“Making Decisions in the Complexity of Healthcare” (Michael Liebman, PhD) [#144]

Brad Power
May 21, 2025

“There's ambiguity in diagnosing. If we take any kind of clinical variable or biomarker, what we can look at in three patients is that, at some point in time, patient #1 and patient #2 may look identical in one or multiple biomarkers, but the reality is, over time, because disease is a process, not a state, they may not be actually on the same trajectories. Similarly, patient #1 and patient #3 are on exactly the same trajectories, but when they come in for diagnosis, they come in at different stages of the disease, so their test results are not the same. This is the kind of complexity that a physician has to deal with every day to sort out the patient that they're looking at and where to actually place them.” – Michael Liebman, PhD

“Increasingly, we try to take advantage of AI, ML, and large language models to read the literature and give us some perspective of what's going on. However, in a recent study of high impact papers, fewer than half of the experiments were reproducible. In other words, the data that's being used to generate these large language models when they aren't highly curated can be misleading and needs to be further tempered, but they can be a good starting point when care is used. Any of these need further validation and should not necessarily be considered a definitive source of evidence to make clinical decisions on.” – Michael Liebman, PhD

“One sensitive area when it comes to trust is at the beginning of the whole medical journey, when you're trying to select an oncologist or a physician or some part of the medical team. A lot of people are uncomfortable and concerned that they will offend their current doctors by requesting to have a second opinion. Indicating that you would feel more comfortable having a second opinion and discussing it openly with your doctor should actually reinforce the direct communication you have with your physician, and if they are truly patient-centric, they will understand.” – Michael Liebman, PhD

Meeting Summary

Cancer patients and caregivers face challenges in coordinating at least three complex systems: you (the patient), your disease, and the practice of medicine. It is important to understand that disease is a process and not a state, and that complicates its diagnosis and potential management, especially since much of the critical data about you and about your disease may be missing, inaccurate, or not yet identified (measured), and the true understanding of disease continues to evolve. Accurate and transparent communication with your medical team is critical to optimizing disease management and your outcomes. A basic understanding of the process of diagnosis, the challenges of clinical trials, and selection of treatment can lead to identifying the right questions for you to ask as well as how to evaluate and interpret the many channels of information. Increasingly, another wrinkle is the possible use of AI In diagnosing and treating “your cancer”, and how you can determine what information you can trust. Are analyses based on “more data” better than those only using “good data”? How can biases, known or unknown, affect your confidence in your decision-making?

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Michael N. Liebman, Ph.D (theoretical chemistry and protein crystallography) is uniquely qualified to lead a discussion on the complexities of treatment decision-making. He is the Managing Director of IPQ Analytics, LLC, after serving as the Executive Director of the Windber Research Institute from 2003-2007. He is an Adjunct Professor of Pharmacology and Physiology, Drexel College of Medicine, Resident Professor of Biology, University of Massachusetts-Lowell, and Adjunct Professor of Drug Discovery, Fudan University. Previously, he was Director, Computational Biology and Biomedical Informatics, University of Penn Cancer Center. He served as Global Head of Computational Genomics, Roche Pharmaceuticals and Director, Bioinformatics and Pharmacogenomics, Wyeth. He was Associate Professor of Pharmacology and Physiology/Biophysics at Mount Sinai School of Medicine. He is an Invited Professor, Shanghai Center for Bioinformatics Technology, and of the Chinese Academy of Sciences. He focuses on computational models of disease that stress risk detection, disease process, and clinical pathway modeling, and stratification from the clinical perspective. He utilizes systems modeling to represent risk/benefit analysis in pharmaceutical development and healthcare. Current applications focus on women’s health: triple negative breast cancer, hypertension, and hypertensive disorders of pregnancy, infant-maternal morbidity and mortality, perimenopause-menopause transition addressing health disparities. He has launched a non-profit to focus on these women’s health issues.

Why do you need to pay attention to how you make medical decisions?

- To improve the accuracy and personalization of your treatment, ultimately leading to better health outcomes
- To integrate and align multiple interconnected factors - you, your disease, and medical practice
- Because your physician has limited time to make decisions
- Because there are psychological biases in decision-making that can lead to errors, as highlighted by Nobel Prize winner Daniel Kahneman's work on slow and fast thinking processes

What are key challenges in making complex medical decisions?

- **Disease complexity**: Diseases are processes, not static states, with varying trajectories and progression rates that are difficult to capture.
- **Biomarker limitations**: Current biomarkers often provide incomplete or inconsistent information, and their interpretation can vary between institutions. They represent measurable entities that we try to associate with our limited understanding of disease trajectories.
- **Comorbidities**: Patients often have multiple conditions that interact and complicate diagnosis and treatment.
- **Heterogeneity**: Patients receiving the same diagnosis can have very different underlying disease characteristics.

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What limitations in information from tests should you be aware of that can impact your medical decision-making?

- **Biomarkers can be misleading** because they may vary over time during disease progression, and different institutions may use different thresholds for positive/negative results.
- **Test results can vary** because different lab equipment and calibration can produce different results, different pathologists may interpret the same sample differently, and normal ranges are often based on population averages that may not reflect you.
- **Test interpretation can be hard** because tests don't capture the full complexity of your disease trajectory, comorbidities can significantly impact test interpretation, and discrete measurements might miss important trends or outliers.

How can you make better medical decisions?

- Consider your disease as a dynamic trajectory rather than a static state
- Collaborate with researchers and clinicians to uncover deeper insights
- Focus on personalized approaches that recognize your variations in disease progression, lifestyle, and environmental factors

How can you create a collaborative, two-way dialogue with your medical team so that they understand your unique situation and concerns and you feel fully informed and engaged in your care?

- Keep a detailed journal of symptoms, observations, and questions, and share a copy with your physician, but don’t expect them to read it during your office visit. Ask probing questions about your specific condition, such as "Are there other perspectives or approaches we should consider?"
- Request clarity on your physician's level of confidence and any uncertainties in the diagnosis or treatment plan
- Seek a second opinion respectfully, framing it as a desire to be fully informed and confident in the treatment approach
- Use nurse navigators as bridges to help translate complex medical information
- Focus on the four key elements of trust – consistency, compassion, communication, and competency – when selecting and working with your healthcare providers

How can AI help in making complex medical decisions?

- Reading and synthesizing large volumes of medical literature
- Identifying patterns in complex disease processes
- Supporting more personalized approaches to diagnosis and treatment

What are some limitations of current AI tools?

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- Large language models can be misleading if not carefully curated.
- Fewer than half of high-impact medical research experiments are reproducible.
- AI should be used as a starting point for investigation, to enhance understanding, not as a definitive source for clinical decisions, or a replacement for human expertise and clinical judgment.

What are the benefits of seeking second opinions?

- Confirm your diagnosis and treatment plan
- Explore alternative treatment options
- Gain additional insights into your condition
- Increase confidence in your medical decisions

How can you navigate getting a second opinion without offending your current medical team?

- Approach your current doctor by saying you want to be proactive about your health
- Ask if they can recommend a colleague for a second opinion that they would trust
- Frame it as wanting to ensure you're exploring all potential options
- Emphasize that you value their expertise and are not challenging their judgment

A good physician should support your desire to be fully informed and engaged in your healthcare. If a doctor reacts negatively to a request for a second opinion, that may be a red flag indicating you might want to seek a more patient-centered provider.

How can you learn more about making medical decisions?

- See our previous conversation with Michael Liebman "Modeling Disease" [#24]
- Contact Michael Liebman at Michael.Liebman@IPQanalytics.com
- Share your treatment needs and preferences and a journal of observations and symptoms with your medical team and ask questions
- See other conversations on cancer care decision-making:
    - “Opening up Access to Cancer Data for Patients" (Frank Nothaft) [#76]
    - “Using GenAI to Assist Rare Cancer Care” (Bill Paseman) [#132]
    - “A Rogue Cancer Patient Gets Better Outcomes” (Ari Akerstein) [#109]
    - "Decisions in Advanced Prostate Cancer" (Rick Stanton) [#8]
    - “Helping Patients Navigate Cancer” (Manta Cares) [#93]

For the video recording of this conversation, please see here.

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Meeting Notes

KEYWORDS

Women's health, computational biology, breast cancer, decision making, trust determinants, healthcare challenges, precision medicine, disease modeling, biomarkers, patient care, second opinions, clinical trials, lifestyle medicine, AI and ML, patient engagement.

SPEAKERS

Michael Liebman (71%), Chris Apfel (12%), Lea Ann Biafora (4%), David Plunkett (3%), Matthew DeAngelis (3%), Cindy Ness (2%), Roger Royse (2%), Mark Taylor (2%)

CHAT CONTRIBUTORS

Rick Davis, Chris Apfel, David Plunkett, Mark Taylor, Ari Akerstein, Lea Ann Biafora, Allen Morris, Roger Royse

SUMMARY

Dr. Michael Liebman discussed the complexities of healthcare decision-making, emphasizing the importance of understanding disease processes and patient-specific factors. He highlighted the challenges in precision medicine, noting the need for better integration of disease understanding and treatment. Dr. Liebman stressed the significance of trust, consistency, compassion, communication, and competency in healthcare providers. He also addressed the limitations of large language models in medical decision-making, advocating for evidence-based resources like UpToDate. The discussion included the role of nurse navigators, the importance of second opinions, and the potential of personalized medicine and lifestyle factors in improving patient care.

OUTLINE

Introduction and Background

- Michael Liebman, PhD, introduced himself and his group, IPQ Analytics, which includes a nonprofit focused on women's health called Woven.
- He has a background in computational biology and genomics, having worked on the original HER2/neu test and as the global head of computational biology and genomics for Roche.
- He is not a clinician and does not provide clinical advice, focusing instead on decision-making and the importance of trust in healthcare.

Challenges in Healthcare Decision-Making

- The concept of the "three-body problem" (patient clinical process, disease understanding, and medical practice) in healthcare explains some of the challenges in the US healthcare system compared to other nationalized health systems.

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- Decision-making in clinical practice is more condensed and less research-based compared to the scientific method.
- It is important to understand the root causes of clinical issues faced by physicians.
- Diagnosing and treating diseases is complex, especially in the context of biomarkers and disease processes.

Accuracy vs. Precision in Medicine

- Accurate medicine and precision medicine are different; a better understanding of a disease is needed before developing a drug.
- Simple approaches to disease treatment are limited and need more comprehensive research.
- There are positive trends in breast cancer survival rates, but the incidence of breast cancer is increasing.
- There is ambiguity in diagnosing and treating diseases due to the complexity of disease processes and the need for better staging and monitoring.

Impact of Comorbidities and Inflammation

- Comorbidities impact disease progression and treatment response.
- There are challenges in diagnosing and treating diseases when patients have multiple conditions.
- Inflammation plays a big role in disease processes and inflammation caused by disease needs to be separated from that caused by stress or other factors.
- Pathology needs to develop a better understanding of disease heterogeneity.

Role of AI and ML in Medicine

- The use of AI and ML can be used to read literature and provide perspectives on medical research.
- Large language models have limitations and need further validation of their findings.
- Trusted resources like UpToDate should be used for clinical decision-making.

Patient Engagement and Second Opinions

- Patients should keep a journal of observations and share it with physicians to enhance communication and decision-making.
- Patients should seek second opinions, especially when feeling nervous about a diagnosis.
- Getting second opinions without offending current doctors is hard.
- Patients should be proactive in managing their care.
- Nurse navigators can bridge the gap between patients and physicians.
- Concierge medicine and other models can improve patient care and physician-patient communication.

Lifestyle Medicine and Personalized Approaches

- Lifestyle factors are important in disease management.
- Personalized approaches are needed.

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- Epigenetic measurements can help understand the impact of environmental exposures and lifestyle factors on disease.
- Nutrition is complex.
- Granularity is needed in medical models.
- Personalized medicine has the potential to improve patient outcomes.
- Better communication between researchers and clinicians is needed.

Reliability of Test Results

- There is inter-rater variability in pathology.
- Consistent testing and calibration is needed.
- PSA (prostate specific antigen) testing has limitations, while other blood tests and a prostate MRI offer potential benefits.
- Evidence-based medicine is important.
- Superior care beyond the standard guidelines is needed.

Conclusions

- Communication between physicians, researchers, and patients is important to improve healthcare.
- Better understanding of clinical problems and the importance of addressing the root causes of disease is important.
- Patients should take control of their healthcare and seek second opinions when necessary.

