and how they're thinking about appendiceal cancer, and then answered questions from meeting attendees.

### Background: Appendiceal cancer is extremely rare.

In setting the stage, Jane Wilkinson, Executive Director of the Koch Institute for Integrative Cancer Research at MIT, provided a few pieces of information about appendiceal cancer.

- It's believed to affect 1 or 2 people per million every year.
- However, recent data shows it's becoming more common.
- It can occur at any age but is becoming more common among people ages 50 to 55.

- There are currently only 10 open trials for appendiceal cancer.
- Patients are often frustrated when appendiceal cancer is lumped in with other cancers such as ovarian and colon.

## KEY TAKEAWAYS (BLAKELY)

Andrew Blakely discussed appendiceal cancer initiatives at the NIH. The NIH is trying to fill the translational research space by working on *ex vivo* tumor modeling in a way that preserves the tumor microenvironment. The aim is to harvest tumor cells—and everything that comes along with them; this captures the environment and provides an opportunity for interrogation that's translatable to the patient.

Based on this research, NIH has developed the Sustainable Microenvironment Analysis of Resected Tissues (SMART) System. SMART is uniquely tailored to study small tumor nodules up to 2.5 mm in diameter. SMART enables harvesting tissues and keeping tissue alive over time, with viability of at least four days; the reason for four days is that this provides adequate time to see if a therapeutic agent produces a response. This platform also enables performing live imaging to see what's happening with tumor cells and immune cells. It's also possible to sustain live imaging for up to eight hours to see the movement of cells within the tissue. This system also makes it possible to stimulate the tumor infiltrating lymphocytes.

Because there can be heterogeneity in a single patient's tumor, it's possible that some of the tumor will respond to a treatment and some of the tumor won't. SMART enables exploring these different responses and adding a sequential treatment to target cells that are resistant to treatment.

Ultimately, the NIH sees the SMART system as filling a certain niche.

- It's an ideal preclinical model to more completely assess drug effects.
- It's an opportunity to assess specific personalized treatments for specific patients with appendiceal malignancies.



- It provides an opportunity to collaborate with outside groups to prioritize new agents.
- It enables granularly assessing the effect of tumor heterogeneity to guide treatment combination and sequencing.

## KEY TAKEAWAYS (HOLOWATYJ)

Andreana Holowatyj summarized what her lab at Vanderbilt University Medical Center is working on and resources the lab is developing for appendiceal cancer. Dr. Holowatyj's lab bridges discoveries from cells to society, has several open clinical studies across different areas, and also runs a wet lab.

Historically, it's been thought that appendiceal cancer isn't hereditary. This thought was so common that several leading healthcare organizations put this claim on their patient-facing websites. However, when Dr. Holowatyj's lab discovered that 1 in 3 appendiceal cancer patients is diagnosed before age 50, it raised alarms for Dr. Holowatyj about an inherited cancer predisposition of early onset disease. This led to gathering data to explore this question.

The result was that Dr. Holowatyj's lab discovered the first genetic link to appendiceal cancer and found that 1 out of 10 patients harbors a deleterious variant in a cancer susceptibility gene. (And this finding was based on studying only 14 genes with a known susceptibility to various gastrointestinal cancers.)

This was a groundbreaking finding that led her lab to recommend consideration of genetic testing for all patients diagnosed with appendix cancers. It also led to wondering whether appendiceal cancer may be an underrecognized indication for hereditary cancer genetic testing and hereditary cancer syndrome.

To learn more about the role of genetics in appendiceal cancer, Dr. Holowatyj's lab has opened the Genetics of Appendix Cancer (GAP) study. This is a nationwide study, enrolling anyone over the age of 18 who has been diagnosed with appendix cancer. The study involves undergoing an extensive family history, participating in several surveys, providing a saliva sample, and asking parents to participate as well.

## KEY TAKEAWAYS (RYAN)

David Ryan, from Massachusetts General Hospital, provided an overview of appendiceal cancer from a clinical perspective and what it's like to take care of patients with appendiceal cancer.

There are different types of cancers that arise in the appendix:

- **Neuroendocrine cancers.** This type of cancer is the most common type of appendiceal cancer, but is usually not a problem.
- **Goblet cell adenocarcinoma.** This is a strange tumor with both carcinoid and adenocarcinoma.
- **Adenocarcinoma of the appendix.** This exists along a continuum. There's low-grade adenocarcinoma, which creates a great deal of mucin in the belly, and high-grade tumors.

With low-grade tumors, surgery can make a difference and appendix surgeons also favor hyperthermic intraperitoneal chemotherapy (HIPEC), although most medical oncologists don't recommend HIPEC and there's a lack of data about it. The amount of mucin in the belly is absolutely miserable and there needs to be a treatment developed.

For high-grade tumors, when you look at the molecular profiling, the higher-grade disease looks very similar to colon cancer. It's known from research that HIPEC has limited efficacy and absolutely no impact on overall survival. Dr. Ryan said, "You can tell that from my perspective, I've moved on from HIPEC for high-grade disease. I am, however, a huge believer in surgery . . . because about 15% of people are actually cured."

It's also important to realize that 5% to 10% of every solid tumor has a germline mutation. Because of the importance of germline, Dr. Ryan is trying to implement universal germline testing at MGH Cancer Center. "You walk in the door with cancer, you get germline testing. I'm actually at the point where I think everybody should get germline testing."

## KEY TAKEAWAYS (SHEN)

John Paul Shen discussed his work on appendiceal cancer at MD Anderson. He noted that low-grade appendiceal cancer is a different disease than high-grade tumors, and high-grade tumors don't generally evolve from low-grade tumors.

Similar to Dr. Ryan's remarks, Dr. Shen said, "Right now, the only really proven treatment for appendiceal cancer is surgery." However, the national clinical practice guidelines still suggest that all grades of appendiceal cancer should be treated with chemotherapy, as if it were colon cancer. But research conducted at MD Anderson found that the chemotherapy used for colorectal cancer (5FU-based chemotherapy) is ineffective in low-grade appendiceal cancer.

Since MD Anderson sees a large number of patients with appendiceal cancer, "It's not a rare disease to us," said Dr. Shen. MD Anderson sees almost 300 new patients per year, including about 40 with goblet cell tumors. Because most patients aren't surgical candidates, the chemotherapy for colon cancer doesn't work well for appendiceal cancer, and there are few clinical trials, Dr. Shen's team created a list of challenges to address to improve outcomes for patients. These challenges include:

- Lack of preclinical models
- Lack of suitable drug targets
- Lack of biomarkers to guide therapy
- Extreme patient-to-patient heterogeneity
- Difficult to measure with CT/MRI imaging
- Difficult to run prospective clinical trials
- Treatment isn't standardized
- Lack of novel therapeutics

Specific areas on which Dr. Shen's team is focusing include conducting clinical trials and looking at improving the staging system, which doesn't adequately risk-stratify patients, especially patients with goblet cell tumors.

## KEY TAKEAWAYS (VOTANOPOULOS)

Konstantinos Votanopoulos summarized how the Wake Forest Organoid Research Center (WFORCE) is using organoid technology to tackle the problem of appendiceal cancer. Organoids can be used to create chemosensitivity data to show the survival or death of a tumor that's treated with different drugs, indicating which drug is best for a particular patient.

However, with a disease like appendiceal cancer, patients don't have one tumor, patients have hundreds of tumors and every tumor is different. When you analyze these tumors, you see that they've evolved genetically and are different.

Because of the heterogeneity of tumors within a patient, Dr. Votanopoulos noted that to cure cancer—any cancer, not just appendiceal cancer—you need to know the following information to approach clonality:

- Number of clones within the patient
- Relative volume of clone volumetrics with the patient
- Virulence of each clone
- Clone specificity to drugs

Today, this information isn't available and it's unclear if the technology exists to tackle this problem. But what can read clonality is our own immune system; not always, but quite often under the right conditions. This may happen with tumor infiltrating lymphocytes (TILs), where the immune system infiltrates the tumor with T cells. While a company is trying to commercialize this, Dr. Votanopoulos doesn't believe it will succeed in appendiceal cancer because appendiceal cancer often attracts a small number of TILs.

