“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]

Brad Power and Nanthana Ravichandran
September 3, 2025

“We want to make precision oncology equitable. We want to make it scalable. And we want to make it as impactful as we can today, across the globe. We don't want to wait for future drugs or future technologies. Those will come, and those will be absolutely vital. The patients I'm seeing are getting younger and younger. We're not talking about, or we shouldn't be talking about, 5-year survival anymore. We need to be talking about 20-year survival. The opportunity and the data that we have at our fingertips gives us a massive opportunity, a massive public health opportunity, to scale precision oncology right now.” – Padman Vamadevan, MD

“When I look at the healthcare system within this realm of oncology, what you notice is a vast underutilization of the Pharmacopeia (the list of drugs and the ways they can be used). It comes to pharmacology, where, on average, these small molecules affect a dozen relevant cellular pathways, but due to financial reasons, they will never get FDA approval… It's a systemic failure in the system the way the system is structured. It’s the same thing with these genomic reports, which are vastly underutilized.” – Travis Christofferson

Meeting Summary

Many advanced cancer patients and their loved ones seek more than the "standard of care" - the generally accepted testing and treatment guidelines. They want personalized, evidence-based treatment plans that reflect the unique biology of their cancer, their values, and their goals. They may be exploring beyond conventional protocols but lack the scientific expertise or time to evaluate which interventions are best evidenced to target the potential drivers of their disease or what these drivers could potentially be. There is a huge amount of scientific research available, but very little of it is applied to individual patients. With 100,000s of cancer research papers published, it is impossible for any doctor to keep up, no matter how experienced, much less a patient or caregiver.

Padman Vamadevan, MD, and Travis Christofferson, MS, are uniquely qualified to lead a conversation about personalizing treatment plans to an individual patient. Padman is Co-Founder and Chief Medical Officer at Astron Health, and Travis is Chief Scientific Officer. Astron Health acts as a personal cancer research team, using advanced bioinformatics, bespoke machine learning, and best-in-class scientific experts to make sense of this research and apply it to each patient’s case. Padman Vamadevan read for a degree in Natural Sciences from Queens’ College, Cambridge, then obtained his medical degree from King’s College, London, and subsequently trained in Academic Clinical Pharmacology. Over the past decade, he has focused on streamlining pathways to personalized cancer treatments by integrating cutting-edge molecular approaches at the intersection of Clinical Pharmacology, Metabolic Oncology, and Precision Theranostics. A recognized thought leader in the strategic use of repurposed drugs as adjunctive cancer treatments, Dr Vamadevan leverages complex molecular data and the latest peer-reviewed research to develop precision therapies that target each patient’s unique cancer profile. Travis Christofferson is a leading figure and thought leader in modern oncology and the author of "Curable, Ketones: The Fourth Fuel", and "Tripping Over the Truth". He earned a bachelor's degree in molecular biology from Montana State University's Honors College and a master's in material engineering and science from the South Dakota School of Mines and Technology. As a former full-time science writer and founder of the Foundation for Metabolic Cancer Therapies, Travis brings extensive expertise to Astron's research initiatives.

Why can personalizing your cancer treatment be better than following the "standard of care"?

- Cancer is highly heterogeneous, meaning your tumor has unique molecular characteristics, specific mutations, and molecular pathways driving your cancer.
- “Standard of care” treatments are often generalized and may not target the specific vulnerabilities of your cancer.
- You can explore targeted interventions beyond traditional chemotherapy, or using existing drugs in more strategic, personalized ways, potentially improving treatment effectiveness and reducing unnecessary toxicity.

What are the key tests to enable personalized treatment?

- A pan-cancer panel of 50-150 genes (genomics DNA sequencing)
- RNA sequencing (transcriptomics)
- Proteomics or at minimum immunohistochemistry (including tests like PDL1)

How can your data be translated into a personalized treatment strategy?

- Use a large language model trained on peer-reviewed papers with your specific genetic mutations and medical profile to identify potential treatments (Extract meaningful drug-gene and pathway associations (using “named entity recognition”, a technique for identifying data types, organizing them, and making associations
- Prioritize interventions based on scientific evidence, mechanistic plausibility, individual patient context, and safety
- Manually curate AI-generated recommendations by scientific experts
- Provide a data-driven treatment hypothesis ranked by strength and supported by references

Can you use ChatGPT or other AI engines for finding promising treatments?