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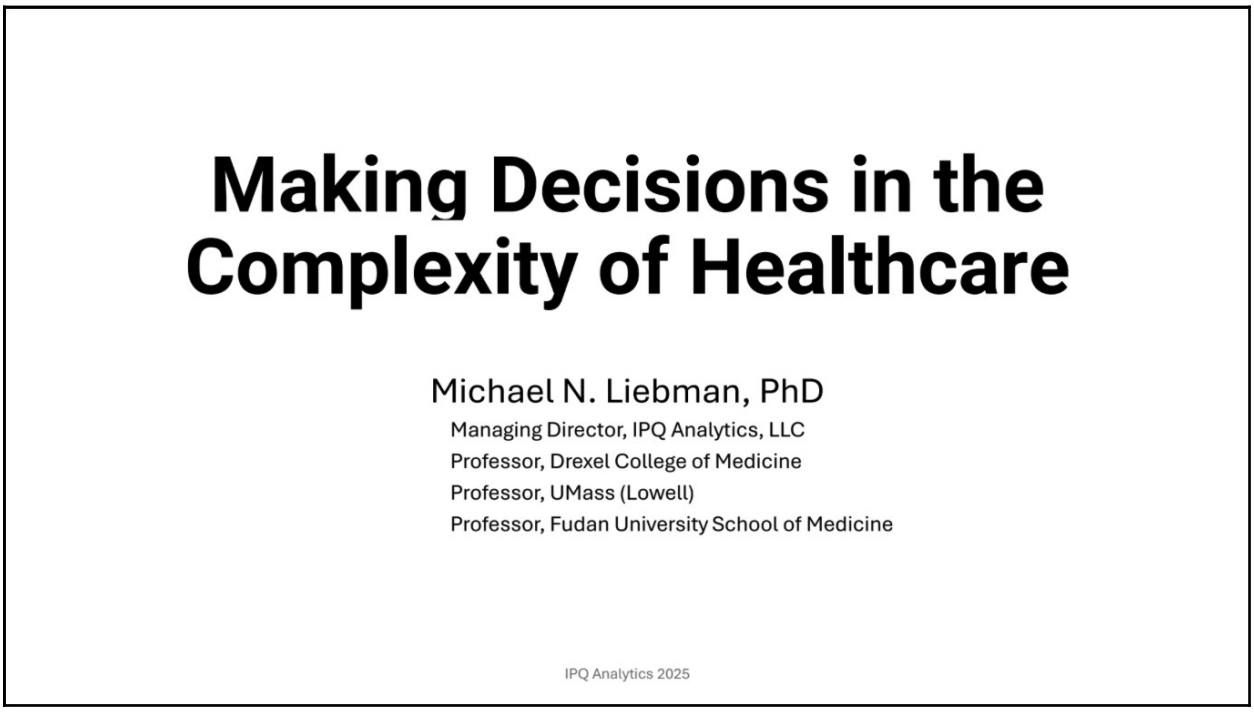
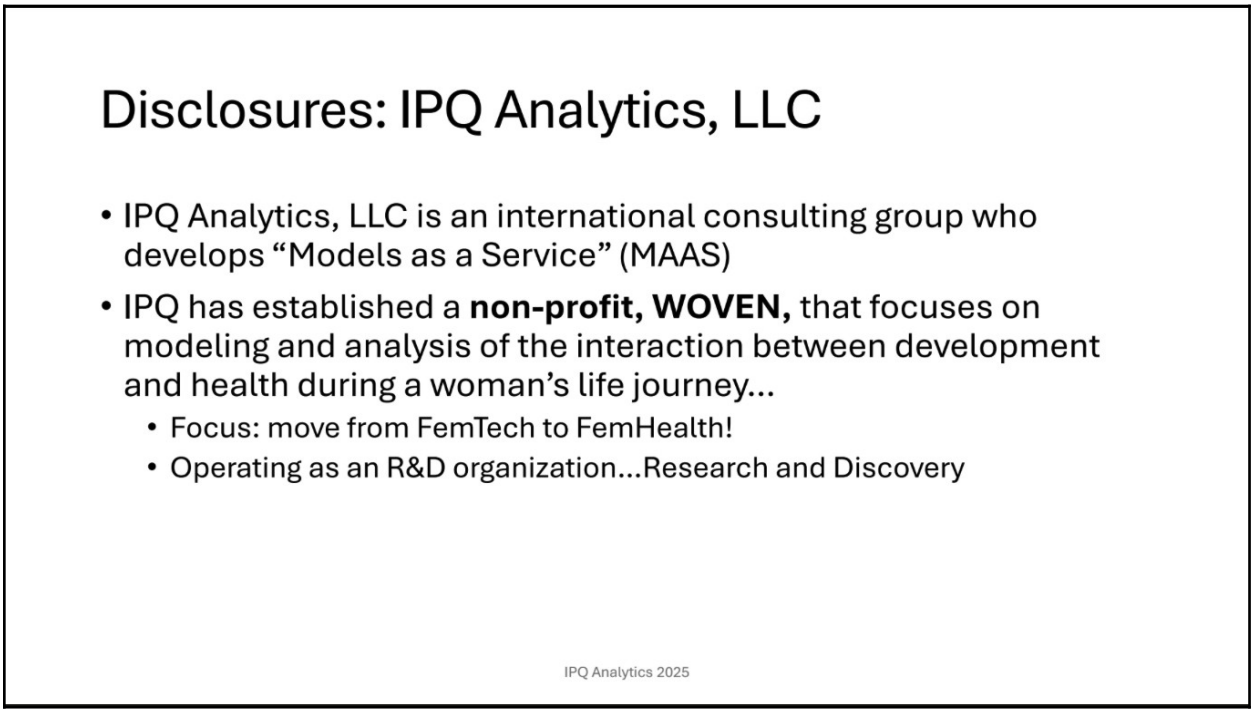
TRANSCRIPT

Michael Liebman
The slides will be available, and I'll give you my email if you want to contact me on other issues.





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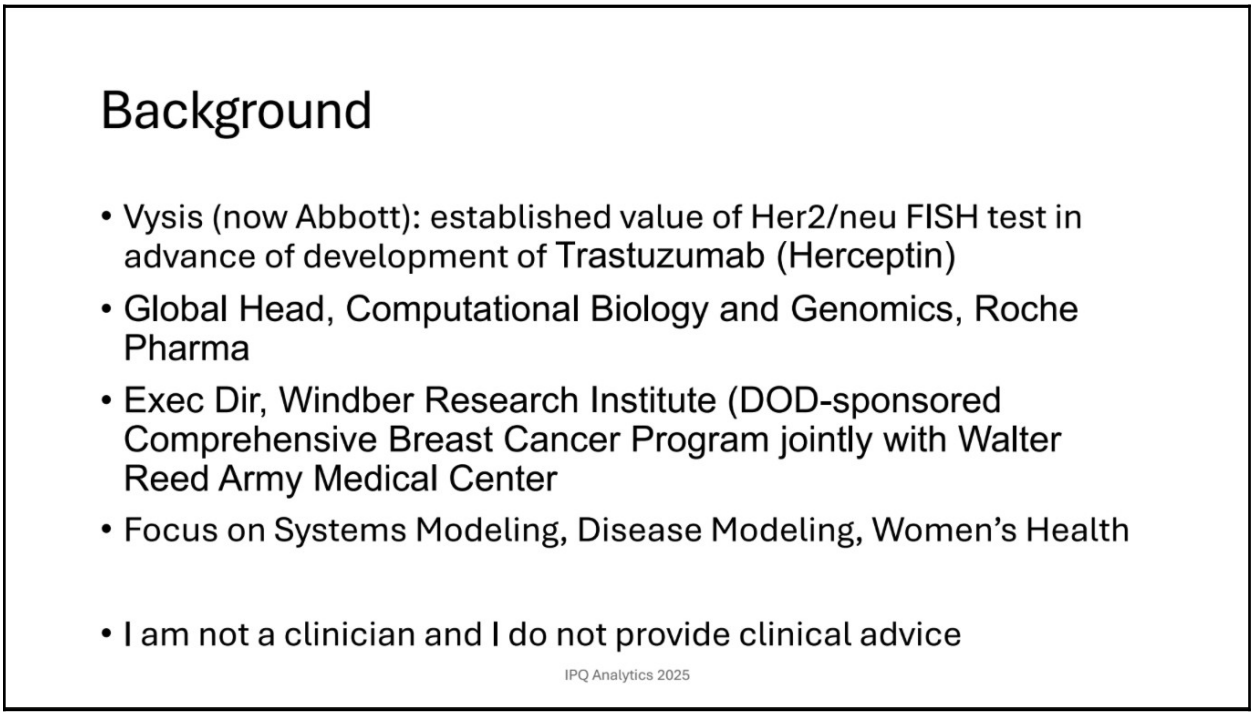
I have a group called IPQ Analytics. It is a commercial group, but we also have a nonprofit called Woven, focusing on women's health. FemHealth, not FemTech. It's an R&D, where “D” is not development, but discovery.



I worked on the original HER2/neu test [National Cancer Institute (NCI) def]. many of you may be familiar with, that was before the drug Herceptin [NCI def] was developed. Part of my job was to figure out what to do with the test. I was global head of computational biology [CLRN def] and genomics [def] for Roche. I was the director of the Windber Research Institute, which is a DOD-sponsored comprehensive breast cancer program, jointly with Walter Reed. I focus on systems modeling, disease modeling, and women's health. I am not a clinician, and as stated before, I do not provide clinical advice. Nothing in here is intended to be clinical advice.

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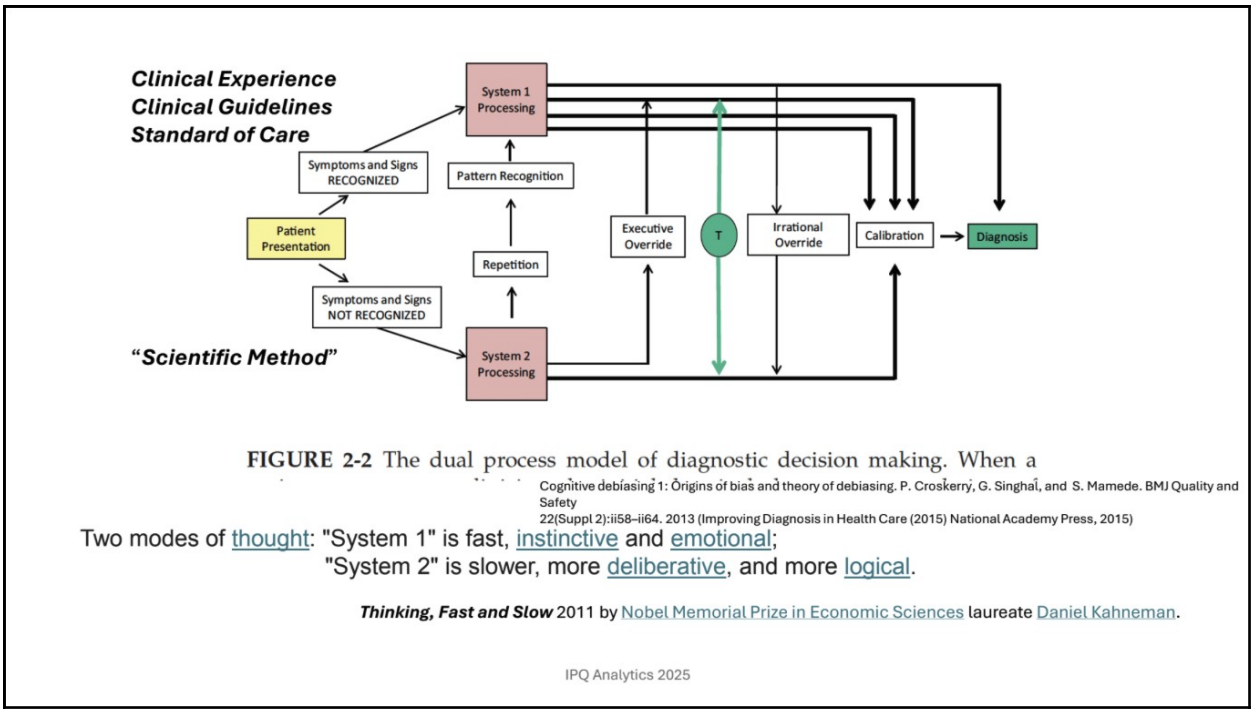
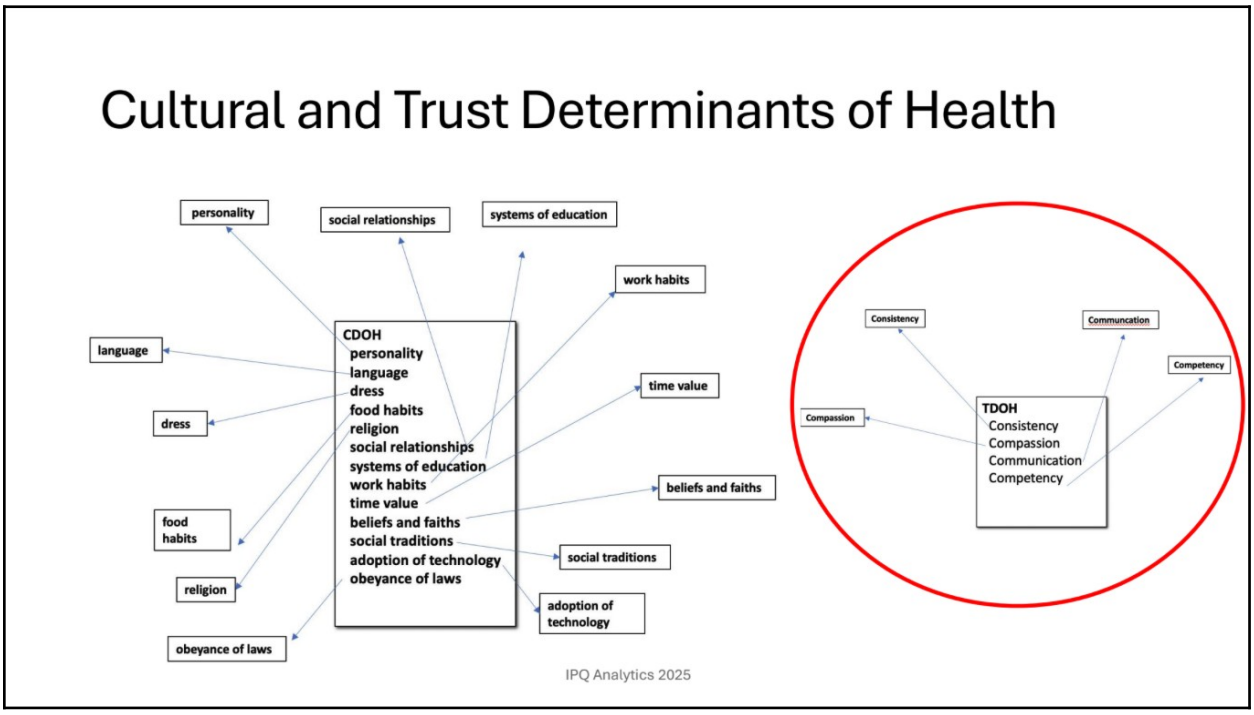


We talk about decision-making. I would refer you to look at the slide and the background from Dan Kahneman, the Nobel Prize winner, about the difference between slow and fast processes of systems thinking. We have to take into account as we consider this in decision-making, the external factors that come into play. As cancer patients or caretakers or researchers, you understand there are many other factors besides pure science. But what I'll try to focus on in terms of decision-making, starts to address the science part itself.



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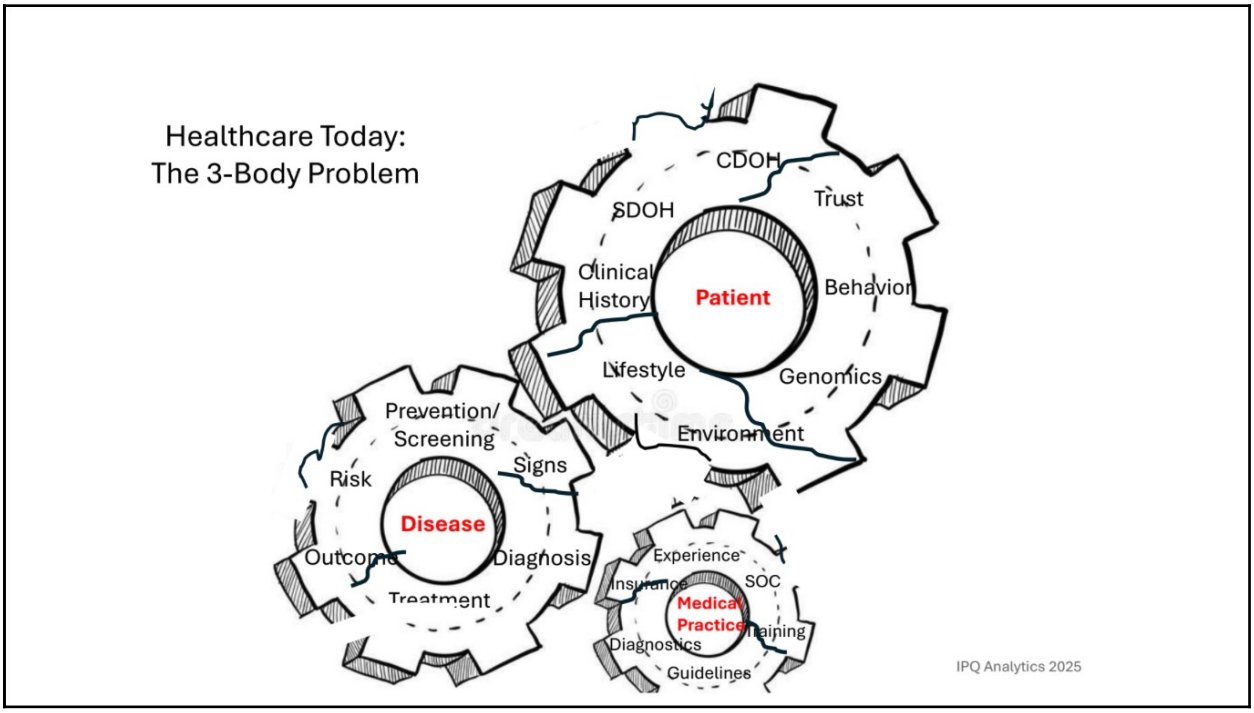
I'll touch on trust. What's critical for any patient is understanding how we've started to go beyond social determinants of health to understand cultural determinants and also trust determinants [health determinants def WHO]. These are very critical. What you're looking at, and hopefully have resolved with clinical advice, is getting consistency, compassion, communication, and competency in your care provider as being very critical elements to support the trust you have in the care and decision-making that should be collaborative.