An idea for a solution would be a platform that creates TILs on demand for any person, any tumor, and under any condition. Dr. Votanopoulos calls this solution OILs (organoid infiltrating lymphocytes). OILs and TILs induce similar apoptosis pathway protein markets in tumor cells.

The OILs idea presents a way to tackle clonality. Dr. Votanopoulos' plan—including several steps that have already occurred—is to establish a surgical specimen pipeline, generate 700 tumor specimens into organoids, secure funding from NCI and from philanthropy, start a company, build a GMP facility, and build a CLIA lab. Then, proceed to a phase 1 clinical trial.



## KEY TAKEAWAYS (YAFFE)

Michael Yaffe is the director of the MIT Center for Precision Cancer Medicine. His lab is focused on improving the treatment of appendiceal cancer through better multi-modality approaches. He offered four main points:

1. **Current combination treatments for appendiceal cancer are NOT synergistic; in fact, they're not even additive.** They work, but they most likely work not because of the effect of the drugs in some synergistic way but because of targeting patient or tumor heterogeneity. The lack of effective tumor biomarkers means many patients are being subjected to adverse side effects without clear benefit.
2. **Many effective drugs in colorectal/appendiceal cancer don't work by the mechanisms that the textbooks tell us.** They work by targeting ribosomes, RNA, and translation and ribosomes. This is going to open up a relatively unexplored therapeutic space.
3. **The timing of drug co-administration matters.** In general, in treating cancer patients, "We pay no attention whatsoever to the order in which we administer things. In my center, the order in which we administer drugs is determined by what the pharmacist decides to send us first." Also, if it were possible to identify a biomarker for patient selection for appendiceal cancer, and if it were known what the driver was, it would then be possible to know which drug to give.
4. **DNA-damaging drugs can be used to induce tumor immunogenicity and markedly enhance the response to immunotherapy.** This can be effective, but it's not easy to do.

# Novel Pathways, Current Roadblocks, and Lessons Learned from Other Diseases

## Facilitator:

**Jane Wilkinson**, Koch Institute for Integrative Cancer Research at MIT

## Panelists:

**Nicole Aguirre**, Memorial Sloan Kettering Cancer Center

**Kerry Benenato**, 76Bio

**Keith Flaherty**, Massachusetts General Hospital

**Christopher Hughes**, Aracari Biosciences

**Sheeno Thyparambil**, mProbe

**Omer Yilmaz**, MIT

## OVERVIEW

While over several decades, clinicians have tried to perfect surgical approaches to the management of peritoneal carcinomatosis, panelists representing different labs and companies shared a host of novel approaches they're pursuing as alternatives to surgery that are intended to yield more personalized treatments and better outcomes.

These approaches include organoid development, targeted proteomics, pretargeted radioimmunotherapy, mRNA, vascularized micro-organs (VMOs) that can be used to test combinations of drugs, identifying biomarkers for chemotherapy and other targeted therapies—and much more.

Other themes from this session include the idea that treating patients with appendiceal cancer shouldn't be a cookie-cutter approach; treatment must be customized to each patient. Also, to boost clinical trial enrollment for this rare cancer and to boost research requires collective action based on the formation of an active community.

## CONTEXT

Each panelist provided a short presentation about novel pathways they're pursuing and how these pathways may apply to appendiceal cancer. The panelists then answered questions from attendees. This session also featured one of a few short videos from patients with appendiceal cancer and family members, sharing comments from their experiences.

## PATIENT PERSPECTIVE

The sister of a patient (Katherine) diagnosed with appendiceal cancer in 2018 shared her family's experience with this deadly disease. Katherine thought she had routine appendicitis, but found out she had appendiceal cancer, which was unexpected and confusing. An oncologist offered a standard treatment, with a "cookbook recipe" for how to treat colorectal cancer. After digging deep into the research, Katherine had a whole genetic workup and ended up receiving a targeted therapy specific for her genetic mutation. This helped extend the length and quality of her life. Katherine died in early 2023.

Her sister's biggest takeaway was, *"This should not be a cookbook. With appendiceal cancer, you can't treat it like run-of-the-mill colon cancer. It's not. It's different. Standard treatment for colon cancer doesn't work. There needs to be more research."*

## KEY TAKEAWAYS (AGUIRRE)

Nicole Aguirre, a surgical research fellow at Memorial Sloan Kettering Cancer Center, described studying pretargeted radioimmunotherapy (PRIT) and a novel two-step method target using self-assembling and disassembling antibody (SADA).

The PRIT method is a delivery system in which an antibody specific for tumor surface antigens is used, followed by radioisotopes for imaging or therapy. Bispecific antibody (BsAb) is an established technology in which one arm binds to an antigen and the other binds onto a radioisotope. The goal is to give tumoricidal doses of radiation to a tumor with very little radioactivity given to background organs, such as the kidneys.

Traditionally, this was done in a single step, but it was catastrophic for the rest of the body. So, it was broken into a multi-step process. Historically, it required a third step, involving a clearing agent to wash unbound antibody and decrease toxicity. A team at Memorial Sloan Kettering has discovered an antibody (SADA) to do this in two steps.

SADA-BsAb self-assembles into stable tetramers (220 kDa) and at low concentrations disassembles into dimers (110 kDa) or monomers (55 kDa) that rapidly clear via renal filtration and substantially reduce immunogenicity in mice.

To apply this novel two-step method to appendiceal cancer requires establishing a tumor bank and some patient models, which is underway in collaboration with other labs that are developing organoids and patient-derived xenographs (PDX models). Once appendiceal cell lines are developed, it's necessary to confirm antigen targets on these cell lines. This will involve screening for GPA33, B7H3, and HER2—all of which have existing SADA antibodies. The Memorial Sloan Kettering team will then begin an imaging experiment to establish a model and dosimetry, and will use a large therapy study to treat the tumor model. Memorial Sloan Kettering has a group of appendiceal adenocarcinoma slides available and has some of them for antigen targets; these are all viable targets for appendiceal cancer.

A project already underway focuses on Glycoprotein A33 (GPA33), which is highly expressed in 95% of colorectal cancers and some other human cancers. In an experiment, SADA was coupled with Actinium-225 proteus; as an alpha particle, it has a very short range of action and does little damage to surrounding organs.

An experiment using mice compared a three-step PRIT treatment plan and a two-step SADA-PRIT treatment plan. This experiment, which is ongoing, looks at efficacy and toxicity of the different treatment plans at different points in time. Conclusions include: two-cycle correlates with improved tumor response; there are no clinical toxicities by weight or appearance; and there's no hematological evidence of myelotoxicity or renal toxicity, but pathology results are pending.

## KEY TAKEAWAYS (BENENATO)

Kerry Benenato described the concept being worked on by 76Bio, a small biotech focused on developing a new platform for targeted protein degradation. Previously, Dr. Benenato worked at Moderna, where she was introduced to mRNA as a therapy and worked on problems of delivery, scalability, and repeatability.

After years of innovation, mRNA as a therapeutic modality has been demonstrated on a global scale. It's safe and effective. It's clear that mRNA-based therapies are poised to address unmet medical need as mRNA offers the opportunity to access targets not feasible with standard biologics.

In particular, mRNA has potential to treat those patient populations that have no other options and to provide a path for treating the previously undruggable. This includes options for patients with rare diseases.

76Bio is harnessing the power of mRNA to develop a novel class of targeted protein degraders. Among 76Bio's work is a validated screening platform that has produced a lead series against multiple historically challenging oncology targets. The company plans to continue to innovate on delivery technology to expand its indications, with the belief that its platform can be powerful.

## KEY TAKEAWAYS (FLAHERTY)

Keith Flaherty, a medical oncologist at Massachusetts General Hospital, relayed experiences building communities focused on uveal and ocular melanoma. While melanoma isn't a rare disease, uveal and ocular melanoma are rare. For many years, they were viewed as too rare for researchers or companies to focus on and were largely seen as undruggable. This didn't change until patient advocates took the lead in forming a community focused on these rare melanomas.