A customized AI-system can address the problem of personalization in cancer care. For example, Astron’s model looks in depth at:

- **Information sources**: Should you use peer-reviewed cancer research papers, guidelines, or a general knowledge base?
- **Weighting**: Your scoring approach should consider literature quality, mechanistic plausibility, disease context, and safety.

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- **Expert review**: You should have human experts review and validate the AI-generated recommendations.
- **Treatment scope**: Do you want to consider standard cancer drugs, non-cancer drugs, off-label uses of cancer drugs, nutraceuticals, and lifestyle modifications?

Other AI tools may not have the specificity and guardrails required to flag safe and well-evidenced interventions specific to your case.

How can you keep current with the latest research?

- Continuously scan and process new research papers
- Consider study design quality, clinical validation, disease specificity
- Have experts who understand cancer complexity and can critically evaluate new research review and curate the data

How can you access personalized cancer treatment services?

- Get comprehensive molecular testing (a pan-cancer panel of 50-150 genes, full RNA sequencing, and if possible, proteomics or immunohistochemistry)
- Work with your current doctor or find a doctor willing to refer you to help order the treatment strategy report, interpret it, and potentially implement the recommendations
- ; the current cost of a research report is approximately $1,150 in the US; they will review your molecular testing reports and provide a personalized research report with potential treatment strategies.

How can you learn more about personalizing your cancer treatment?

- Be proactive in discussing molecular profiling and potential targeted treatments with your medical team; consult with doctors who are open to integrative and precision medicine approaches
- Explore services that provide detailed molecular analysis and personalized treatment recommendations (for example, contact Astron Health through their website to book a free consultation)
- Stay informed about the latest research in precision oncology
- Read the meeting summaries or watch the video recordings of conversations we have had with other providers of personalized treatment services:
    - “Matching Patients with Treatments” (Istvan Petak, MD, PhD) [#107]
    - “Integrating Diverse Test Results for Cancer Patient Guidance” (Joe Lennerz, MD, PhD, MSc) [#142]
    - “How AI Is Shifting the Dynamics of Your Next Doctor Visit” (Ezra Cohen, MD) [#121]
    - "Personalized Drug Dosing" (Paul Van Camp and Jeff Krolick) [#68]
    - "Clinical Guidance from Proteomics" (Sheeno Thyparambil) [#26]
    - "Proteomics and Clinical Decisions" (Panel Discussion) [#19]
    - “Multi-omic Analysis Guides the Decisions of Brian McCloskey” (Rana McKay, MD, and BostonGene) [#98]

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Meeting Notes

KEYWORDS

Precision oncology, molecular profiling, personalized treatment, bioinformatics platform, drug repurposing, synthetic lethality, longitudinal data, empirical outcomes, clinical trials, patient-centric, integrative oncology, molecular tumor board, data-driven, public health impact, therapeutic interventions.

SPEAKERS

Padman Vamadevan (61%), Travis Christofferson (20%), Brad Power (12%), Richard Anders (6%), Will LaValley (1%), Raphael Leong (<1%)

CHAT CONTRIBUTORS

Russ Hollyer, Rick Davis, Allen Morris, Helen, Richard Anders, Alexander Lalov, Raphael Leong

SUMMARY

Padman Vamadevan and Travis Christofferson from Astron Health discussed their precision oncology approach. They highlighted the limitations of conventional oncological treatments and the potential of personalized molecular profiling. Astron Health's platform uses bioinformatics and large language models to analyze raw molecular data, creating personalized low-toxicity intervention plans. They emphasized the importance of empirical data and longitudinal studies. A case study on colon cancer demonstrated their methodology, using repurposed drugs like celecoxib and caffeine. The service costs £950 in the UK and $1,150 in the US, aiming to make precision oncology accessible and scalable.

Access

- Clinicians are the key decision-makers, as Astron Health sells exclusively through clinicians in the US.
- Patients can request their physicians to use Astron Health's services.
- If a patient's physician is not willing to refer, Astron Health can work with the patient to refer them to one of their partner clinicians.

Cost

- The cost to patients in the US is currently $1,150.
- In the UK, the cost is 950 pounds.
- As the report generation becomes more automated, the cost to patients is expected to decrease significantly.
- They hope to semi-automate the process so that it becomes a clinician-level function, with the cost attributable to the clinician and patients receiving the report as a bonus of working with that clinician.