Healthcare itself is a fundamental problem I call “the three body problem”. Coming out of a physics background, we have the issue of the patient with a lot of factors that tie into that, the disease itself, and the practice of medicine. We find these three gears not only are missing parts and are cracked, but they don't fit together very well. That's very notable, especially in the US healthcare system, possibly less so in some of the other nationalized health systems. This is part of the challenge we have because all of these factors enter into making the best decision for your care, which is the important thing, not necessarily care for the entire population.

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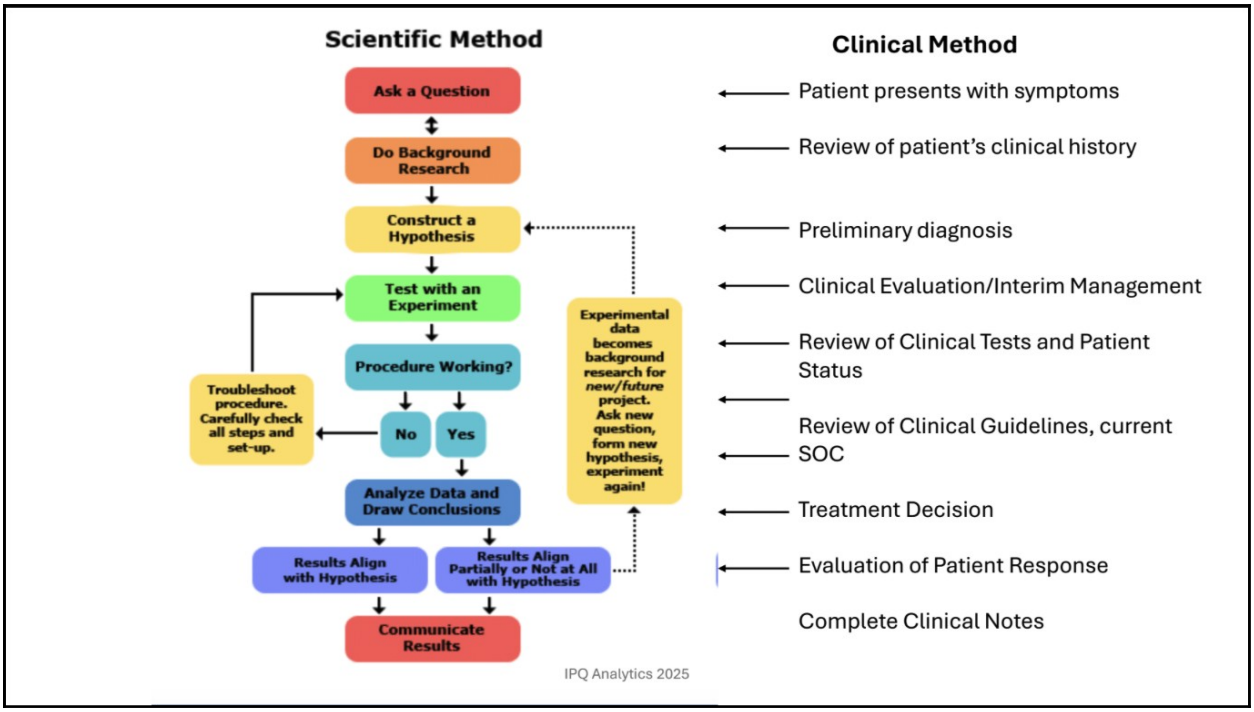
Challenges in Healthcare

- **Inappropriate Medical Testing**:
  - Unnecessary tests cost **$200B annually**, cause **30,000 deaths/**year
    - https://www.healthcarefinancenews.com/news/unnecessary-medical-tests-treatments-cost-200-billion-annually-cause-harm
- **Misdiagnosis in Medicine:**
  - **10-15%** of all diagnoses are in **100-200 Million misdiagnoses**/year, **80,000 serious harm**
    - https://www.medscape.org/viewarticle/933116
- **Inappropriate Medication:**
  - From 2014-2018, **43 Billion doses** of inappropriate medication cost **$25.2 Billion** (Medicare Part D)
    - https://agsjournal.onlinelibrary.wiley.com/doi/abs/10.1111/jgs.16779

These challenges are costly in terms of people and $’s!

IPQ Analytics 2025

There are challenges in healthcare, and these challenges are very expensive, both in terms of personal health, death, and monetary value. These are three specific classes of these challenges. You may have heard about them anecdotally, but this gives you an idea of the size of these actual problems that exist.



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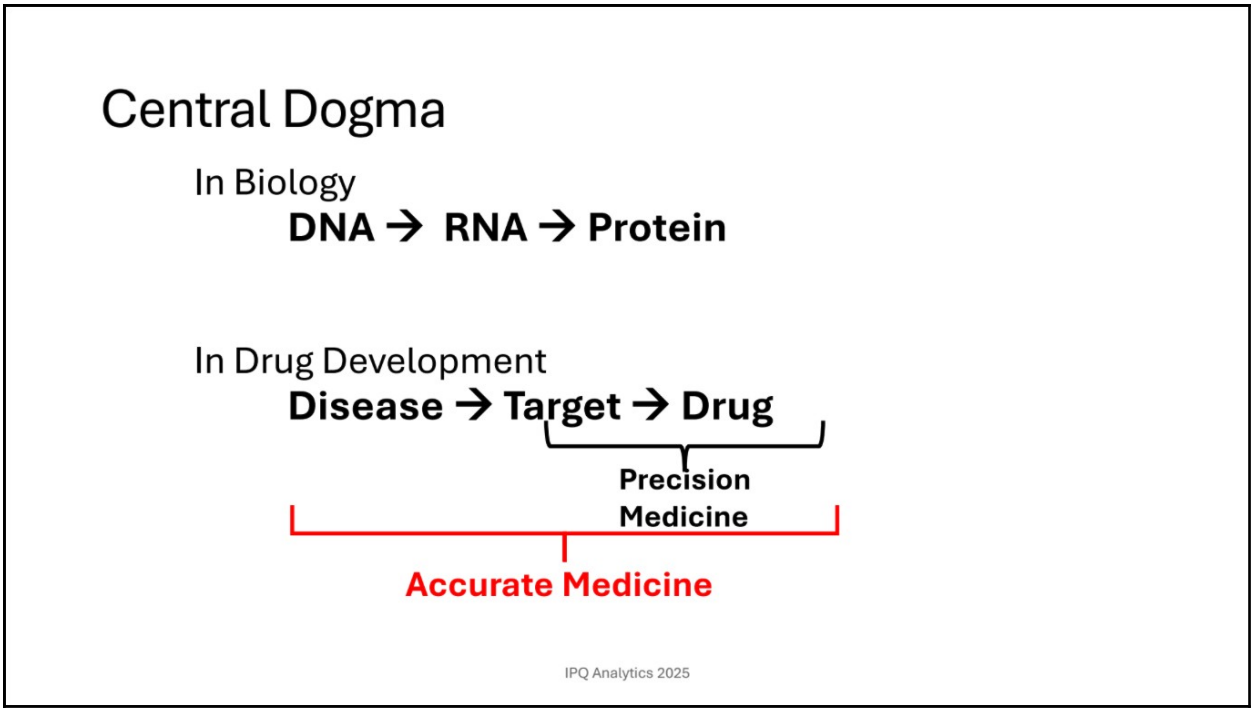
The clinical process, the way medicine is actually practiced, fits in very well with the scientific method. I've shown their alignment here. The difference is, if this scientific method is being applied, say, in a graduate program or a research lab, we have months to years to work on this. We don't have that luxury in clinical practice.

A lot of the decision-making has to be done in a much more condensed manner, without the background of some of the detailed research. What I've focused on in what we do is trying to work from the clinic back to understand what are root cause issues the clinicians are facing. I'll point to some of those just to give you an idea. Because as patients, you mainly see the interpretation or the guidance the physician is generating. Not necessarily what that uncertainty is, and to some extent, clinicians don't deal with it.



In biology, we have a central dogma [def: *something held as an established opinion*] that DNA produces RNA, which produces proteins. In drug development or treatment, we talk about having a target and a drug, and that's really how precision medicine has evolved. The challenge, having spent 12 years in pharma, is that very little effort is spent on understanding the disease. From things we've done over the years and discussion with a number of colleagues, this is really a weak point in going from understanding the disease to a drug versus a target, which may come out of genomics or the other type of correlative analysis. I call that the difference between “accurate medicine" and “precision medicine”. I'm going to point out some of the examples where that falls apart.

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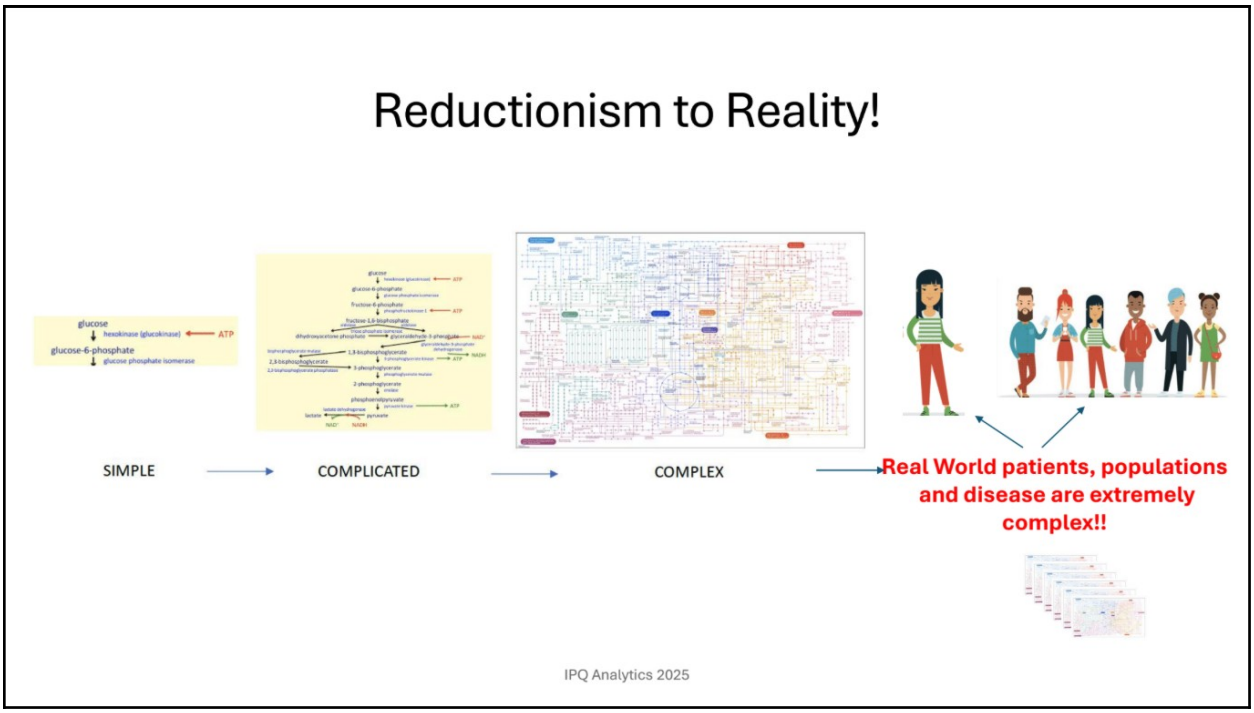

We tend to reduce things. If we're looking at a specific reaction and mutation in a specific enzyme in a pathway that tends to be relatively simple, we think we can actually act on that. However, the reaction and element are part of a more complicated pathway, even to a larger extent, when you look at the network of interactions that constitute biology, and the reality that real world populations are going to differ. This simple approach can work, but the simple approach is always going to be meeting these challenges. That's really where we need to start to appreciate and carry out the research to support making a simpler decision with much more background.

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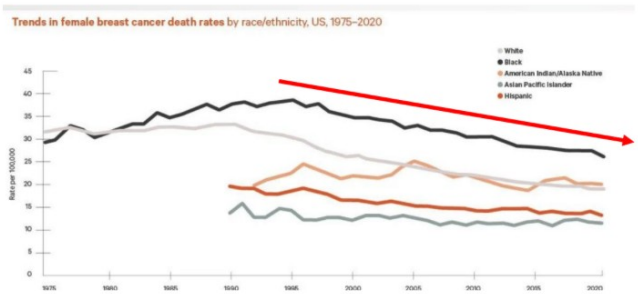
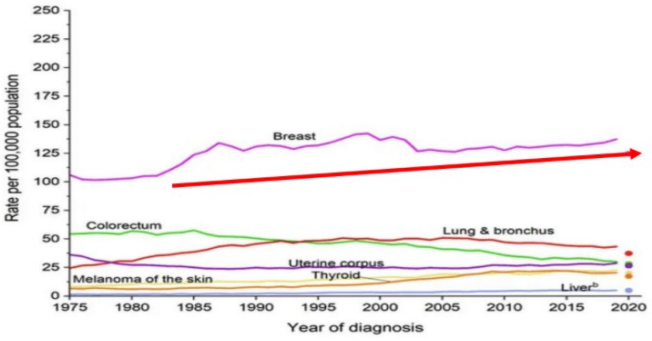
Breast Cancer Death Rates (1975-2020)



Breast Cancer Incidence (1975-2020)



We talk about breast cancer death rates and acknowledge that women with breast cancer are surviving longer in almost all population groups. What we haven't really focused on is the incidence of breast cancer has continued to go up. We work in a treatment-based medical practice, or practice of medicine focused on treating the disease, and it's much more difficult to try to understand why this incidence [*i.e. occurrence*] is going up. That's a research area we're involved in. I'm happy to give more explanation of that to anyone who's interested, but that's not the topic for today.