Another lesson from Dr. Flaherty's previous experience was the power of the NCI-MATCH clinical trial, which started in 2015. That was a platform trial and the demand for enrolling patients was outrageous, with 6,000 patients accrued in record time. The trial simultaneously investigated dozens of therapies in phase 2 and patients were enrolled across numerous centers. This included big academic medical centers, smaller academic medical centers, and community-based sites. Half of all accruals came from community-based sites.

It turned out, a massive percentage of patients with rare tumors were accrued to this trial. There are already many trials for common cancers but few trials for patients with rare tumors, leading to a big influx of patients with rare tumors.

Dr. Flaherty also focused on the problem of having too few therapeutic insights. He suggested focusing on functional diagnostics, especially *ex vivo* functional diagnostics where it's possible to, for instance, investigate monotherapies as well as combinations of available therapies (the discovery platform doesn't necessarily have to be drugs, though) and *in vivo* functional diagnostics.

For clinical research in rare tumors, Dr. Flaherty also suggested throwing the kitchen sink at molecular characterization, which means continuing to do DNA

sequencing and also doing RNA sequencing; leapfrogging one-drug-at-a-time investigation; and capturing data to learn from every patient. He called for individual therapies offered to patients under single-patient INDs.

## KEY TAKEAWAYS (HUGHES)

Christopher Hughes, chief scientific officer of Aracari Biosciences, described microphysiological systems, which are complex models of tissues the company’s developing that may have some application for appendiceal cancer.

Dr. Hughes commented that there are well-known problems with clinical testing. Among the problems are that monolayers and monocultures aren’t representative of *in vivo* conditions, since tumor cells growing in a plastic dish don’t model the environment of a tumor cell in a human body. Also, “mice lie to us all the time,” he said. It’s not that hard to cure cancer in mice but it’s hard to translate that to the clinic, since mouse physiology is very different from human physiology.

A piece of good news is that in the FDA Modernization Act of 2021, applicants for market approval for a new drug may use methods other than animal testing to establish the drug’s safety and effectiveness. Alternative methods may include cell-based assays, organ chips and microphysiological systems, and other options.

What Aracari does is develop vascularized micro-organs (VMOs). This involves creating a living vascular network with arteries and veins, and then being able to build tissue, including tumors. This concept is important because all organs are vascularized, vessels help pattern tissues, most cells are within 100 microns of a blood vessel, and all nutrients and drugs are delivered through the vasculature.

Dr. Hughes explained that multiple tumor types grow in vascularized micro-tumors (VMTs) and said, “We’ve yet to find a tumor that won’t grow in this platform.”

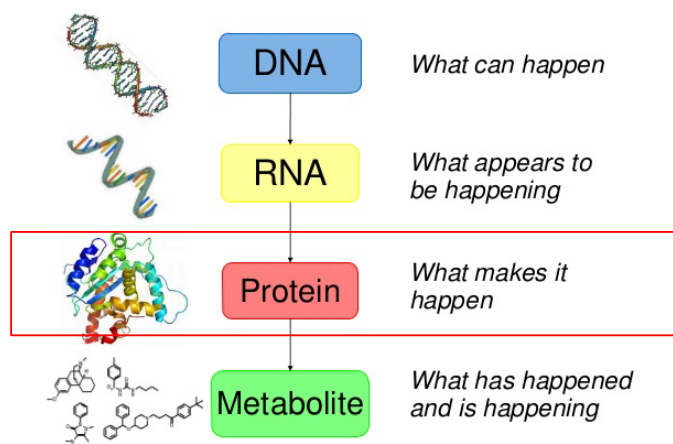
The value of this concept is then testing drug responses in VMTs. Research has shown that drug responses differ in three-dimensional VMTs compared to a two-dimensional monolayer. “You can miss really interesting drugs if you’re just putting tumor cells in a plastic dish,” Dr. Hughes said. He added, “We’ve done lots of different drugs with lots of different tumors.” This includes looking at drugs for colon cancer and triple-negative breast cancer.

Now, Aracari is interested in using a similar model and process to look at appendiceal cancer. The requirements include tissue (which could be provided through collaboration with a committed surgeon), a good platform (which Aracari has), and a plan. The general plan is to look at different combinations of drugs. “The idea would be to test FDA-approved drugs, de-risked drugs, find what combinations work, and then hopefully physicians could run with that.” Aracari is looking to do this with colorectal, breast, and prostate cancer, and would love to also include appendiceal.

## KEY TAKEAWAYS (THYPARAMBIL)

Sheeno Thyparambil, senior director (R&D) at mProbe, spoke about clinical proteomics and the work of mProbe. mProbe is a CLIA-certified lab that does clinical proteomics and provides information to an oncologist who uses this information to make decisions about therapy. In contrast to other organizations that look at RNA and DNA, mProbe looks at protein, as most drug targets focus on a protein.

Figure 1: mProbe’s focus within the central dogma of biology



Source: Pierre-Edouard Sottas, *The Biological Passport in 4P-Medicine*, e-health 6.6.14. <https://www.slideshare.net/thearkvalais/13-pierre-edouard-sottas-the-biological-passport-in-4-pmedicine-ehealth-6614>.

When an oncologist puts in an order, mProbe works with the pathologist team to get the tissue block in house. Sections are cut on mProbe's slides, called DIRECTOR slides. After a high-resolution scan, the pathologist then marks the tumor areas. mProbe then uses a laser to micro-dissect the tumor area and puts what's extracted into a mass spectrometer. In a clinical setting, this means looking at 72 known biomarkers. This leads to a simple clinical report that goes back to the oncologist.

The clinical report indicates agents that are likely to work and agents that are less likely to work. This report informs on chemotherapy options, targeted therapy, and immunotherapy.

Informing about chemotherapy is extremely important, since chemotherapy dominates therapeutic regimens. A 2018 report found that almost 79% of presenting patients with cancer were eligible for chemotherapy, yet the same report found that only 31% responded to chemotherapy and 69% didn't respond to chemotherapy.

Based on the importance of biomarkers, mProbe is running biomarkers in its lab. Dr. Thyparambil divided these biomarker assays into chemotherapy agents and targeted therapy agents.

## KEY TAKEAWAYS (YILMAZ)

Omer Yilmaz of the Koch Institute for Integrative Cancer Research at MIT described his lab's work, which has focused on developing models to study colon cancer progression. This includes modeling the different kinds of tumors and the ways in which colon and appendiceal cancer spread throughout the body.

One way in which his lab studies cancer is by using organoids. This involves taking biopsies from mice and from humans and growing normal organoids. Then, in the laboratory setting, researchers take the organoids and turn off or on genes associated with the cancer being studied.

One approach used in his lab is to leverage mouse colonoscopies to transplant organoids and implant them into the wall of the mouse's colon. These organoids will give rise to a primary tumor. The opportunity provided by this approach is to try to discover new therapeutic targets.

An example of research taking place is an experiment where the *SOX17* gene is turned off and transplanted into the colon of recipient mice. When this occurs, less than 10% of the recipient mice form tumors compared to almost 80% who form tumors if *SOX17* isn't turned off. "We think that *SOX17* plays an important role in regulating how the colon cancer cells regulate tumor progression," Dr. Yilmaz said. "We think it does this by regulating how these colon cancer cells interact with their immune microenvironment." He said that his lab is interested in testing *SOX17* with other tumors, and appendiceal cancer would be a great model to test.

In summary, leveraging this colonoscopy-based approach to cancer organoid transplantation allows rapidly modeling predicted cancer-associated genes and studying how a tumor interacts with immune cells and targeted therapies.

# Oncology Discovery in 2023: Evolution or Revolution

**David Weinstock**, Vice President of Discovery Oncology, Merck

*NOTE: The views and opinions expressed are Dr. Weinstock's only, and do not represent the views and opinions of any institution or agency or any of their affiliates or employees.*

## OVERVIEW

Investing to develop new therapies to treat and cure patients is extremely important. But drug development is hard, risky, and slow—and there are enormous challenges in the oncology space. By being aware of these challenges and the difficulty and complexity of developing new cancer drugs, researchers and companies can avoid mistakes, increase their chances of success, and improve the use of their current and future investments.