Competition

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- ChatGPT was mentioned as a potential alternative for analyzing genetic mutations and suggesting treatments.
- Astron Health differentiates itself by having a bespoke LLM trained on over 100,000 peer-reviewed papers and a weighted evidence system.
- They claim their approach is more comprehensive and safer than using ChatGPT, which could potentially suggest harmful treatments.

Objections

- Some conventional oncologists may be reluctant to prescribe repurposed drugs because it's outside their wheelhouse.
- The complexity of the data and the need for frequent testing might be overwhelming for some clinicians.
- Regulatory considerations were mentioned as a reason for selling exclusively through clinicians in the US.

Need

- Conventional oncological treatment options sometimes fall short.
- There's a huge technological overhang that clinical medicine struggles to keep up with.
- Most molecular testing reports end at a diagnostic stage, not providing clear, actionable treatment strategies.
- Precision oncology has historically been viewed as expensive, inaccessible, and often inefficient.

Questions

- How does Astron Health manage the complexity of all the omics data and treatment recommendations?
- How does Astron Health's approach compare to using ChatGPT or other AI engines for finding promising studies?
- What types of molecular testing does Astron Health recommend (e.g., WGS, WES, proteomics, RNA)?
- How does Astron Health keep its data current with new research?

OUTLINE

Introductions, Overview of Astron Health and Personalized Treatment

- Padman Vamadevan from London and Travis Christofferson from Lake Placid, New York, co-founders of Astron Health, discussed precision oncology and services provided by Astron Health.
- The new paradigm uses molecular profiling to develop personalized treatment strategies.
- There are limitations of conventional oncological treatments and a need for personalized approaches.

Challenges in Precision Oncology

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- The challenges in precision oncology include the vast amount of research data and the need for personalized treatment protocols.
- A bioinformatics platform is needed to translate raw molecular data into personalized treatment strategies.
- Precision oncology should be accessible and efficient for all cancer patients, with a focus on interventions that are already available and being prescribed safely.

Case Study and Methodology

- Travis Christofferson presented a sample case report from a patient with colon cancer.
- He explained the methodology used to identify valuable targets and drug repurposing strategies, for example, the use of myricetin to inhibit MEK1 and MEK2, and caffeine as a direct inhibitor of PIK3CA.

Clinical Trials and Data Integration

- The current process uses manual curation with a goal of automating the bioinformatics pipeline.
- Longitudinal data collection is important.
- There are challenges in managing complex data.

Challenges, Conclusions, and Future Directions

- There are cost, accessibility, and effectiveness issues in getting personalized services.
- The goal is to make precision oncology equitable and scalable.
- Existing drugs are underutilized.
- There is a need for a more comprehensive approach to cancer treatment.

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TRANSCRIPT

Brad Power
This is the Cancer Patient Lab.

We’re honored to have with us Padman Vamadevan, who's in London, and Travis Christofferson, who is in Lake Placid, New York, although he's normally in Colorado. They're going to be leading a discussion with us about their approach to precision oncology and some of their services.

This webinar is for information purposes only and not medical advice. We try to arm our patients and caregivers with information they can take to their medical team. We are nonprofit 501(c)(3), and we depend on the kindness of people who make donations to bring you services like this webinar. You can do that very easily on our website, where there's a prominent donate button.

Padman Vamadevan 1:13


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Transforming Molecular Complexity into Clinical Clarity

Presentation - Cancer Patient Lab (3/Sep/2025)

Thank you so much for inviting us here today, Brad and to all of you for showing up. My name's Dr. Padman Vamadevan. I'm the co-founder and Chief Medical Officer here at Astron Health, based in London. Although we have a very cross Atlantic team, I'm here together with my co-founder, Travis Christofferson, and also one of our founder associates, Raphael Leong. Today, we just wanted to introduce you to a new paradigm that we believe could fundamentally enhance the way that clinicians can use molecular profiling to develop robust, personalized treatment strategies for patients like yourselves.