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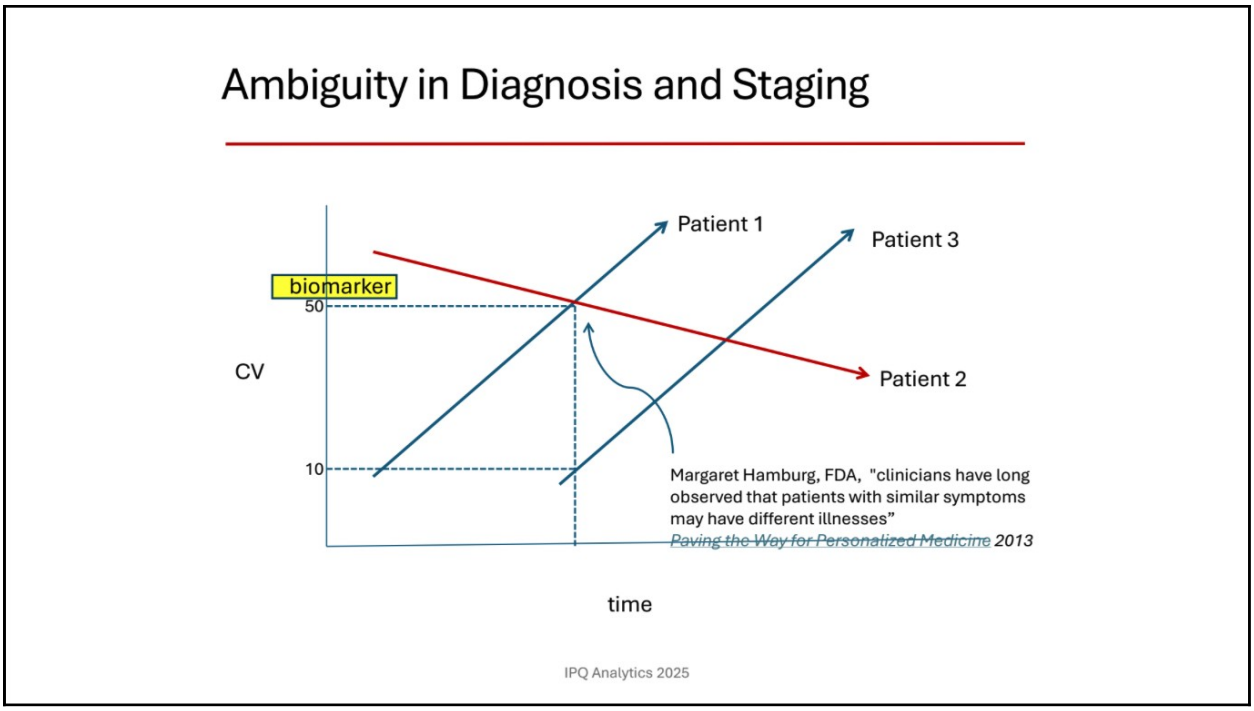

There's an ambiguity [*i.e. uncertainty*] in diagnosing. If we take any kind of clinical variable or biomarker, what we can look at in three patients is that at some point in time, patient one and patient two may look identical in one or multiple biomarkers. But disease is a process, not a state. The reality is, over time, they may not be actually on the same trajectories. Similarly, patient one and patient three are on exactly the same trajectories, but when they come in for diagnosis, they are at different stages of the disease. This is the kind of complexity a physician has to deal with every day to sort out the patient they're looking at and where to actually place them.

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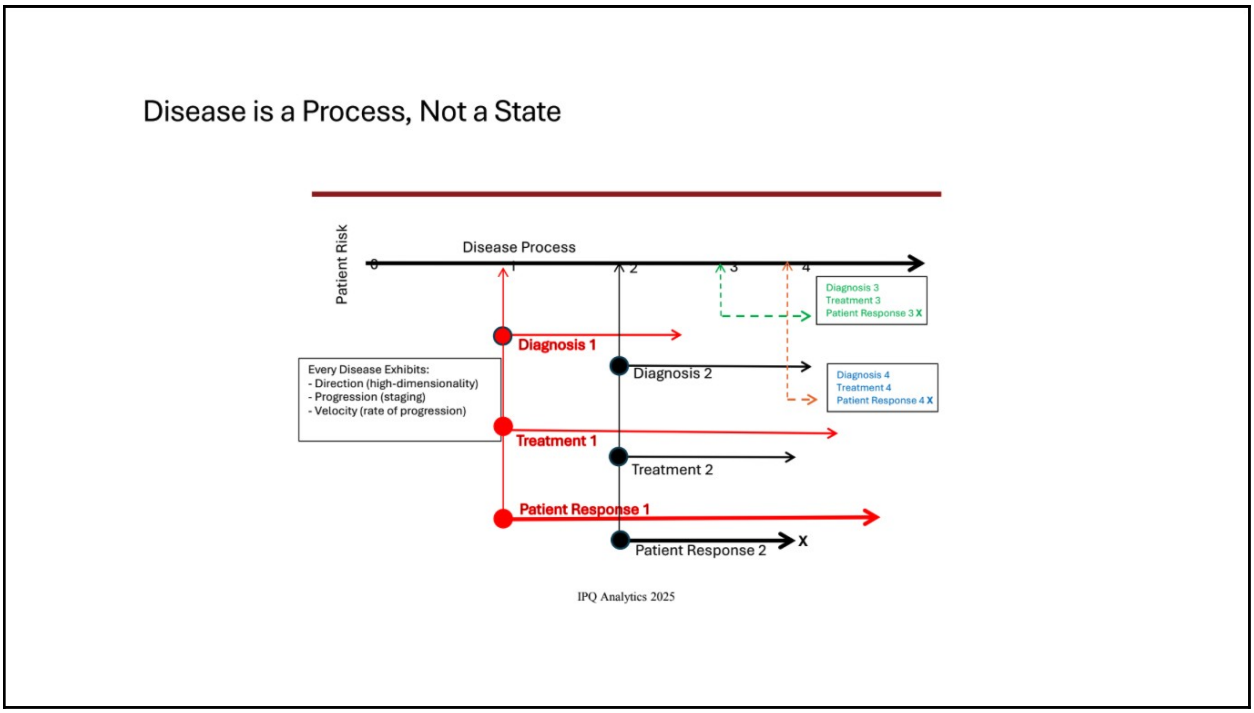

We treat this in a more rigorous manner by talking about, as I said, “disease is a process, not a state”. It evolves over time. We don't know what each disease process is, primarily because it's unethical not to treat a patient when they come in with a set of symptoms, and so we don't follow disease as an observational track. What we really need to understand is that a patient who comes in at different points in time may actually get a different diagnosis, resulting in different treatments and responses.

To really define disease, sometimes we talk about a vector [def], but we need to know the dimensionality of this process. We need to know how far along that process is, also called staging, and how rapidly they're progressing. All three of those parameters, which actually constitute mathematically a tensor, would be necessary to optimize treatment for a patient when they actually present.

The challenge we have is we're using technologies that can come up with biomarkers or diagnostics without knowing the disease process, and try aligning them to optimize how they could provide information about what stage the patient is in and how rapidly they're progressing. The reality when we look at certain markers, even HER2, is that it doesn't work unilaterally [*def: in a singular direction*]. It may increase and decrease over time during the course of the disease.

Markers like this are not optimally designed, because we don't know what the disease process is. We have to understand these markers may not give us as much information as we would like.

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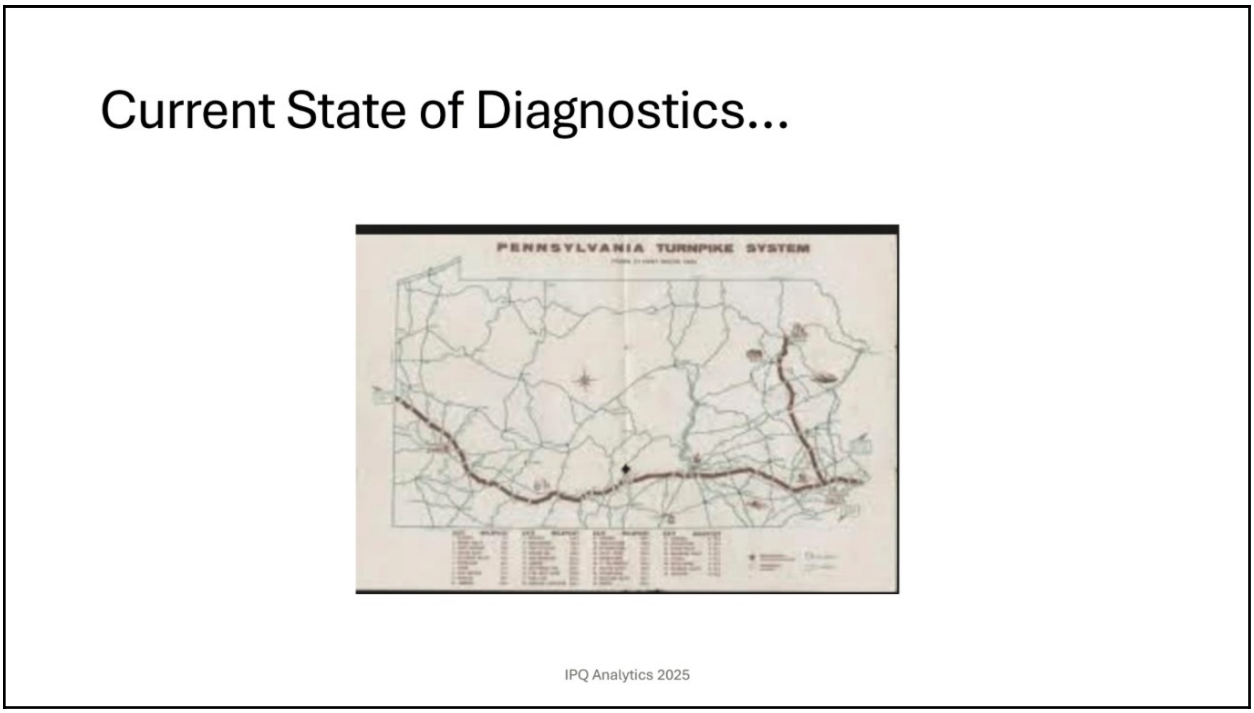

I liken it to looking at a car driving on the Pennsylvania Turnpike. The car starts in Ohio. You want to know where it is. You may measure how much gas was used or wear on the tires. You do know it will relate to where the car is. Details may vary if they stopped at a rest stop. In addition, the technologies we have can give us measurements not actually related to either the path or the progression. Understanding how much windshield fluid was used doesn't really tell us anything about the state of the driver or the car, but we may be able to monitor the data in a continuous manner.

We need to always keep in mind that not all measurements are going to be consistent or appropriate for what we're trying to detect in these diseases.

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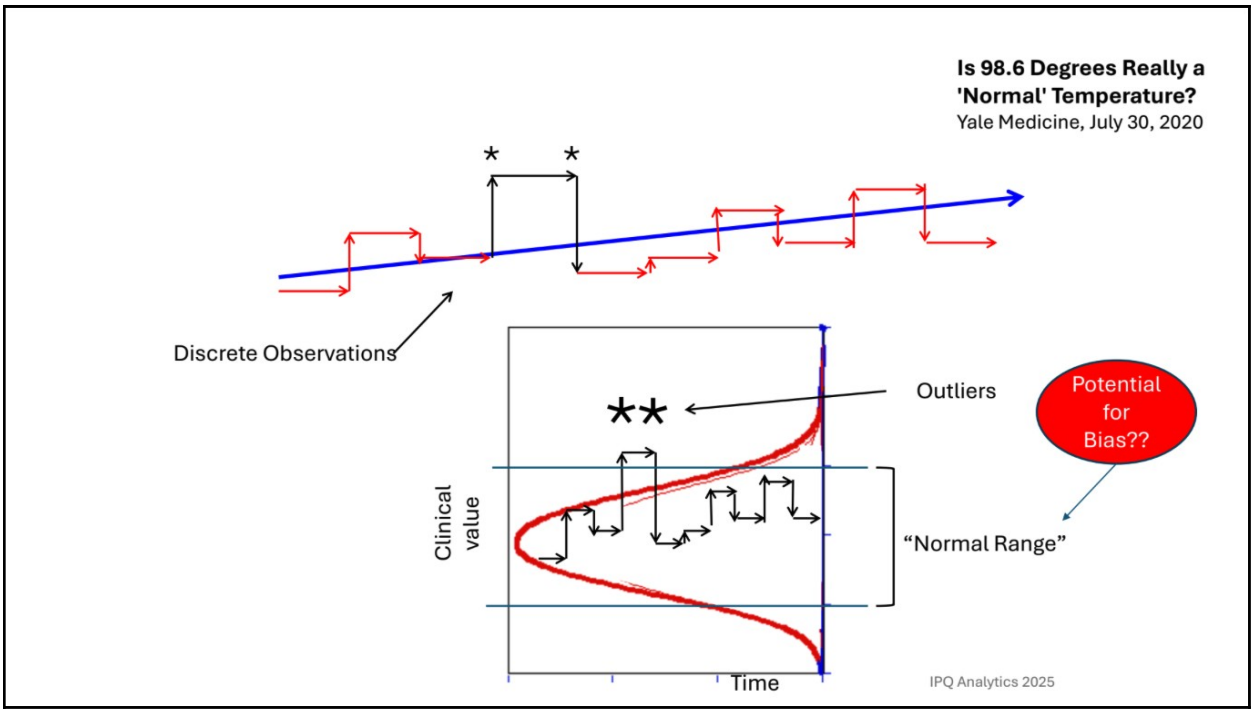
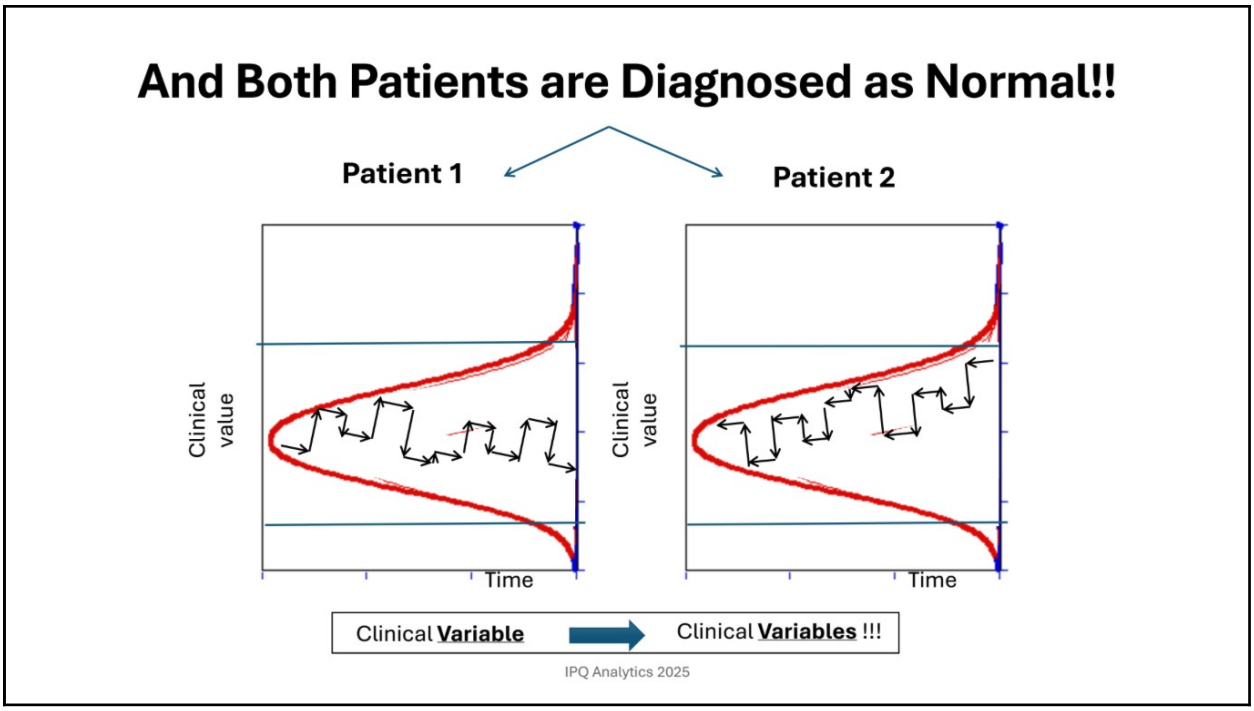
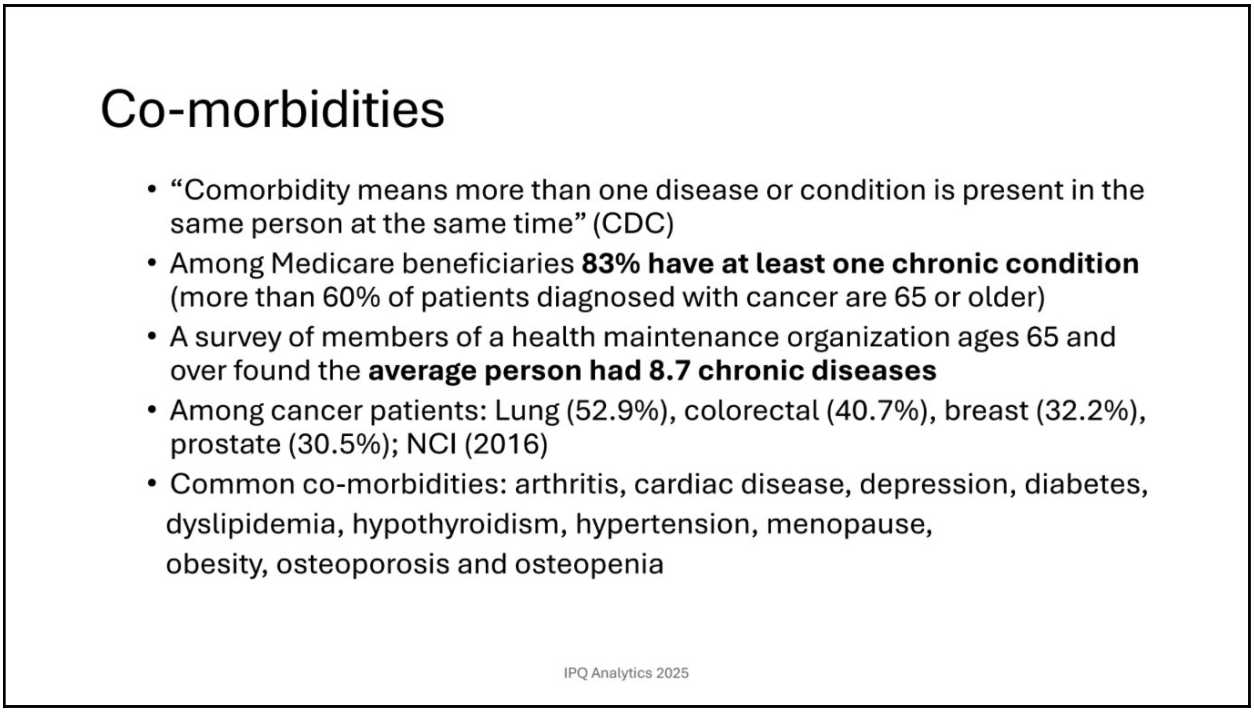