## CONTEXT

David Weinstock discussed the evolution in his thinking, having been an academic at Dana-Farber Cancer Institute for 14 years and now being in industry at a big pharma company. (All of the opinions he expressed were his own and did not represent any opinions from Merck or any other institution or agency, or their affiliates or employees.)

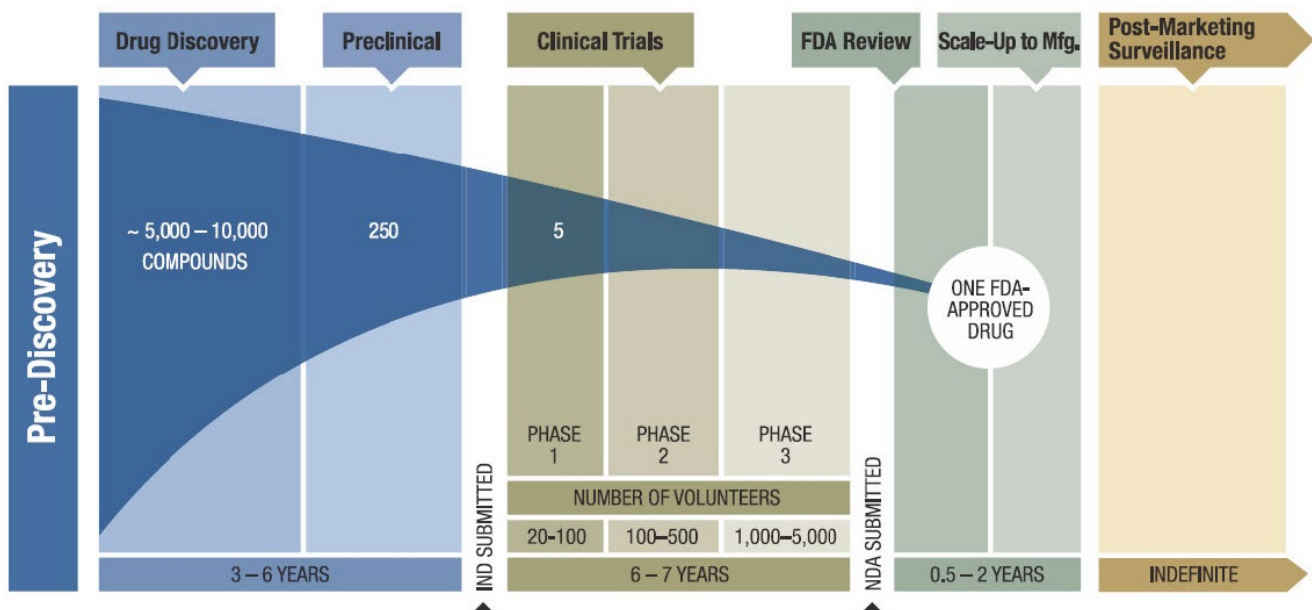
## KEY TAKEAWAYS

**Drug development is very hard, very risky, and very slow.**

As shown in the figure below, the process of drug development is very hard and very risky. The pre-discovery phase starts with looking at thousands of different compounds, followed by moving forward with hundreds of compounds into preclinical studies. Eventually, a few compounds will proceed into phase 1 clinical trials, then phase 2, and phase 3. If all goes well, this will yield one FDA-approved drug. This process will likely take more than 10 years and could require billions of dollars.

One premise is that to get more approved treatments for appendiceal cancer, it's necessary to put more money and effort into the beginning of this process to fund more research, ultimately yielding more drugs. This of course assumes maintaining the same probability of success for any individual project as the current probability of success, which isn't necessarily an accurate assumption.

Figure 1: Drug development is very risky





## Amid tremendous successes, oncology discovery faces multiple enormous challenges.

In describing how hard it is to bring a new drug to market, Dr. Weinstock recognized tremendous successes in the field of oncology discovery but laid out six huge challenges.

1. **Predicting the future.** Wayne Gretzky famously said to skate where the puck is going to be, not where it's been. But predicting the future is very, very hard, because developing a drug means trying to predict the competitive landscape, the regulatory landscape, and the reimbursement landscape in 7 to 10 years.

In one example that Dr. Weinstock shared from his time at Dana-Farber, he was involved in an extensive effort to find a treatment for Burkitt lymphoma, which tends to cause massive lymphomas in the jaw that were previously 100% fatal. After identifying a potential treatment, going through a saga to get access to the drug, completing studies among mice, and designing a clinical trial to test this treatment, the trial had finally begun. Among the first few patients in the trial, a few had very positive responses. Then, as treatment was about to begin on the fifth patient, CAR T cells became the standard of care. This was unexpected and couldn't have been anticipated. The study was cancelled because the landscape had suddenly changed—the therapy they were proposing to give would have prevented patients from being able to get CAR T cells because it was so immunosuppressive.

2. **Bucking the trends.** Keytruda is an absolutely amazing therapy that's curative for several types of cancer and for many patients. "It is unbelievable. It is a true revolution. Why does this happen? We have no idea," Dr. Weinstock said. And, when combined with chemotherapy for some cancers, it produces even better outcomes. It's now approved for over 30 different cancers and is an approximately \$25 billion per year drug that's changed the treatment of cancer and rewritten textbooks.

So, as a result of Keytruda's success, a common refrain in the biotech and pharma world has been, "We should make another immune checkpoint inhibitor," with the hope of finding the next Keytruda. The industry has behaved as lemmings, said Dr.

Weinstock, which has cost hundreds of billions of dollars, and it hasn't worked out. At this point, "We've got to have an enormous amount of skepticism," he said. Still, in 2020, two-thirds of active trials in cancer were T cell modulators.

Another trend that merits skepticism is the idea of "synergy." This comes up frequently as researchers repeatedly claim, "Our drug is synergistic." However, analysis has shown that synergy is a preclinical phenomenon, and, in reality, there's no synergy, and the term shouldn't be used anymore. This doesn't mean that combinations aren't a good idea—they are—but there are patients who benefit from combinations without achieving synergy.

3. **Expecting to fail and then learn from it.** On the wall in Merck's Cambridge office is the quote, "It's a missed opportunity if we fail to learn from what doesn't work." This is obviously correct, but just expecting to fail and then learn is too simplistic.

For example, there are situations when a patient has mechanisms of resistance to a therapy. Dr. Weinstock said he's skeptical of strategies that are going to overcome resistance to a particular therapy, because the processes are almost always extremely complex. Expecting to fail and learning from it when it involves overcoming resistance isn't worthwhile.

Similarly, creating data that isn't very robust and then chalking it up as a learning experience isn't very worthwhile, but often occurs.

Dr. Weinstock quoted statistician George Box, who said, "All models are wrong, but some are useful." Box said, "Since all models are wrong, the scientist must be alert to what is importantly wrong."

We need better models to make better drugs; models are tools for asking questions.

4. **Focusing on both efficacy and toxicity.**

Dr. Weinstock commented that as an academic, he was focused on efficacy—does it make the tumor smaller, and could it possibly cure people? However, as an extreme example, there are substances, like bleach, that can kill cancer cells in a dish spectacularly well. But if you give these toxic substances to a human being, they'll also kill the person.

Now, working in industry, Dr. Weinstock noted that he's learned that the therapeutic index may be the most important tool in all of drug development. The therapeutic index is the difference between what you can get in terms of efficacy and what you get from toxicity. What's important is the difference between the effect on cancers and the effect on the rest of the human.

There are grades of toxicity standards, shown below.

Grade 5 is death, Grade 4 is life-threatening consequences, and Grade 3 is severe or medically significant consequences. At these grades, the toxicity is obviously too high. But even Grade 2, deemed "moderate," means a person is sick up to the point of having to go to the hospital. If a person received a Grade 2 treatment for 12 months, that's not really tolerable. That leaves only Grade 1, termed "mild." Dr. Weinstock described Grade 1 as, "You might be able to work, but you might not." So, "We actually need drugs that have Grade 1 toxicities" he said, maybe some Grade 2 but Grade 3 aren't going to fly.