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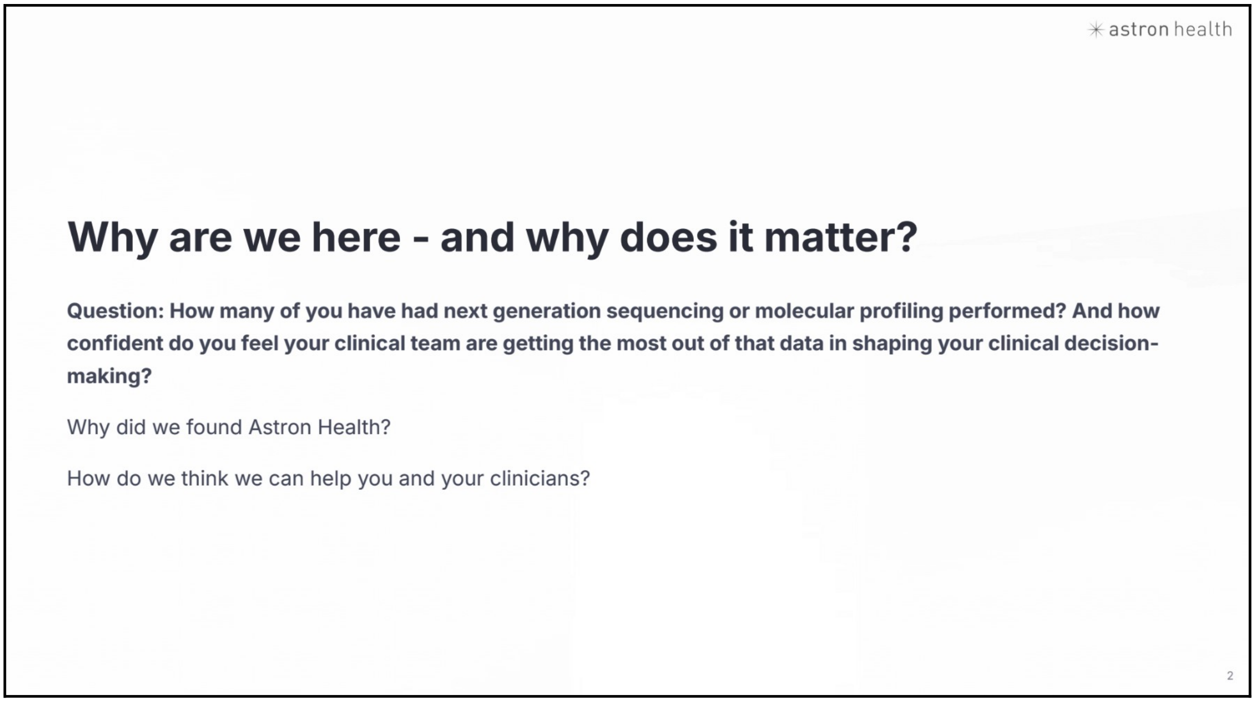

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Why are we here - and why does it matter?

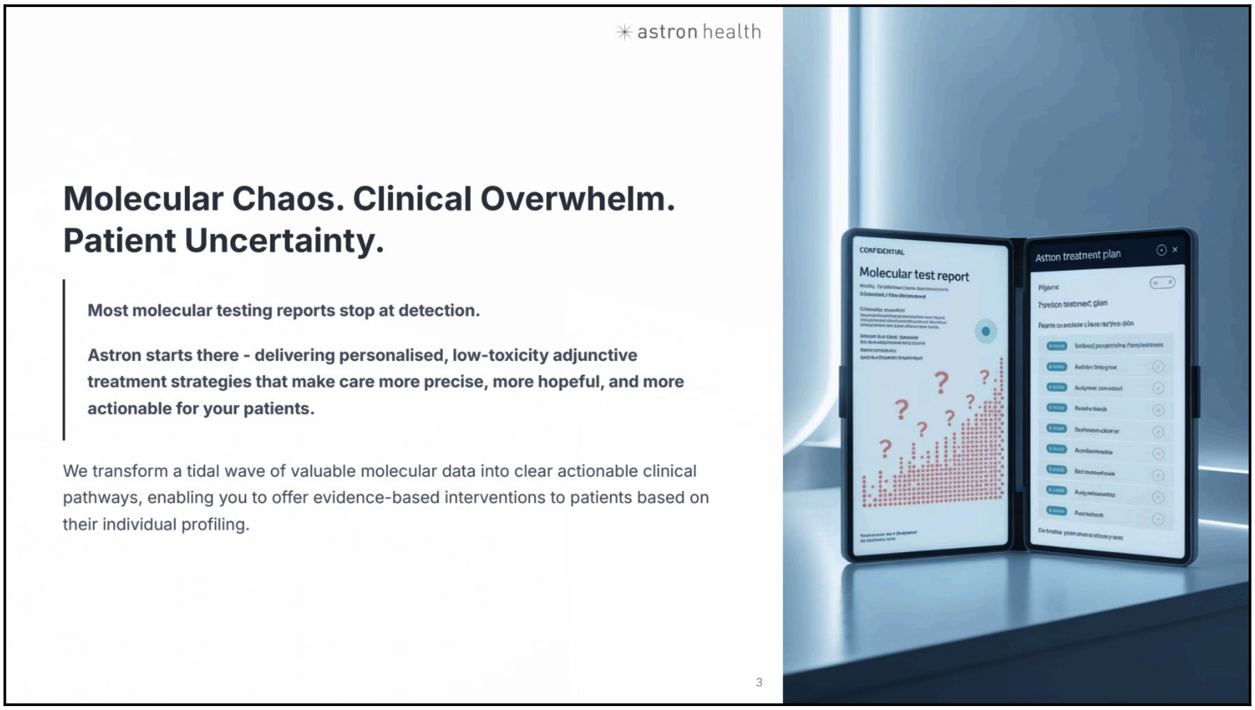
Question: How many of you have had next generation sequencing or molecular profiling performed? And how confident do you feel your clinical team are getting the most out of that data in shaping your clinical decision-making?