In fact, most measurements are not continuous [def: *measured on a continuous scale, i.e. time*], although we're starting to have some wearables to break down that barrier. If we look at this slide, where each of these are measurement points, we see a trend. These discrete [def: *easily counted*] measurements with the asterisks, where we've looked at a distribution [def: *referring to a function describing the probability of different outcomes in a random variable*] of measurements over a large population, would be considered outliers. This is the kind of thing that shows up in a normal report, but the potential for bias and how this normal range has been developed could be significant. It really needs to be calibrated for patients like you, not just a normal general population.

“Making Decisions in the Complexity of Healthcare” (Michael Liebman, PhD) [#144]



You also need to understand that if patient 1 is following this pattern, and patient 2 is following this pattern, they may be determined to be normal, because they've never exceeded that distribution. They've never had outliers, but they are on different paths and should be managed in different directions. Again, this is the kind of thing that adds to the complexity of making a diagnosis and supporting any decision-making of a physician in talking with their patients.



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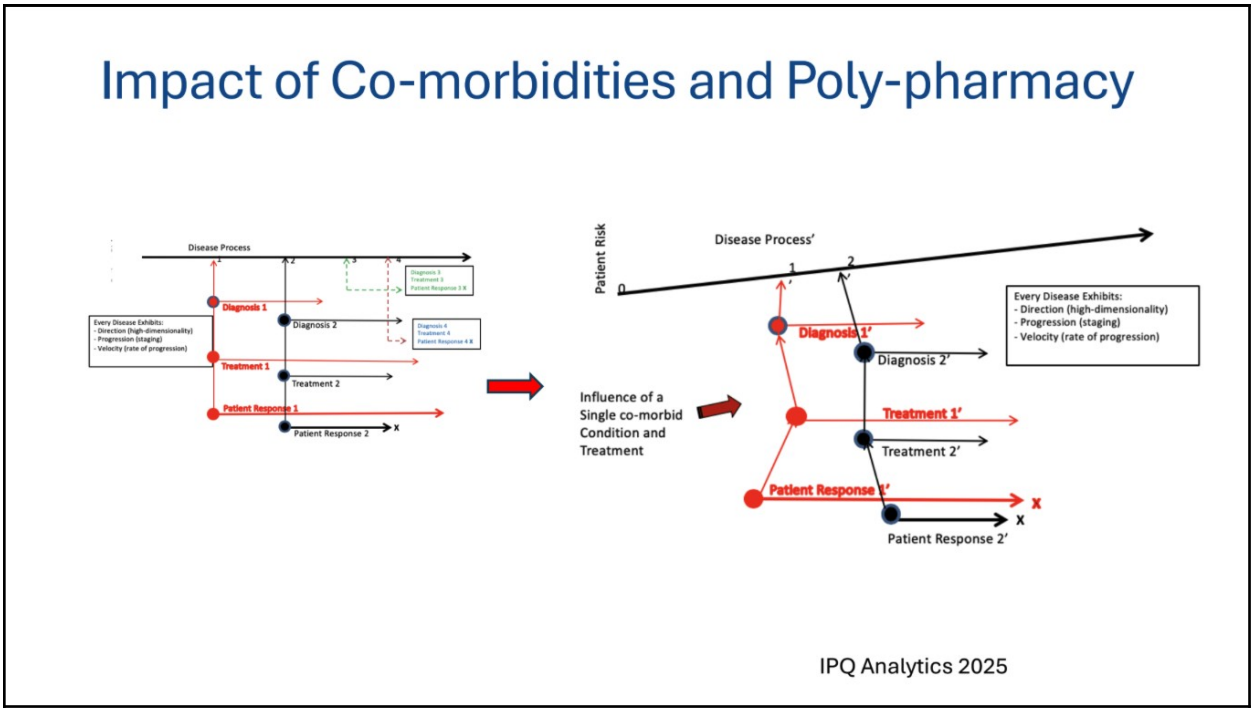
Comorbidities is another major area that sometimes gets overlooked. On average, many patients are going to have as many as eight or more conditions. Among cancer patients, this slide gives you an idea of the percentages of comorbidities in these different categories of cancer. These are some of the more common ones. What does that do to the actual progression of the disease and the diagnosis?



If the disease process is being altered by the comorbid condition, it's going to not only affect the disease progression, but also the response to diagnosis and response to treatment. This is just to point out the complexity that has to be addressed, or at least be made more transparent, to understand some of the limitations we have and how we can practice medicine today.

Obviously we can't define all the parameters. We don't do experiments on humans under ethical conditions, so we don't have the ability to come up with higher resolution models. A lot of the digital twin [def: *virtual representation of an object or system*] data is trying to enable approximations of this to then enable and improve patient care, in the absence of doing experiments.

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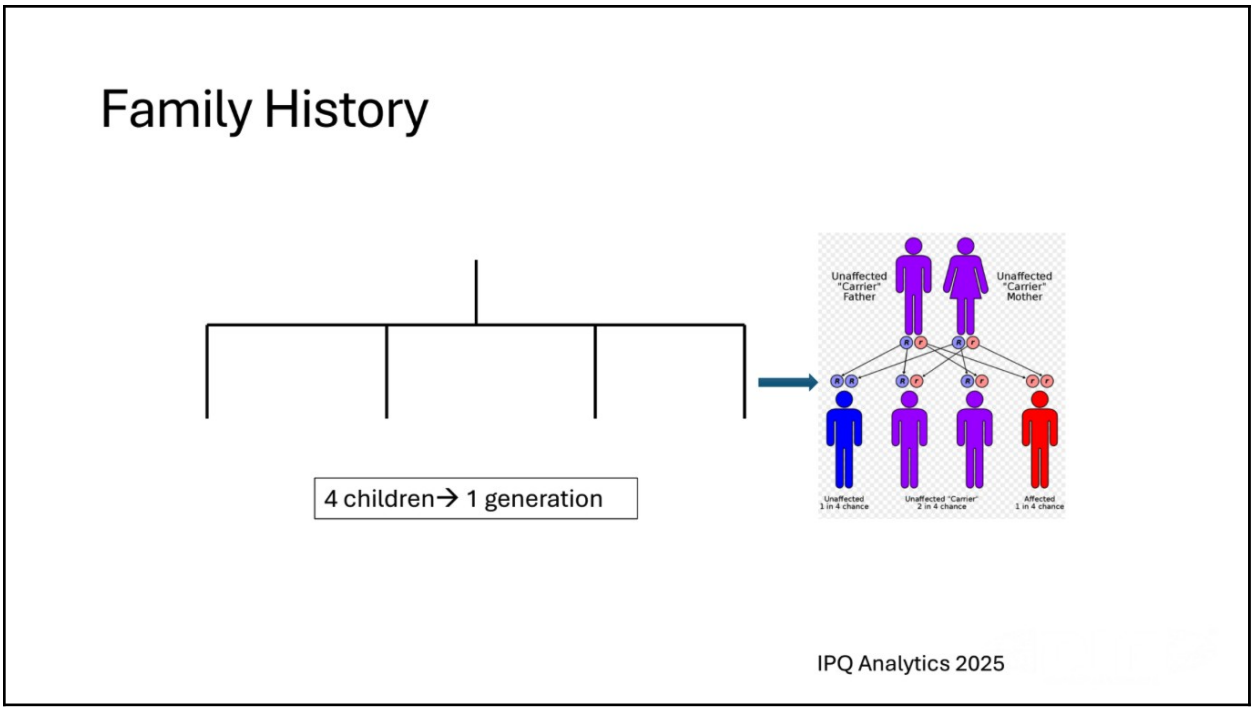
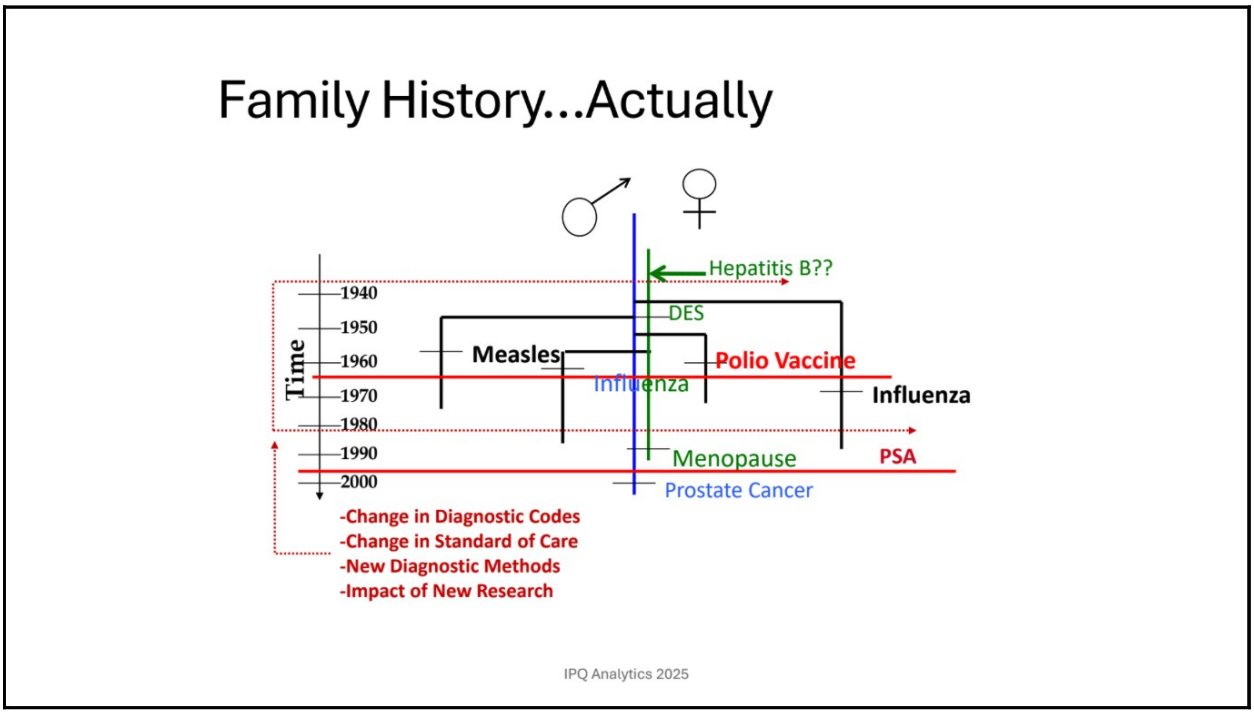


Here’s a slide about family history. Probably all of you have had questions about cancer within your family. When you look at pedigrees, they're drawn like this and we talk about them conventionally as having shared risk from the genetics of the parents. But the reality is, this is not what a family looks like.