- Defining what "best-in-class" means.** Within the industry, there will be a successful drug on the market that's doing well for patients and making money, and researchers will believe, "Ours is better, we can supplant it." Sometimes that's true, but often it's not.

But, coming up with a "better" version of a drug isn't so simple, since "better" includes multiple factors including the potency and the toxicity. As an example, Dr. Weinstock described a drug that did exactly what it was supposed to do, but in the wrong cells—meaning that ultimately the drug wasn't better than the existing drug on the market.

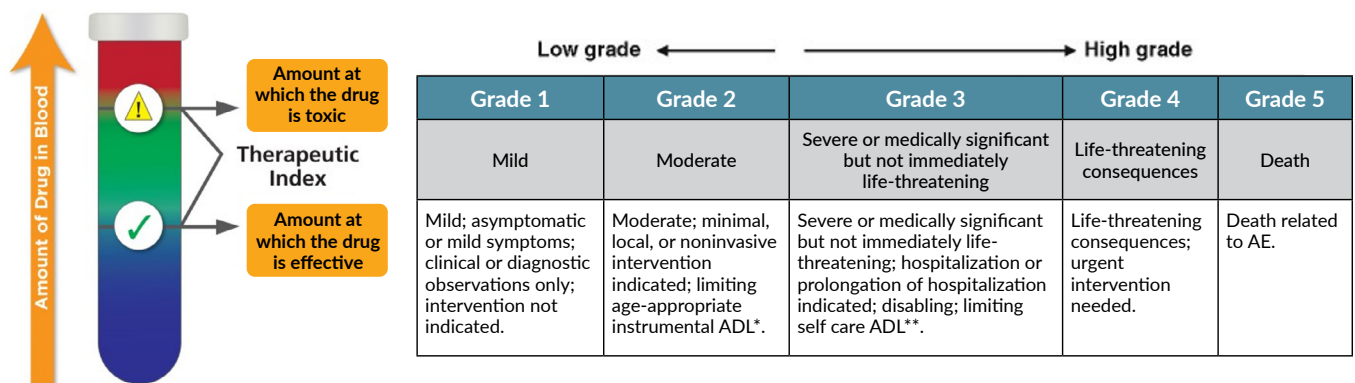
- Overcoming the technology trap.** It's cool to see new technologies and think about how they can transform things. But even the most amazing, most transformative technologies come with enormous challenges. There's field-wide cynicism. There are challenges getting reimbursement for novel therapies. There are challenges in the standard of care in competitive offerings.

Individually and in combination, these challenges illustrate the difficulty and complexity of bringing a new treatment to market, even a treatment that leverages an amazing technology and shows enormous promise. Most ideas have fatal flaws and ferreting out the good ideas is really hard.

However, figuring out the best use for current and future investments is extremely important and can pay massive dividends, in benefitting patients and producing attractive returns.

A prime example is for endometrial cancer, where there have been no advances. Just recently a new study was published showing that chemotherapy plus Keytruda was a significant advance compared to the current standard of care. Even though Keytruda has been around for a decade, new applications are continuing to emerge. This shows the potential to extend the uses of existing therapies while also investing in developing new ones.

Figure 2: Therapeutic index and grades of toxicity standards



# Regulatory Pathways, Government Policy, and Related Considerations for Rare Diseases and Beyond

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## Facilitator:

**Greg Simon**, Simonovation, LLC

## Panelists:

**Christopher Austin**, Vesalius Therapeutics

**Belen Carrillo-Rivas**, Imvax

**Collin Hovinga**, Critical Path Institute

**Philip Katz**, Hogan Lovells US LLP

**Andrew von Eschenbach**, Samaritan Health Initiatives

**Clarence Young**, ProPharma Group

## OVERVIEW

Researchers and companies often view regulators as an adversarial barrier to be overcome. But regulators have a necessary role in protecting the public health. By understanding regulators' context, frameworks, data needs, and mindset, sponsors can build trusted relationships and increase the speed of the regulatory process. In many instances, the earlier and more proactively that sponsors engage with regulators, the better. Regulators often want to engage constructively with industry in helping sponsors have successful programs and approvals. To expedite the approval process, the FDA has established priority review and accelerated approval pathways, which are pathways often used for oncology drugs.

Another concept for accelerating regulatory approval is platform trials, which reuse an existing trial infrastructure and can improve the ability to reach and enroll more patients, faster.

## CONTEXT

The panelists discussed current regulatory processes, shared best practices, and offered suggestions for accelerating regulatory approval.

## PATIENT PERSPECTIVE

In a short video, Marianne Yerkes shared her story and offered her perspective to the appendiceal cancer community. Ms. Yerkes' cancer journey began in August 2021. At the time, she was working for the US Agency for International Development (USAID) in Honduras. Ms. Yerkes had no personal or family history of cancer.

She began to worry that she might have appendiceal cancer but was rebuffed by a doctor at the US embassy. She was then told by another doctor that she didn't have cancer but would need a hysterectomy. Finally, a radiologist confirmed a malignancy but said it was likely ovarian cancer. She ended up having the wrong operation for the wrong cancer. At no point did any doctor suspect or test for appendiceal cancer. Finally, a biopsy taken during the surgery for the suspected ovarian cancer indicated appendiceal cancer. This ultimately led Ms. Yerkes to an appendix cancer specialist who deemed her cancer inoperable. At this moment, Ms. Yerkes has stage 4 adenocarcinoma of the appendix, goblet cell pathology.

Since finally getting an accurate diagnosis, not everything has been doom and gloom. Ms. Yerkes has woven a larger care network, explored multiple options, and recently enrolled in an NIH trial.

She commented that patients are desperate to stay alive longer and are eager to enroll in trials. In her role at USAID, she was deeply engaged in collaboration and co-creation—bringing people together to consider creative new options and solutions to complex problems. She knows that this approach works and is needed in rapidly developing treatments for appendiceal cancer.

## SESSION FRAMING

In opening the session, Greg Simon offered four observations.

1. **Those in the cancer ecosystem need to overcome existing biases.** People have biases in how they think and act, such as confirmation bias. These biases are limiting and are holding us back.
2. **It's necessary to rethink scarcity versus surplus.** Patients are the scarce resource and researchers are the surplus resource. This imbalance needs to be corrected by involving patients on research teams. The patients must be in charge.
3. **The paradigm needs to shift to focus on prevention.** Today, fighting cancer consists of chasing shotgun pellets after they've left the gun. The emphasis needs to shift to prevention and catching cancer at stage 0 and stage 1, when it's possible to get rid of it. However, today there's no funding or reimbursement in early detection.
4. **Dealing with rare diseases requires artificial intelligence (AI).** The amount of data in the cancer and rare disease ecosystem is beyond human comprehension. The only way to deal with 7,000+ rare diseases is by changing everything to utilize AI and machine learning.

## KEY TAKEAWAYS

**To make progress on appendiceal cancer and other rare diseases, it's necessary to change the culture and operational structure of the biomedical community.**

The starting point, said Christopher Austin, is grounding the industry in a moral argument that the current state of diseases such as appendiceal cancer and the approach to treating and curing these diseases is unacceptable. "People who are sick need us all who blessedly are not sick today to act differently," Dr. Austin said.

At the operational level, this means creating different structures, mechanisms, and incentives to create new treatments far faster—such as three to five years instead of 10 to 15. There must be changes to incentivize data sharing, as opposed to withholding data. There also must be changes to the culture, which celebrates the myth of the lone researcher in contrast to the collaborative team.

"This is a team sport," said Dr. Austin, "but the unfortunate reality is that the environment we live in was set up to play scientific golf."

Andrew von Eschenbach agrees that the system was designed to create golfers, each pursuing their own individual goal. But, he said, "The game has changed from golf to basketball." What matters now is integration and interoperability—Dr. von Eschenbach sees the need for both in the research agenda, in the regulatory framework, and in the delivery concept.

As part of the change that's needed in medicine, Dr. von Eschenbach sees more opportunity for looking at disease mechanisms horizontally, across diseases. He mentioned, for example, that multiple cancers—prostate, lung, appendiceal, and more—have neuroendocrine tumors. As a result, there may be biological processes in common.