Why did we found Astron Health?

How do we think we can help you and your clinicians?

Having watched a few of the Cancer Patient Lab videos, I think they are a phenomenal source of education for patients and clinicians and scientists alike. We know that patients like you understand the complexity and heterogeneity of cancer. As you know, conventional oncological treatment options can sometimes fall short, and the reason we built Astron was to try and give each patient and each doctor the confidence that they are doing absolutely everything possible to personalize cancer treatment based on molecular science.

Before Astron, we spent over a decade together at a biotech that worked trying to develop real world clinical studies looking at the potential of drug repurposing as adjunctive treatments in cancer. So very much in addition to standard of care, sometimes we saw the power of these approaches, but we also saw their limits when they were used generically. Some patients did better than expected, but unfortunately, too many plateaued, too many relapsed, and so often we felt that we were treating the disease using over generalized principles, rather than targeting the specific vulnerabilities of that individual patient's cancer. And an example of this was a study that we published in 2019 in glioblastoma multiforme, where the top line was that in 96 patients, the median survival of those patients was almost double expected. But unfortunately, when we looked a little bit deeper at the patient cohort that was driven by about 40% of extreme responders, we really were unsatisfied with that. We wanted to do more for the other 60% and we thought that the thing that we were missing was the personalization of our approach. We were using the same standardized adjunctive protocol for every single patient, and some were benefiting and others weren't. And trying to translate that overhang where we were trying to sort of match all the research data that was out there into personalized treatment protocols was something that we just couldn't keep up with. There are thousands of studies being published every year, hundreds of molecular vulnerabilities in each tumor type. We're barely scratching the surface and that's why we built a strong bioinformatics platform powered by large language models that becomes your personal cancer research team. It's designed to be built for patients and their clinicians. Clinicians need data, they need transparency, they need clarity, and they need all of that in real time whilst you're in the consulting room with them, and that's what we try to offer.