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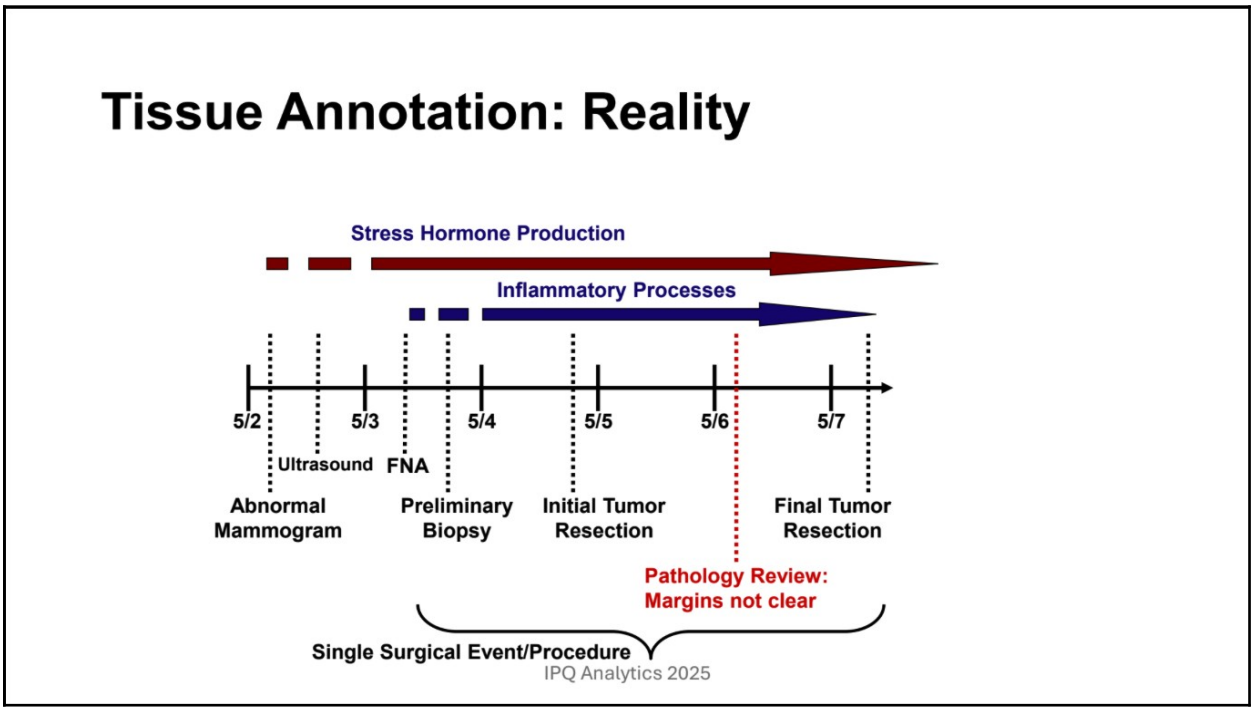
Those four children were born at different points in time. The mother is different at each birth because she's undergoing change during her gestational, delivery, and postpartum periods. The changes in diagnostic codes may be very different and impact these individuals separately. We need to understand this is what a real family looks like, not what I showed you before.

When we start to try to compute risk, whether it's genetic/polygenic risk factors or any of the correlations, we're always going to be approximating how that information is being used in a reduced manner. If you just take the example we use in breast cancer, the fact that your grandmother had breast cancer, your mother had breast cancer, and you have breast cancer - it doesn't mean you all had the same type of breast cancer. That may be a critical factor that needs to be incorporated. It may be that you did have the same breast cancer, but the diagnostic criteria were changed in those time periods. That's the level of granularity we bring into these models to try to enhance transparency going forward.



We talk about inflammation as being a major issue, and when we do a tumor resection (this would be following a patient over the course of treatment, from mammogram, ultrasound, fine needle, aspirate, biopsy, resection and clearing the margins), we find the patient shows inflammation. But, some of that inflammation is from manipulation of the patient. Some of the stress hormone production is from the natural response a woman would have to an abnormal mammogram. Even when we're looking at the tumor tissue that's been removed, we need to understand there are underlying processes independent of the disease. We have to start to separate those so that we are tackling the disease and not some of these ancillary activities.

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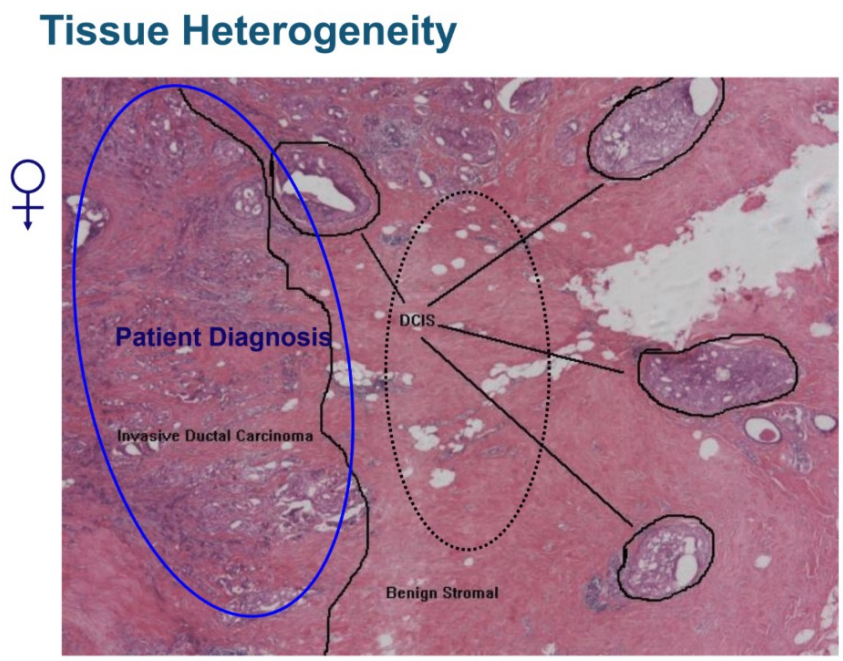
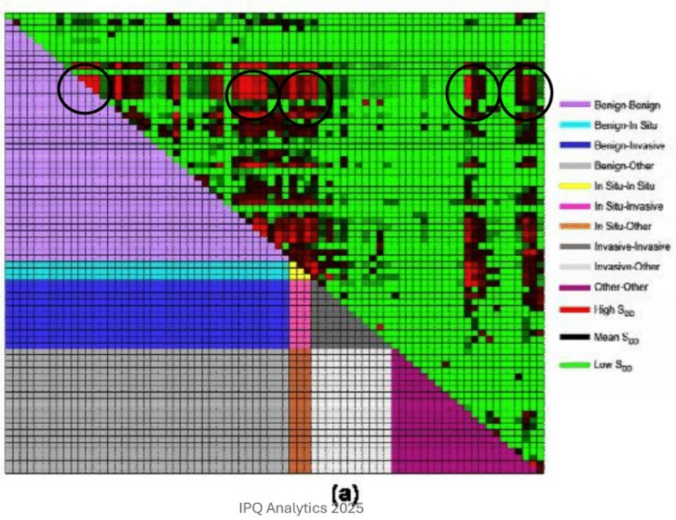


We talk about looking at PATH [*pathology]* slides, and this is from one of our patients who had invasive ductal carcinoma [NCI def], and DCIS [NCI def]. When we did micro dissection and analysis, these DCIS regions were very different from DCIS when it's with a typical Doctor hyperplasia, or when it's DCIS itself. And so there are limitations in what we're looking at when we're looking at things like the pathology and heterogeneity.



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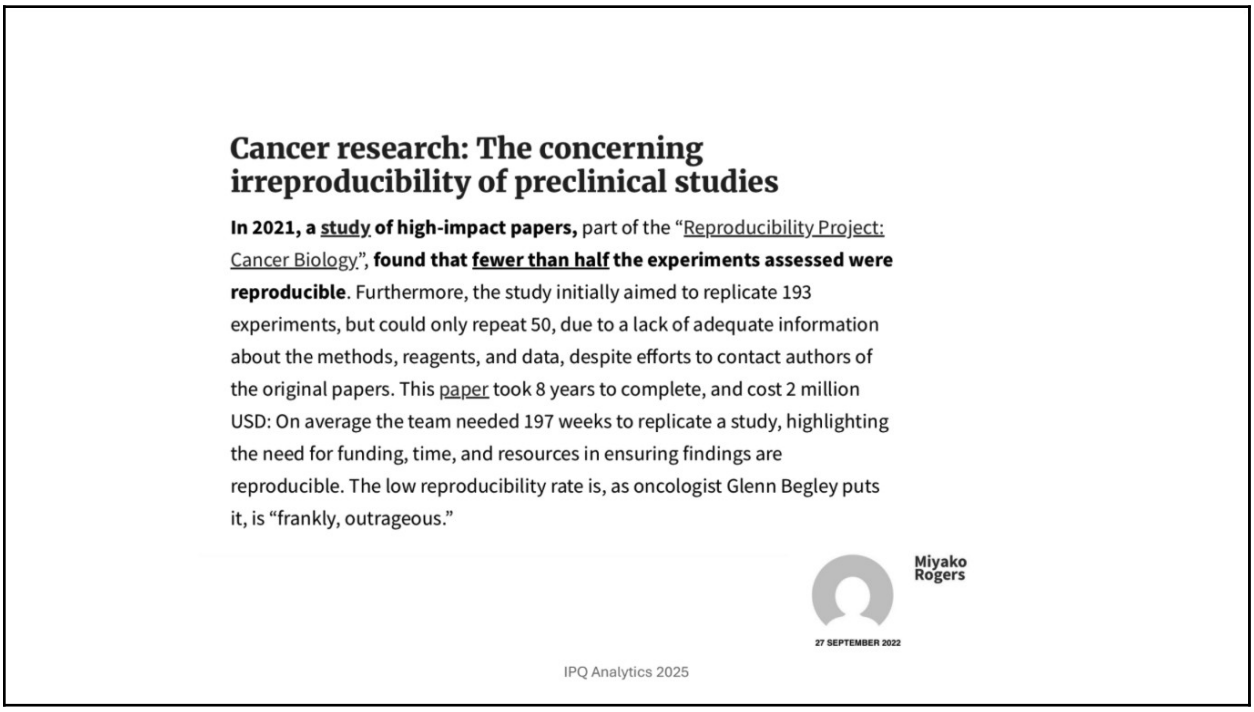
What we've actually done is shown that there are patterns of heterogeneity that persist, that are actually very sensitive to other state factors about the patient. Pre- and post-menopausal women have a different pattern of heterogeneity. Smokers have a further difference in the pattern of their heterogeneity.



We're trying to take advantage of AI, ML, and large language models [LLMs]. Using them to read the literature and give us some perspective of what's going on. This is the reality, however; when a study was done of high impact papers, fewer than half of the experiments were reproducible. In other words, when the data being used to generate these large language models is not highly curated, the results can be misleading. These models need to be further tempered, but they are a good starting point. Any of these need further validation and should not necessarily be considered a definitive source of evidence to make clinical decisions on.

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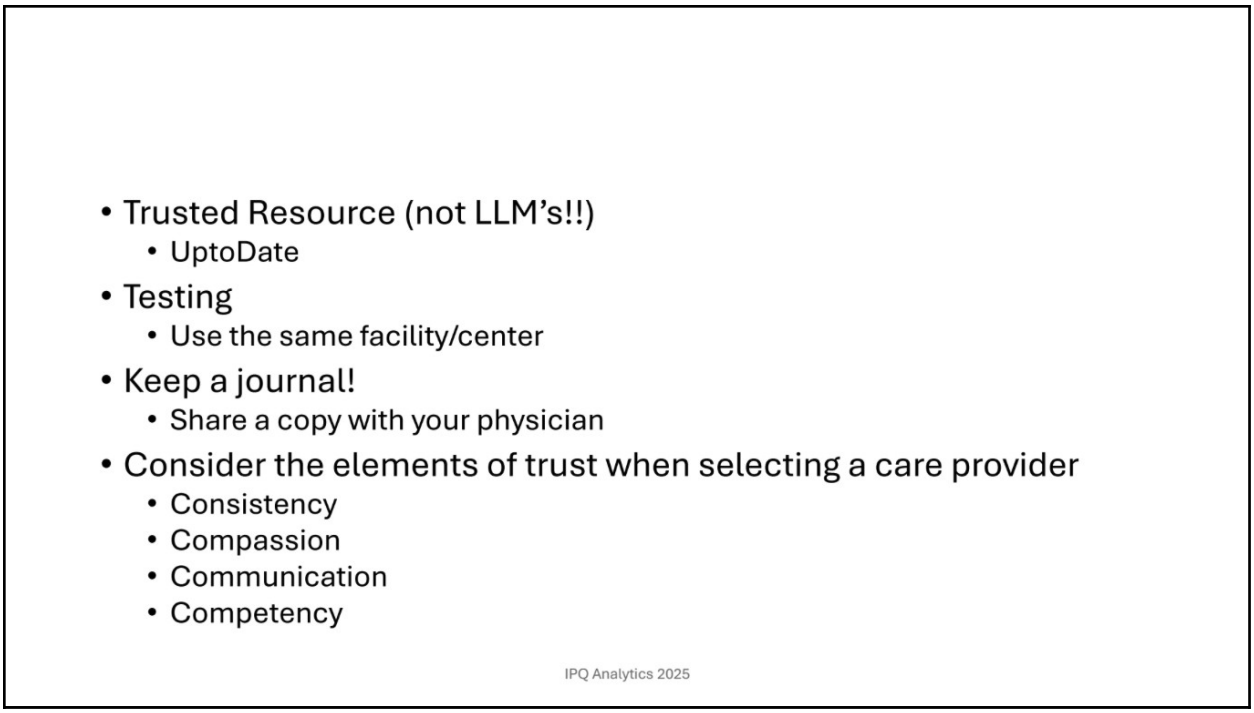

As I began with the issue of trust, we all need to have trusted resources instead of LLMs. Most of the physicians I've talked to use a reference called UpToDate. It's something you can access over the web. There is a subscription charge, but there's a lot of detail updated on a regular basis of high quality information, ranging from symptoms, treatments, epidemiology, risk factors, etc.

If you are having testing done, and this is, again, not clinical information, we recommend testing at the same facility or center so you can remove some of the variability that may occur because of differences in equipment maintenance and calibration. That's just a general recommendation based on our laboratory experience.

You should keep a journal on the computer, make notes of things you're observing or sensing, and share a copy with your physician. They may not have the opportunity to read it while you're there, but they're not going to be able to gather all the information that you either may or may not remember or won't have time to share with them during your visit. Giving them a copy of this gives them something they can refer back to or look at again, to enhance the communication with your physician.

In general, the elements of trust are probably critical. When you select a care provider, you would like consistency in how they manage your case and how they interact with you. You like compassion in that they're going to listen to what you have to say and communicate clearly with you. What are they telling you? Besides just some facts, are they communicating a degree of confidence or a degree of uncertainty so that you can make a better decision? And of course, behind all of that is what is their competency? How are they trained? How current are they on things going on in the field?