**There are best practices to working more effectively with regulators and improving the speed of the regulatory process.**

Philip Katz, a lawyer who represents clients in matters with the FDA, said the most common mistake he sees is assuming that the FDA is an immovable adversary. He tries to help his clients understand that the people at the FDA are very smart, very informed, and trying to protect, preserve, and promote the public health. But their charge is different from the goals of a company. A result is that there's often a lack of trust between the FDA and companies; companies are distrustful of the FDA and the FDA is skeptical about drug companies.

Mr. Katz advises clients to understand where the regulators are coming from, what's motivating them, and what frameworks they're using. He suggests that clients present information to the FDA within the context of the FDA's framework. FDA operates within a legal system that requires them to approach each decision with science at the forefront, but they're also thinking about what they're allowed to do, e.g., whether something will get them in trouble or create a loophole. Regarding the latter, there's a constantly swinging pendulum. At some points, the FDA is seen as being too tough on industry and not letting drugs come to market that might be helpful to patients. So, the FDA starts to loosen up, and is then accused of being too easy, in the pocket of industry, and granting approvals of drugs that aren't very effective. The pendulum is constantly swinging, so you have to be aware of the dynamics.

Within this context, there are actions that can be taken to expedite the regulatory process. Belen Carrillo-Rivas, senior vice president and head of regulatory affairs at Imvax after working for more than a decade at Pfizer, described the importance of understanding the regulatory environment, understanding what the regulators care about, and taking advantage of opportunities for constructive engagement. She recommends being proactive in engaging with the FDA.

It's Ms. Carrillo-Rivas' perspective that the regulatory community wants to work closely with industry to develop unbiased guidance and wants to provide sponsors with what's needed to have successful programs and approvals. She believes that building trust is possible and sees it happening.

Clarence Young of ProPharma Group mentioned different avenues available to companies to work with the FDA to expedite drug approval, based on the specific situation.

- **Priority Review.** Typically, the FDA takes about 10 months to complete its review. But if a sponsor qualifies for Priority Review, it reduces the clock to six months, which can be substantial.
- **Accelerated Approval Program.** Originally devised in the 1990s, this pathway allows drug approval based on intermediate clinical endpoints that are viewed as reasonably predictive of the expectation that a product would go on to demonstrate clinical efficacy. Often, in oncology, these accelerated approvals are based on single-arm studies in patients with refractory disease. The idea is that if a tumor response is demonstrated in these patients, that information might be sufficient to support accelerated approval. The caveat is that the sponsor is still responsible for generating clinical data that ultimately supports the clinical benefit of the drug.

Over the last few years, a review has been undertaken of all accelerated approval decisions from the last decade or so; about 85% of these approvals are for oncology drugs. In the review, in about 50% of approvals, clinical benefit was ultimately demonstrated. In a handful of cases, products were withdrawn from the market. One finding was that when confirmatory clinical studies were underway at the time of an approval decision, it took about 3.5 years for the data to become available about whether a drug delivered a clinical benefit. If studies weren't underway at the time of submission, it took 7 years for the data to be collected showing if there was a clinical benefit.

As a result, the FDA is now strongly recommending that sponsors seeking accelerated approval have studies underway at the time of their application. This will limit the amount of time patients have uncertainty about whether a product is beneficial or not.

Ms. Belen Carrillo-Rivas added that in recent years there has been congressional interest in the Accelerated Approval pathway, which has led to greater discussions about potential reforms, including increasing FDA authority to withdraw approval if the confirmatory studies don't show effectiveness or endpoints aren't met.

Dr. von Eschenbach offered a suggestion that can help accelerate the approval process. He suggested restructuring the agency by dividing it into program staff and review staff.

- **Program staff** engage in conversations with sponsors at the earliest part of the submission to facilitate, align, and expedite.
- **Review staff** is firewalled from program staff and serves the sole process of reviewing, based on the science.

In Dr. von Eschenbach's view, this fits with the FDA's mission of promoting and protecting the public health. "Promoting" is in the hands of program staff and "protecting" is in the hands of review staff. This would make the submission, review, and approval process faster, more efficient, and less expensive.

## **Collaboration through industry consortia and platform trials can accelerate approvals and decrease costs.**

One of the reasons for the slow, expensive process of bringing a new drug to market is the clinical trial process. Every trial requires standing up infrastructure, identifying sites, conducting training, and education—all of which take substantial investments of time and resources. Once a trial is completed, everything is torn down.

Collin Hovinga from Critical Path Institute said that platform trials have numerous benefits. In addition to reusing infrastructure, which saves time and money, a platform trial makes it easier to access and enroll patients and to test multiple drug therapies.

In commenting on the lack of trust and adversarial relationships between sponsors and regulators, Mr. Hovinga mentioned situations where multiple sponsors collaborate in a non-competitive space. Such situations can involve participation from regulators, who are often comfortable engaging in discussions, since discussions aren't product specific. These interactions can focus on common questions and building out shared infrastructure. This is another example where collaboration can benefit sponsors and patients, while creating greater alignment and better relationships with regulators.



# Potential New Business and Legal Structures, and New Sources of Capital, to Fund Biomedical Innovation

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## Facilitator:

**Andrew W. Lo**, Laboratory for Financial Engineering, MIT

## Panelists:

**Jennifer Levin Carter**, Sandbox Industries

**Stephen Curtis**, BrightEdge/American Cancer Society

**Marshall Summar**, Uncommon Cures

**Thomas Trimarchi**, BridgeBio

**Fernando Vieira**, ALS Therapy Development Institute

## OVERVIEW

A rare disease only affects a limited number of patients, but in aggregate, rare diseases actually affect large numbers of patients. As a result, focusing on rare diseases, especially rare cancers, has become more common for researchers, pharma companies, and investors.

In focusing on rare diseases, there are approaches and business models that are successful in taking science from the lab and translating it into products provided to patients in the clinic, while producing good returns for investors. These lessons can be applied to appendiceal cancer, with a starting point of forming a community; sharing data, knowledge, experiences, and best practices; identifying what works and where gaps exist; and collaborating on a research plan and an innovative adaptive clinical trial design.

## CONTEXT

The panelists shared their perspectives on rare diseases and innovative business models to fund research and innovation. Participants then asked questions and shared comments.

## KEY TAKEAWAYS

### **Rare diseases, including rare cancers, aren't that rare.**

The definition of rare disease differs by country. The FDA defines a rare disease as a disease that affects fewer than 200,000 people in the country, which is about 1 case per 1,600 people. Approximately 5% to 8% of the US population is affected by a rare disease.

By some estimates, there are more than 10,000 rare diseases and over the last several years about six new rare diseases have been identified each week. More colloquially, a disease could be considered rare if it's uncommon enough that a general practitioner wouldn't be expected to be familiar with it or how to treat it.

In some cases, rare diseases have become chronic diseases, primarily as a result of collaborating on standards of care and new therapeutic development through information sharing. Examples include Down syndrome, cystic fibrosis, and sickle cell anemia.

In terms of cancer, the RARECARE Cancer Coalition defines a rare cancer as fewer than 6 cases per 100,000 people per year, which is the definition adopted by the American Cancer Society. To date, nearly 200 different types of rare cancer have been identified and more than 100 of those are considered "very rare" with fewer than 0.5 cases per 100,000 people per year. In the US, 1 in 5 cancer patients are diagnosed with a rare cancer.

Jennifer Levin Carter went a step further. "We're not defining rare cancer the right way, because actually, all cancers are rare," she said. As an example, in 2008, one type of cancer was non-small cell lung cancer. Today, there are at least 15 to 20 subtypes of non-small cell lung cancer.