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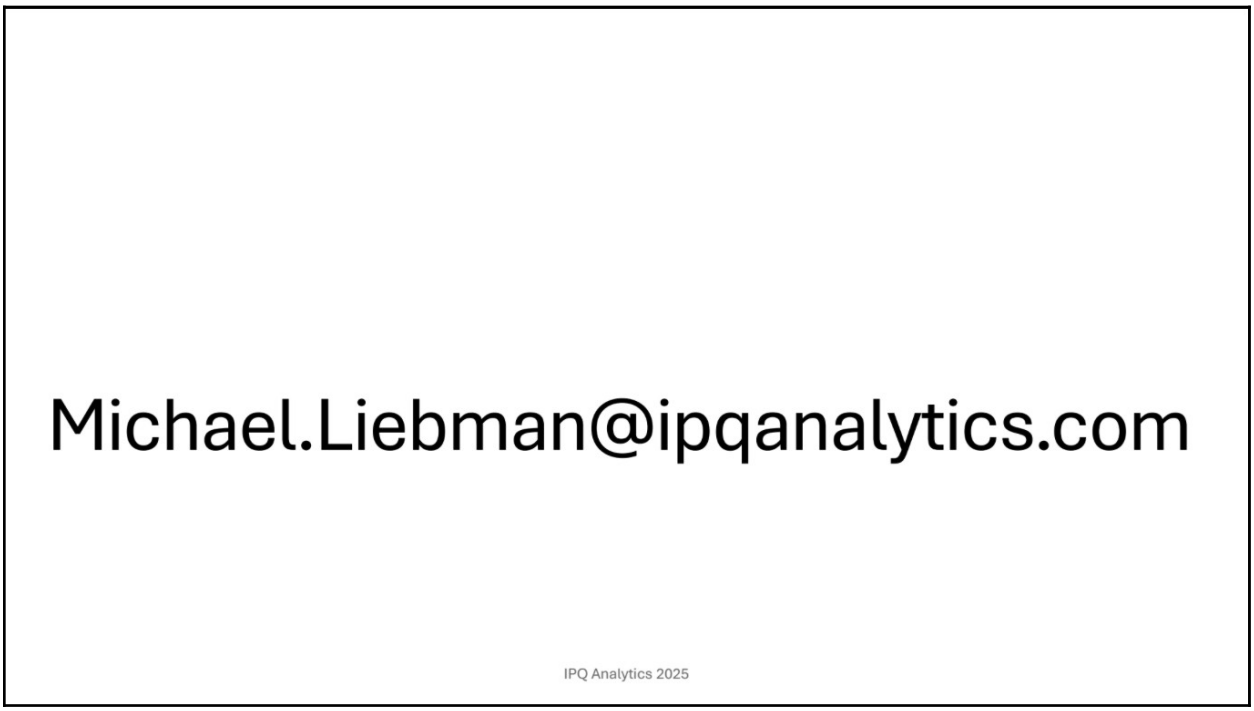

You don't want to be restricted to what they're asking. You'd like to be able to tell your story, because that's more important. For example, we're building models of how women go through menopause and have breast cancer risk. Well, they may see their gynecologist once every two years. There's no way they're going to be able to tell their gynecologist what's been going on over the course of two years. They may not even be able to tell them what happened this week. The gynecologist also wouldn't know what to do with that level of detail at that point in time. These journals are things I think that will become more prominent and more useful as time goes on, and deal with the pressure the physician has with their short visit.

David Plunkett 25:00
I want to add that communication does need to be a two-way process. It's not exactly a journal, but I keep a template, and it has a list of things I'm paying attention to. I print off a copy and hand it to my oncologist when I go in every six weeks. There are some topics for discussion and some things that are just me monitoring things that are ongoing. I am careful to ask each time, “this is what I've been paying attention to. Is there anything else I should be looking for or paying attention to?” Keeping that back and forth going is important. I hand them the sheet of paper and I keep it to one page so that they can refer to it in their own time, or throw it away or whatever. But we're not relying on me remembering to say something when I'm actually sitting in the chair, it helps to have the physical page to go by.

One sensitive area when it comes to trust is at the beginning of the whole process, when you're trying to select an oncologist, physician, or some part of the medical team. A lot of people are uncomfortable with the idea of offending their current doctors by asking for recommendations for second opinions. I've still not come up with any good guidance on how to go about getting a

second opinion without offending your current doctor. If I have to choose between one or another. “I've only just met these people, how do I make that decision?” It's awkward, and I haven't found any good guidance for that.

Michael Liebman 27:17
Let me give you two things on that. One is when working in breast cancer, we're dealing with triple negative breast cancer [*aka TNBC - an aggressive type of invasive breast cancer, source*] patients. The fundamental challenge is a patient who’s triple negative at one center may not be triple negative at another. Oncologists know that, and that is an example of a real problem. Treating triple negative patients is difficult. We look at clinicaltrials.gov and we see that the pharma companies don't seem to understand this key challenge, because they're developing drugs without actually evaluating the individual tests. Most of them are just looking for a diagnosis of triple negative breast cancer to recruit patients, and they’re getting heterogeneity in their patient populations. They could have drugs that work very well for subgroups, but they're not going to have identified them appropriately. That's one of the issues.

The other issue is when I ran the Breast Cancer Center, my counterpart was the Chief of Surgery of Walter Reed, a colonel, and part of my job was going down to him and explaining to him how to interact. I've learned over the years how to interact with patients, physicians, and that’s what I was explaining to him. I wasn't trying to challenge anything he does or by doing something incorrectly. I needed to know exactly what he did and what he felt comfortable with, what he felt confident with, and what he didn't feel comfortable or confident with, because that's where I could try to help. In this case, what you're saying to your physician in the beginning is “I'm really concerned about my diagnosis and my treatment, and I want to make sure I have the greatest confidence in everything”. That's why I would consider it necessary to always get a second opinion just to be able to have that confidence.

Mark Taylor 30:07
I can see two themes coming up. One is: “How does the medical world deal with subtleties in medical information, whether it's diagnosis of a triple negative breast cancer or seeing trends within the normal range?” And the second one is: people struggling to get time with their doctor to really discuss these subtleties.

I wonder if anyone's looking at a new model for medicine, where the role of the patient and the doctor is changed and augmented with a system to guide the treatment. I know it'll be a complicated process to switch, and I'm sure it will come eventually. I'm keen to know if anyone knows of any hospital or any startup that's looking at how you change the dynamic to handle these subtleties, and the lack of time for the doctors.

Michael Liebman 31:10
The issue is the lack of time, and I'm not proposing this is the best solution, but to some extent, this has been dealt with by concierge medicine. The idea that your physician is limiting their practice to a certain number of patients, and they're dedicating a certain amount of time to your case, and following your case much more closely. That's a bit of a reaction to this, because I've

seen physicians who've gone out of conventional practice into concierge. One of the reasons was they felt pressured and they didn't like the turnaround. I'm not saying it's the best solution, but it is something to consider.

The other thing we've dealt with in our breast cancer center was using things like nurse navigators, who help with translation. Frequently, the patient is not necessarily predisposed to understand everything the physician is saying. The physician, with limited time, may not know the best way to communicate to the patient what they really need to know to make sure the patient understands. The nurse navigator provides that bridge between the two so the right questions can get asked and the right points can get explained. That's one thing I know that has been beneficial, but I'm not sure how general it is in application. I'm sure there are other centers trying other models for healthcare as well.

Matthew DeAngelis 33:14
I'm a cancer patient and a cancer research advocate. I want to ask a question about patients driving their own care and biomarkers. I’m interested in your advice about what patients can and should do to drive their own care by asking their provider to do biomarker analysis on their samples, if available, or doing it themselves, if the patient wants to do it. How to translate that information into care decisions in the here and now, and how to refresh that over time, where the state of the art keeps changing. What my biomarkers tell me about my treatment options today might be different three months from now, or six months from now.

What can patients do to drive that on our end, to make sure you have the best info available and that you're making data-driven decisions about your care using the latest technology and results available?

Michael Liebman 34:13
There's a difference between using the latest technology available and using validated technology. I think the current incidents with President Biden is a good example where you have PSA [*Prostate-Specific Antigen testing, def*]. PSA is easily accessible to anyone who wants to have it tested, but the guidelines from the USPSTF (U.S. Preventive Services Task Force), for someone over 70, say it's not an effective measure because of the downside risk. That doesn't mean you shouldn't do it, or you can't do it, but it means is an evidence-based approach, the risk outweighs the benefit of having that kind of test.

That's why I pointed to UpToDate. UpToDate uses that kind of information and presents it to you so that you can see all the biomarkers being used, which ones have evidence in supporting them or constraints. I would always ask, “Is this biomarker something we should be measuring?” It may be that your physician isn't aware of it and there may be new information that could be of value. There should be nothing wrong with bringing it up with your physician.

In terms of doing it on your own, the variability among testing labs is a problem. That's why I pointed out that having testing done at the same center or the same site for consistency is valuable, because for most of biology and medicine, it benefits from looking at differences, not

absolute measures. If you have a mammogram done or a chest X ray at the same center all the time, they can look at that with much more confidence than if you had it done at three different centers over time. It's the same with lab tests.

Matthew DeAngelis 36:35
That's a dilemma for patients, because you mentioned getting second opinions. One barrier to getting a second opinion is if you've been treated at a certain center up until a certain point. You know that going outside, they're going to ask for all new tests, and you have that question of whether or not the data are comparable. It makes you wonder whether or not if they’re doing patient-centered testing. I've controlled my samples, I've controlled my data, wherever I go. I wanted to go to this lab to solve that problem. But we're not at all set up for patients, especially at the start of their journey, to handle things like that.

Any thoughts about where things are headed in that regard? Is that something you could foresee?

Michael Liebman 37:22
You should have control over your data or images and to be able to take them to another center. You should know that they may disagree with the way a test was run or have a different opinion. That's just something that you have to take into consideration as to whether you want to be retested, or not. But in terms of having control, that's one thing you should have access to all of that. Having it in a centralized resource that you can just tap into gets into all kinds of privacy and security issues that we haven't yet been able to deal with effectively.

Lea Ann Biafora 38:17
I am an oncology nurse of 35 years. Ben and I started a company 13 years ago to help cancer patients navigate all aspects of their journey, nationally and internationally. I appreciate when you said some key things that are so critical. Consistency is so critical. I really applaud you for bringing that up because I don't think enough people talk about it.

As far as second opinions, I just wanted to add when you're asking for second opinions, it's really better if you approach it a different way because often patients do not want to upset their physicians. One way we've approached this a little differently is saying “Well, you know, we'd like to explore different clinical trial options”, or, you know, just get a different perspective. The good physicians are the ones that want you to be an engaged patient. The old guard, like my grandparents, didn't want to ever question the physician. We have to really change that conversation and approach. This is your life and you have every right to ask the questions. It's not being disrespectful. It's taking control, being engaged, and looking for the right information. Each physician has their own bias, historical experiences and training. There's a lot of beauty in having different perspectives because there are such changes and differences in even the testing. Thank you for bringing those critical pieces up.

Roger Royse 40:42

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Rick Davis has a question for you: He says he's unclear on what services you provide. How is your modeling practically applied?

Michael Liebman 40:52
We have two activities. One is we build models of disease as a process, starting from the clinic and working back where we're focused on stratifying the disease and patient. It's a fundamental model. On the commercial side, we work with pharma and biotechs. We work with healthcare systems and physicians. We work with payers sometimes who want to know if certain tests are merited, or we work with government agencies and internationally. We're working in Mexico, Chile, Europe, Australia, and China.

On the nonprofit side, what we're undertaking is the same kind of approach, but focused primarily on women's health. The reason we're doing that is, not only is it an underserved area, but to remove the dependency on profit margin so that we could go into the level of depth we wanted without that being directed on what to do.

The two areas we work in are infant and maternal morbidity/mortality and hypertensive disorders of pregnancy, like preeclampsia. The other is we've been building a model of how women go through perimenopause and menopause. Uniquely, they don't all go through it the same way. They need to understand what those differences are and why they're different. Our model starts with puberty and looks at all the hormonal transitions and exposures over their lifetime and clinical history. That also means they have individualized risk for breast cancer or cardiovascular disease or osteoporosis, not just a general risk. What we're trying to do is move from correlation to causality in these models. The nonprofit side is purely that there are potential commercial uses, but we're doing it to try to enhance the public good in women's health and working with underserved populations as well.

Cindy Ness 43:41
I wanted to ask you about the area of lifestyle medicine / lifestyle management. It seems like you work at the systems level with organizations. Just wondering if you have any thoughts on or if you can comment on what you're seeing now. Are you seeing anything in terms of the view of where lifestyle fits into the picture, not as an alternative, but part of best practices? What do you think the appetite is in institutions for it at this point? There's a lot of observational research, not so much randomized controlled trial research. How is it thought of?

Michael Liebman 44:38
We are working with a group that does epigenetic measurements, and the reason we're doing that is our modeling is based on developmental changes and clinical history. With the epigenetics, we can also start to look at external, environmental exposures, lifestyle factors. We think it's an important thing that hasn't been addressed. It adds to the complexity. As I say to my clinical friends, you have to be operational. You have the short time to do the evaluation. You have to keep in mind the patient's needs, the guidelines, standard of care, reimbursement, all of these other factors. You don't have the time to do the research.

That's why we can try to approach the strategic side of what are the unknowns you're not dealing with? Are there ways we can complement what you need? That is how we drive what we're doing. We take on a lot of that complexity. I'm not going to tell you we have solved it by any means, but if we don't start to address it, we'll never get there. We're trying to introduce it, see what works, see what doesn't work, and then go to the next step. It's all critical. I always use this nutrition example: two people are sitting at the same table eating a cheese sandwich and an apple. They're not eating the same thing. The cheese is different. The bread is different. It was stored differently. The apple was shipped. You can't do a simple nutritional model. I mean, people do it, but in terms of the accuracy, you're not quite sure what you're leaving on the table that could be critical. This granularity is always going to be critical, but when it is going to be critical and could you miss it. That's what's taking away from your solution.

Cindy Ness 47:06
You're making the case that granularity, or what is now maybe being referred to as a more personalized kind of approach to maybe diagnosis and treatment, you're going to find that whether it's in the standard of care space / lifestyle, epigenetic kind of space. That's what you're advocating for.

Chris Apfel 47:39
Thank you for your presentation and your important work on HER2 expression. It has moved the field forward. But HER2 has different expression degrees, so the classification positive or negative is really a question of where you set the norm and the border.

I wanted to get back to the reliability of test results, because most lab tests are now run in a CLIA-certified lab. In 1988 there was a Clinical Laboratory Improvement Amendments Act because of the challenges on reproducibility. Now, if you have your hemoglobin, calcium, or whatever test taken that is highly controlled, highly standardized. There are a lot of checks and balances in place to make sure these lab results are valid. In principle, those results are highly valid. I would like to stress that the second there are, of course, things like CA 125, where the results are really lab dependent and where the norm values are and there is individual calibration to be done. If you want to follow this up, it should be done in the same lab, but that's usually noted in for those specific markers. I want to emphasize that so the group doesn't feel that if you get a test result at one institution, it will very likely be different at another institution. I hope you agree on that.

Michael Liebman 49:24
I agree with that in general. There's the potential, especially with imaging and some of these other modalities that the instruments are calibrated differently. In addition, while you are talking about a cut point for like triple negative, when I first was working on the test, that was the way it was done. Now we have not positive and negative. We have low HER2, and we have ultra low HER2, we don't even have cut points and the challenge is it is 1% that's negative. Or is it 10%? While the measurement may be done similarly, different institutions use different thresholds. What we've done in our research is we don't use the thresholds at all. We use the direct lab values, and have found staging to be very different from what's being done right now.

Chris Apfel 50:27
There is a problem when you measure something in a biological system that there is some variability. When I'm thinking of prostate biopsies, and you look at the inter-rater variability in these corner cases, there is significant variability from pathologists to pathologists looking at the same slides. We are talking here about humans. Humans are very complex biological systems, not only biological, but also many other dimensions to it.

Michael Liebman 50:59
We're just trying to make that transparent.

Chris Apfel 51:03
The other comment I want to make is on second opinions. I saw Rick Davis’s comment, and I wanted, in principle, to emphasize that one should not be afraid to ask for second opinions. There is good literature on it that a second opinion often leads to better outcomes, and often can be associated with a less aggressive approach that is associated with better outcomes. One should always consider a second opinion. The way to phrase it in my mind is to say, “I'm really nervous about this. What you're saying to me makes sense, but I would love to see whether there are also other perspectives on it and therefore, is there anybody you would recommend if you wear my shoes to seek out for a second opinion.” Usually somebody who is professional should react accordingly, and if that person doesn't react accordingly, you are better off looking for somebody else.

You mentioned UpToDate as an important source. You also mentioned evidence-based medicine, PSA testing, and Joe Biden's diagnosis. What is going on with prostate screening is tragic - the PSA testing has been not recommended by societal guidelines for a certain period of time and led to the so-called progression of diseases that are now diagnosed often at a later stage.

Now the challenge with a PSA is its low sensitivity and specificity, and the low area under the rock curve that has historically led to a lot of unnecessary biopsies and a lot of uncertainties that have their own significant medical complications. There is a rational argument against PSA. But the problem is there are other score blood tests that are better. There is a PHI score. There is a something called, I think, T4 score that has higher sensitivity and specificity, and nobody talks about it. That's number one, number two, we also know a prostate MRI has very similar sensitivity and specificity to a biopsy to identify high grade, clinically relevant prostate cancers. Nobody talks about this.

When I'm thinking of looking up-to-date, I consider what is validated and evidence based? I would like to comment that a lot of what is up-to-date and evidence based is from a health economic perspective, i.e. what insurance companies or the society is willing to pay for it, and it gives you a good average therapy. If you want to have superior care or superior screening, you have to go beyond - up-to-date is not sufficient. Here we have Roger Roy's example, who got his Gradle test then his prenova test, and therefore his pancreatic cancer was detected early. I

spoke yesterday with somebody who had a prenovo test and now has kidney cancer that wasn't there four years ago. Nobody recommends in the medical society or up-to-date to have cancer screening for many cancers at the age of 60/65 that are usually not screened for. Many patients are ultimately dying due to this. Up-to-date is good for standard of care, but if you want superior care, if you want to be proactive.

Michael Liebman 55:15
I was promoting UpToDate versus LLMs because there's always going to be something new that's not up-to-date. There are a lot of comments about UpToDate, but LLMs don't have any real control. The ease of accessing them when patients have concerns and want some very quick answers. That's where a more reputable source, like UpToDate, will be much better to base something on.

Chris Apfel 56:02
On the LLMs, I would like to push back on that a little bit. The LLM has the advantage that you can talk to it and you can ask it questions. First, it's much harder to read, for a lay person, to read up-to-date.

Number two, there are differences. We know that the challenges with ChatGPT is the hallucination, etc. You can go to Perplexity, and Perplexity will give you good sources and provide you with the references. You should check out Perplexity. It's pretty amazing.

Michael Liebman 56:42
For most cancer patients, they don't know the difference and the nuances between the different LLMs. They use what they hear about, and what you hear about most is ChatGPT. That is a more general issue. I did comment that if you curate your own research papers, then the LLMs can be very useful, but you have to curate them.

Roger Royse 57:24
Any closing comments you'd like to make, Michael?

Michael Liebman 57:36
Physicians are dealing with this the best they can in a very complex domain. Researchers don't understand it. There needs to be even better communication between physicians and researchers. I have spent 12 years in academics where, this is a bit of my bias, there's excellent research being done in academia, but most of it is not really directed at the clinical problems that exist. It's assuming it will have clinical relevance, but not necessarily understanding what the actual clinical problems are.

Invariably, when I've interacted with clinicians and first ask them what their questions are. After some time, I find those are the surface questions, but they're not the real issues that frequently need to be addressed. They don't always ask them because they don't think they have a way to solve them, or the time to address them, or if there is a way to address them. Better

communication is also critical not just with the patient, but with clinicians and researchers, to help move medicine ahead.

If anyone wants to reach out with other questions or for more details, please feel free to contact me on my email, Michael.Liebman@IPQanalytics.com.

“Making Decisions in the Complexity of Healthcare” (Michael Liebman, PhD) [#144]

CHAT DISCUSSION

00:43:08 Rick Davis: I'm unclear what services IPQ provides. How is your modelling practically applied?
00:44:07 Mark Taylor: Hi, I don’t know how to raise my hand
00:44:09 Mark Taylor: I have a question
00:44:22 ari akerstein: Replying to "I have a question"

Hit “react” you’ll see it there
00:45:26 Lea Ann Biafora: raising hand because I cannot find the emoji.
00:48:33 Rick Davis: AnCan refers to docs largely at Centers of Excellence who display the 4 C's Dr.Liebman identified.
00:48:55 Rick Davis: Support Groups can and do do the same thing as nurse navigators.
00:54:44 Dr. Chris Apfel: I'd like to comment on
Second opinions
Reliability of test results.
UpToDate & PSA screening recommendations.
00:56:14 Rick Davis: Any doc who is offended by a 2nd opinion request should be canned! That's our opinion at AnCan.
01:00:09 allen morris: Comment: Interlaboratory variability is mitigated by a regimented requirement of proficiency testing - such as offered by API (American Proficiency Institute) and (vetted) controls on every run.
01:04:57 David Plunkett: "The difference between theory and practice is that in theory there is no difference, but in practice there is."
01:07:34 Roger Royse: fyi that has not been my experience. I get labs every six months and I go to two different labs (because I don't trust a single lab any more than I would trust just one doctor) and I almost always get different values for many markers
01:08:24 Lea Ann Biafora: Reacted to "fyi that has not bee..." with 👍
01:10:22 Rick Davis: We talk about these tests on AnCan PCa support groups - regularly
01:11:31 Rick Davis: If you believe the reports, Biden did not get screened for 10 years. That's the issue right there. The guidelines are at fault.
01:12:53 Rick Davis: Also the docs who were serving Biden. He had risk factors that warranted screening. ND he was no Average Joe (excuse the pun). He should have been tested. Maybe he was???
01:13:50 Dr. Chris Apfel: Reacted to ""The difference betw..." with 👍
01:13:55 Mark Taylor: Reacted to "fyi that has not bee..." with 👍

“Making Decisions in the Complexity of Healthcare” (Michael Liebman, PhD) [#144]

ARTICLES RECOMMENDED BY MICHAEL LIEBMAN

Many Top Cancer Centers Produce Misleading Ads, Study Suggests - Cancer Therapy Advisor

https://www.cancertherapyadvisor.com/news/top-cancer-centers-misleading-ads/?utm_source=eloqua&utm_medium=email&utm_campaign=NWLTR_CTA_UPDT_SS_SPON_DAILY_Zynyz_547907_052225&hmemail=UZYD2IrJDKt9j7932L7VYTsPPgVGptww6I0Dn796%2BuI%3D&sha256email=1b0560f89075975dcfc4876c60e5a9d28c07531dd37133ffae73f7c547fa15d5&hmsubid=&nid=&elqtrack=True

May 21, 2025
Many direct-to-consumer television advertisements produced by leading US cancer centers are either ethically ambiguous or transgress established ethical standards for advertising, according to research published in the Journal of Cancer Policy.
“The results of our study suggest a concerning pattern in cancer center advertising, particularly among top-ranked institutions, and highlight the need for promulgating and further encouraging adherence to ethical standards in marketing cancer care,” the researchers wrote.
To examine how well top cancer centers in the US comply with standards for TV ads, the researchers identified the top 20 cancer care providers, as ranked by US News and World Report for 2024-2025. The team reviewed ads released by these care providers between 2019 and 2024.

There were 31 TV ads from 12 institutions that addressed cancer care specifically. The researchers analyzed these ads, comparing them to guideline recommendations from 4 sources. Ads were divided into 3 categories:

- Compliant: Ads that did not contain any obvious breach of the guidelines
- Borderline: Ads that included claims that did not obviously transgress the guidelines but had the potential to be misinterpreted in ways the guidelines warn against
- Transgressive: Ads that explicitly violated at least 1 of the guidelines.

Sixteen ads (52%) either transgressed at least 1 of the standards for ethical advertising (29%) or were deemed borderline cases (23%). Four (33%) of the 12 institutions did not produce any ads that violated the ethical guidelines. Eight of the nine ads categorized as transgressive were produced by institutions that were ranked among the top 10 providers.

Looking at the ways in which the advertisements were transgressive, the researchers found that 4 ads (13%) failed to clearly set out the eligibility criteria for novel treatments. Four ads (13%) implied that innovative therapies were accessible only at the institute in question, without clarifying the target cancer or demographic.

The researchers also noted that 11 ads (36%) “ fostered unrealistic expectations through broadly positive — but irrelevant to patients’ informational needs — claims about the institution or overreliance on patient testimonials without specifying typical patient outcomes.”

The researchers suggested the transgressions could be related to the marketing leadership within institutions being unaware of the guidelines or them being “poorly incentivized to learn about the guidelines.” Additionally, the organizations that developed the guidelines may have “inadequately promulgated them,” among other potential explanations.

“These findings underscore the delicate balance between providing necessary information to patients and avoiding potentially misleading marketing practices,” the researchers wrote. “As cancer care continues to advance and treatment options become more complex, ensuring ethical advertising practices is becoming increasingly crucial for supporting informed patient decision-making and maintaining public trust in health care institutions.”

Disclosures: There was no funding listed for this study, and the study authors reported no conflicts of interest. Please see the original reference for disclosure information.

Baldassarre AJ, Palmer A. Marketing cancer care: A content analysis of ethical compliance in television advertising by top-ranked U.S. cancer centers. J Cancer Policy. Published online May 10, 2025. doi:10.1016/j.jcpo.2025.100591

“Making Decisions in the Complexity of Healthcare” (Michael Liebman, PhD) [#144]

The Trouble With 'Do Your Own Research' for Drugs
— An excerpt from Avorn's book, Rethinking Medications

https://www.medpagetoday.com/opinion/second-opinions/115722?xid=nl_mpt_DHE_2025-05-22&mh=a18fcab4af5a00488091b32c0c05695e&zdee=gAAAAABm4vYYT230h_77FRr0E931sGQigyILE91cN4gwqAbIZVoXh_74Qg6Vt11vjVL7eFB_YbhrO8jgdYk7ZDY5Zh2PNCs1lfS-STQhMr4N-nPVCUQ1iYBK4h6aTSxP0n6Gjcp_khLH&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily%20Headlines%20Evening%20-%20Randomized%202025-05-22&utm_term=NL_Daily_DHE_dual-gmail-definition

Ideally, the approval of a new drug should be exclusively the province of science, but for a more than half-trillion-dollar-a-year industry, it couldn't possibly remain so. The same libertarian posture of the earlier twentieth century -- the spirit that opposed government's right to require accurate drug labeling and prevent toxicity -- lives on in the insistence by some advocates on the far right that the government shouldn't even be in the business of determining whether a drug works or not. Physicians and patients could determine which drugs work best and which don't, their argument goes, through decisions reflecting their individual clinical experiences. This is such a bad idea that it's hard to know where to start in debunking it. Here are some basics: Some of the detailed data the FDA receives from a drug's manufacturer is considered the company's private property and is kept secret, so any outside reviewer isn't playing with a full deck.

Furthermore, evaluating the results of a clinical trial can be tricky:

- Were the study groups truly comparable at the start of the trial?
- Were the randomization and blinding done appropriately?
- What statistical methods were used to compare outcomes?
- If the differences were statistically significant, were they also large enough to be clinically meaningful?
- Were the patients studied comparable to people a doctor is treating or (as often occurs) healthier and younger?
- If the comparison drug was a placebo, how does the new drug stack up against all the evidence on other relevant treatment choices out there (perhaps including nondrug options) that weren't in the trial?

Beyond all that, the issue of selective publication of favorable results has bedeviled all of us who look to the peer-reviewed medical literature to guide our decisions about how well drugs work, a problem several researchers have documented. A worrisome analysis of this issue was published in the New England Journal of Medicine by Erick Turner, MD, a psychiatrist who had spent several years at the FDA reviewing new drug applications. While there, he noticed that the more favorable studies that crossed his desk were more likely to end up being published in medical journals than the less favorable ones. Once he left the agency, he and his colleagues followed up on the concern that drugmakers who sponsor studies have in the past published the

results they liked and spent far less effort to get non-favorable trial findings into the medical literature. Turner et al. reviewed the raw data on 74 clinical trials submitted to the FDA evaluating 12 different antidepressants and found that almost a third of them had never been published. Virtually all those that depicted favorable outcomes made it into medical journals; but of the studies with negative or questionable results, nearly all were never published, or appeared with a positive spin on the results.

How are we clinicians or our patients supposed to independently rethink these approval decisions, if the totality of the evidence never sees the light of day? Put differently, Turner's study found that if you looked at the then-extant medical literature you'd find that 94% of published trials of antidepressants found the drugs were effective; by contrast, only about half of all the original studies submitted to the FDA showed the medications worked.
In response to problems like these, reforms were passed in 2007 to require public disclosure of plans for all clinical trials before they are launched. The less good news is that disclosure of their results is still far from complete.

Still, many libertarians argue that Americans should be able to "do their own research" to decide which drugs work and which don't. But going over the terabytes of data the FDA receives for a new drug submission takes large teams of smart, dedicated, specialized scientists months to get right. Over many years, we've found how hard it is to do this work well in our educational outreach programs when we try to synthesize such data to guide doctors toward better prescribing decisions. So how could it make sense to let individual freedom decide what drugs are available for use? Surely no responsible government scientist would advocate for that, right?

One odd presentation of this anti-big government perspective was offered in an op-ed in the Wall Street Journal that argued for an approach in which the FDA wouldn't assess the effectiveness of new drugs. Instead, the author proposed, the agency should just make sure new products aren't terribly unsafe and then release them to the magic of the marketplace, so doctors and patients could figure out which ones work and which don't. Efficacy could be tested later in post-market studies.

That strange op-ed was written by Andrew von Eschenbach, MD, appointed by George W. Bush as FDA commissioner in 2005. While at the FDA, von Eschenbach, whose clinical expertise was as a prostate surgeon, prolonged the agency's yearslong refusal to approve greater access to the morning-after contraceptive pill despite its proven safety and effectiveness. Apparently, he felt there are some issues the marketplace shouldn't be allowed to decide on its own.
The same motif of laissez-faire, caveat emptor has inspired a nationwide "right to try" movement for unapproved medications, pursued aggressively in several states by conservative legislators seeking to enable patients to take unproven drugs. But this is a solution to a problem that doesn't really exist. For many years, to avoid being in the middle of this unwinnable debate, the FDA has allowed any physician to ask a company for access to an investigational drug that hasn't been approved by the FDA. The agency itself approves about 99% of such requests; when there is an access problem, it's usually the company that resists making the product

available. But if a drug hasn't been determined to work, should such liberated patients expect their health insurer, or a government program, to pay for it? And if there is a dangerous side effect, would they expect society to cover the costs of caring for those consequences as well? When my colleagues and I wrote a paper for the New England Journal of Medicine about this issue, we used a common term to describe the policy: "compassionate use." The editors wisely made us change that to "expanded access," pointing out that there's not necessarily anything compassionate about helping people take an untested drug that may not work and could hurt them.

Jerry Avorn, MD, is a professor of medicine at Harvard Medical School in Boston. He is the author of Rethinking Medications: Truth, Power, and the Drugs You Take, from which this piece was excerpted.