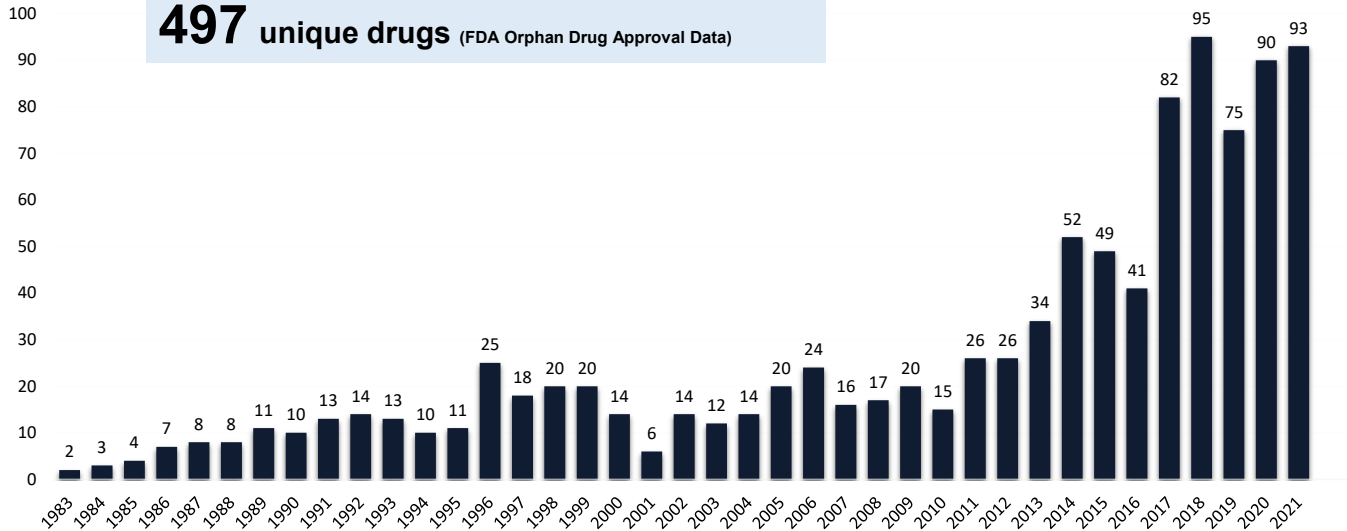
### **There's a growing number of therapies for rare diseases.**

There's a huge number of therapeutic approaches being taken including gene therapy, small molecule, enzyme replacement, and many more. As a result, since 1983 there have been more than 1,000 drug approvals for orphan drugs, including about 500 unique drugs. Over the past five years there have been about 100 drug approvals per year and in the past five years, more than 50% of all drug approvals have been for rare or orphan diseases. About half of those are for cancer. As an example, of the 15 to 20 subtypes of non-small cell lung cancer, there are now drugs on the market that target almost every one. The progress has been similar for breast cancer.

Figure 1: FDA Orphan Drug Approvals by Year



**1,078** Orphan Drug approvals since 1983  
**497** unique drugs (FDA Orphan Drug Approval Data)



One reason that industry has been interested in developing drugs for rare diseases is the higher probability of success. These successes come despite the fact that rare disease clinical trials have typically enrolled about half as many patients and taken twice as much time, and the cumulative cost of developing a rare disease drug exceeds \$500 million.

**One major challenge in developing new therapies: reimbursement.**

Dr. Carter hailed the tremendous scientific progress being made in areas such as DNA technologies, RNA, and proteomics. But she said a major issue is paying for treatments. “One of the biggest barriers is reimbursement,” she said. This was a driver for the creation of Sandbox Industries, which is the managing partner of the venture capital fund for the Blue Cross Blue Shield plans. The intent of this fund is to look at how to get payers, providers, and industry to collaborate to drive adoption of innovative technologies while also working on issues of reimbursement.

**Learnings about potential business models for appendiceal cancer can be gleaned from other diseases.**

Lessons can be learned about investment models in other diseases that may be applied to appendiceal cancer.

**BridgeBio**

BridgeBio was formed to address the valley of death, the space between academic and medical research labs and company-sponsored R&D pipelines where many potentially transformative innovations die. Among the issues are that early-stage science has the lowest probability of success and the longest time to market, and requires the most money. When looking at early science focused on rare diseases, the risk is even greater because the market size is small. This makes for a challenging investment case for any individual treatment for a rare disease.

The idea behind BridgeBio is to apply the financial principle of diversification by creating a portfolio. While each individual investment may be risky, by creating a portfolio the risk is reduced and an investor can realize a favorable return. Research indicates that the necessary portfolio size is about 20 to provide the necessary diversification. What makes this strategy effective is that the investments are almost completely uncorrelated, which is very different from most financial assets.

The uniqueness of this strategy has attracted different forms of capital, including raising about \$1 billion in equity and \$2 billion in debt.

BridgeBio’s strategy has focused on addressing each of the major issues with the valley of death: probability of success, cost, and timelines. To increase probability

of success, BridgeBio focuses exclusively on genetic diseases where you can quantitatively connect the dots from the genetic defect to patient symptomology and for which they believe they can target the genetic source directly or immediately proximal to that. To decrease costs and accelerate timelines, BridgeBio centralizes some horizontal R&D activities (such as chemists), but most activities are decentralized, with nimble, agile teams and minimal overhead. Essentially, every project is a small, focused, dedicated team that is its own company. This approach has resulted in great efficiency in BridgeBio's pipeline. In the last seven years the company has gotten 15 molecules into the clinic at a cost of about \$10 million or less. Furthermore, BridgeBio has two approved products for which they've licensed the commercial rights, and, by the end of 2023, they expect to have four ongoing phase 3 trials and others close behind.

In the context of appendiceal cancer, the recent discovery of a genetic link (see the session 1 summary), opens up many more opportunities, but it's not strictly necessary in order to employ a model like BridgeBio's. As Mr. Trimarchi noted, there are many promising targets for rare diseases sitting on the shelves of academic research labs that haven't been pursued—because those researchers are outside of well-known biotech hubs like Cambridge and San Francisco, or because the disease being targeted is either actually too small for traditional biotech investors to care or *perceived* as too small for them to care.

### ALS Therapy Development Institute (ALS TDI)

This is a unique organization in that it's a nonprofit biotech. ALS TDI has the mission of a nonprofit, is focused specifically on ALS, and has deep roots in the ALS patient community, with patients informing the research focus.

As a biotech, ALS TDI is product oriented, with a focus on inventing and advancing drugs to get treatments to patients with ALS as quickly as possible. Funding comes mainly from grassroots philanthropy, which essentially provides ALS TDI a new Series A round of financing each year. This funding is used for discovery and to build institutional knowledge.

Over the past 20 years, ALS TDI has raised about \$150 million, which has contributed to advancing two drugs to Phase 2 trials, with two other promising programs in preclinical development. ALS TDI has its own lab with

30 scientists working full-time on ALS drug discovery.

Dr. Vieira said that ALS TDI considers the following when deciding where to invest: Do we know a lot about this target space? Where can we have impact on the most people? Where is nobody else working? In the ALS space, for-profit investors are primarily only interested in investing in a therapeutic if there are Mendelian genetics that tie directly to it. As a result, ALS TDI invests some of their efforts in the Mendelian genetics space, but is more focused on areas where less is known (e.g., sporadic ALS) and where they, as a nonprofit, can make strides to de-risk assets to the point where for-profit investors might find them attractive.

### Participant Discussion

Following brief presentations by each panelist, attendees engaged in a robust Q&A period, asking questions and offering comments.

- **New IP or repurpose?** A question was asked about whether it's a better to invest to find new indications for existing therapies or to develop new compounds. There's no definitive answer. A few panelists stressed having a therapy that's "shelf ready" or ready to be "handed off to a company." This is often a new therapy, but not necessarily.

Dr. Curtis said that a new target with clear IP opportunities is typically seen as the cleanest path to a commercial opportunity. However, if there's a repurposing opportunity, there are a lot of stumbling blocks potentially in the way to enable it, but it could provide a faster road to having impact for patients.

- **Rare diseases have a unique financial characteristic that makes them particularly attractive for investment.**<sup>1</sup> Because rare diseases are typically so different and the therapeutic interventions to treat them often are as well, the correlation between rare disease programs tends to be lower—that is, the success or failure of one rare disease program has nothing to do with the success or failure of another rare disease program. If we consider a portfolio of such programs, this uncorrelated property allows for greater diversification and can reduce the overall risk if you have enough 'shots on goal.' BridgeBio's business model capitalizes on this aspect of rare diseases.

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1 See Fagnan, D. E., N. N. Yang, J. C. McKew, and A. W. Lo, 2015, Financing Translation: Analysis of the NCATS Rare-Diseases Portfolio, *Science Translational Medicine* 7 (276), 276ps3.

- **Forming a community, and taking an inventory of knowledge and best practices.** A question was raised about how to structure a collaborative community and finance that to assist patients with appendiceal cancer right now. When a community gets organized, participants first need to share their information, experiences, and best practices to develop a broader set of best practices, which also serves the purpose of developing the next generation of key questions. In other diseases, this has been an important first step in, ultimately, significantly boosting survival rates in a relatively short period of time.

As part of forming a community, one participant suggested quickly taking an inventory of what's known, what data exists and is accessible, what works, what trials are underway, what gaps exist, and more. As one participant stated, "Until we know what is actually there, what's available, we can't really move forward . . . once we know what the problem and the scope are, then we can talk about innovative funding models."
- **Innovative clinical trial design.** Several participants stressed the importance of pursuing innovative trial designs, which provide access to patients who are often excluded because they're sick. (Trials were discussed in more detail in the wrap-up session.)
- **Don't forget diagnostics.** Funding for molecular diagnostics is much less than funding for new drugs, but diagnostics are extremely important. The good news is that an increasing number of companies are looking into early detection. Also, Professor Lo pointed out that while diagnostics may have lower profitability, they also have lower risk. He sees potential for a business model focused on a portfolio of diagnostics that have a particular theme.
- **Stay optimistic and persistent.** Len Lichtenfeld, formerly of the American Cancer Society and now chief medical officer at Jasper Health, noted that for many years the same drugs were used to treat melanoma and breast cancer. As recently as 2009, there was a tremendous amount of negativity in the field. But with new drugs and treatments such as immunotherapy, "The changes we've made in the last 10 years have been remarkable," he said. He's optimistic that the same success can be experienced in appendiceal cancer. The key, he said is, "knocking heads together." It's getting the right people in the room and having a passionate patient advocate say "enough."
- **Constant iteration.** One participant proposed creating clear clinical practice guidelines for appendiceal cancer. Then, while treating patients, conducting clinical trials and collecting evidence, constantly iterating the guidelines. A panelist commented, "That's not novel; that's how you should do it in the rare disease community."

# Wrap-Up, Next Steps, and Closing Remarks

**Andrew W. Lo**, Laboratory for Financial Engineering, MIT

## OVERVIEW

The challenge is now turning the ideas and energy from this gathering into meaningful progress for patients with appendiceal cancer. The best way to do that is through economic incentives where everyone receives payment for their contributions, though the currency for this payment will differ based on each person and organization's incentives.

Professor Lo put forth a specific proposal to form a consortium or a holding company that protects each person/organization's IP, and then to initiate a multi-center adaptive platform trial for appendiceal and other rare cancers. He's optimistic that investors will have interest in investing in this platform trial and in the portfolio of products/companies participating in this trial. This concept benefits and pays everyone in that researchers are likely to secure funding for their ideas, companies can conduct a faster, lower-cost trial and have exposure to investors, investors will have access to a portfolio of promising treatments—and most importantly, patients such as Kathy Wallman will be able to participate

in clinical trials of innovative therapeutics that have the chance to have a meaningful impact on their life.

## CONTEXT

In wrapping up this meeting, the conversation shifted to urgent, tangible actions to rapidly accelerate bringing treatments to patients like Kathy Wallman and others with appendiceal and other rare cancers.

## KEY TAKEAWAYS

**It's necessary to get a bunch of busy, talented, competitive people to collaborate—which requires aligned incentives.**

This gathering brought together an amazing collection of smart, talented, creative, committed individuals and organizations. Professor Lo raised the question of how is it possible to get such a group to collaborate? He shared an example of the 2009 DARPA Network Challenge, a collaboration success story that featured financial engineering (see box).

### 2009 DARPA NETWORK CHALLENGE

In 2009, to celebrate its 40<sup>th</sup> anniversary, DARPA (the Defense Advanced Research Projects Agency) orchestrated an innovation challenge.

The challenge was that DARPA was going to locate 10 large red weather balloons in random locations across the United States, and the first individual or team to identify the locations of these 10 balloons would win \$40,000.



DARPA announced this challenge ahead of time to give people and teams time to prepare. Hundreds of teams registered. A team from MIT led by Sandy Pentland won, identifying the location of the balloons in 8 hours, 52 minutes, and 41 seconds. (Note: this was in 2009, prior to the widespread use of social media.)

The key to the MIT team's success was the financial incentives they put in place. The MIT team announced that they wanted people's help and would compensate them for their assistance. The team's plan was to give away all of the prize money, dedicating \$4,000 per balloon.

The payment model was:

- If a person was the first to email the MIT team with the location of a balloon, the individual would receive \$2,000 (provided that the MIT team won).
- If a person told a friend about the location of a balloon and the friend was the first to email the MIT team with the location, the person who spotted the balloon would receive \$2,000 and the friend who emailed would receive \$1,000.
- If a person told a friend who told a friend, the person who found the balloon would receive \$2,000, their friend would receive \$1,000, and that friend's friend would receive \$500. And on and on.

As a result of this incentive structure, 10,000 people participated in the MIT team's hunt for these balloons.

The ultimate lesson: **the way you get people to help is to ensure that everyone gets paid.**

The reason Professor Lo gave this example is that the lesson learned applies to appendiceal cancer. The way to get busy people to focus on a topic is: **Pay them. It's a matter of incentives.**

While the need for payment is essential, the particular currency may differ for each person. For example, patient advocates care about new therapies; academics are motivated by publications, peer recognition, and funding; philanthropists are motivated by having impact; politicians care about support from constituents; and the currency for corporations is profit.

In the case of appendiceal cancer, Professor Lo commented that the easiest challenge may be to get money; the hardest part is to organize the talent and figure out what the currencies and business models are.

### Next steps: a proposal for action

Professor Lo outlined a proposed set of next steps:

- **An online survey** that allows each person to express their interest in participating in an ongoing group focused on accelerating treatments for appendiceal cancer. As part of this survey, each respondent can submit a simple description of how they're interested in contributing.
- **Consortium creation.** A new business model will be developed in the form of a consortium or a holding company. Before a person or entity participates in this consortium, it's essential to make sure that all IP is properly protected. A next step will involve contacting the tech transfer offices at the institutions of all who want to participate to make sure it's possible to participate.

- **Adaptive platform trial.** The ideas that are generated will lead to a multi-center adaptive platform trial for appendiceal and other rare cancers. This trial will be able to test multiple therapies at the same time with appendiceal cancer patients. Professor Lo is optimistic that for-profit investors will be willing to fund this innovative platform trial in exchange for some level of ownership of the portfolio in the trial.
- **Ensuring everyone gets paid.** There should be the ability for each participant and contributor to receive payment based on what currency is most relevant to them. That could be research dollars or royalties, financial returns, social impact, research papers, and getting new drugs to patients.
- **Concept organization.** Bringing this all together will take leadership to organize and oversee it. Professor Lo will work with Steven Wallman to determine leadership, likely a small group of individuals.

There seemed to be an enthusiastic reaction to this concept. Participants offered comments such as:

- This should work.
- This is a great idea . . . and coming into this I was a little skeptical of what would come out of it.
- The FDA will like this idea and will want to help.
- Many issues are likely to emerge once design of the trial begins.
- Measurement of response is critical, as is incorporating biomarkers.



## THE FINAL SAY FROM KATHY WALLMAN

Following the original video that Kathy recorded to welcome workshop participants, she underwent a second cytoreduction surgery. To close the workshop, Kathy recorded a second video from the hospital, just days after her surgery. She provided a brief update on her status, sharing that the results of her surgery were “optimum, optimum, optimum”—her tumor burden was down to zero, and all visible disease had been removed.

Despite the difficulties of her experience, Kathy is incredibly grateful and optimistic that work underway can bring solutions to patients with appendiceal cancer and other kinds of rare diseases. In closing the workshop, Kathy thanked everyone for attending and participating, thanked her care team, and encouraged participants to continue to collaborate.