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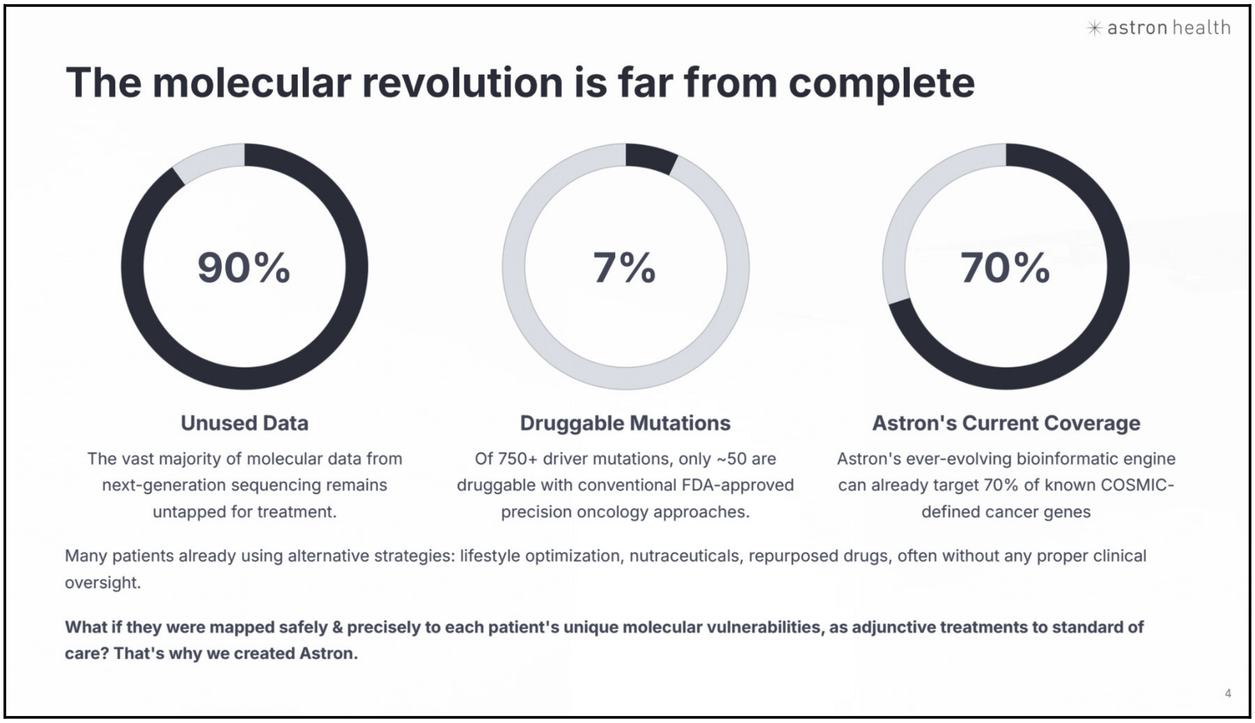
Molecular Chaos. Clinical Overwhelm. Patient Uncertainty.

> **Most molecular testing reports stop at detection.**
>
> **Astron starts there - delivering personalised, low-toxicity adjunctive treatment strategies that make care more precise, more hopeful, and more actionable for your patients.**

We transform a tidal wave of valuable molecular data into clear actionable clinical pathways, enabling you to offer evidence-based interventions to patients based on their individual profiling.

In terms of the core of the problem, we as a society have invested heavily in molecular testing in cancer over the last decade. A lot of the talks that you've done at CPL have been around groups doing phenomenal work to improve outcomes and really sort of amazing solutions. I saw the call you did with Laura Towart and the team given last week, but unfortunately, with the core molecular testing that often appears in the consulting room, most of that testing in terms of the report ends at a diagnostic stage. The report gets printed. It tells the doctor and the patient what mutations might be present, what genes might be over expressed. It might list a few FDA approved drug options or clinical trials that may or may not be available in your geography, and that's it. It's really not uncommon for a next generation sequencing report to be brushed over in a clinical consultation, because there just isn't the clarity or the optionality or the time to do the research to enable that clinician to actually do anything about it. There's a huge technological overhang which I think that clinical medicine struggles to keep up with, and that's really where we begin. We try to take the tidal wave of raw molecular data, DNA, RNA proteomics, microbiomics, immunomics, everything to try and translate into a clear, curated treatment strategy based on the breadth of available peer reviewed data. The platform is built to do one thing, to turn all of those nuggets of raw molecular data into personalized low toxicity intervention plans that clinicians can use today for their patients. The other part of the problem in precision oncology in my opinion is that it historically has been viewed as expensive, inaccessible and often inefficient, and I appreciate that lots of you are patients who are trying to solve the riddle of their own disease at an N equals one level in real time. But it's also important to take a step back, and it's pertinent to remember that many cancer patients globally have no evidence for testing or precision oncology interventions at all. They never even get to the starting line. And so for us, I think our priority is to try and change that baseline for everyone, and to do so at scale. And to do that, we've really tried to hone and focus our approach on what we can do today using interventions that are already available and being prescribed safely. We're just trying to do it smarter and more precisely.



The molecular revolution is far from complete

Unused Data

The vast majority of molecular data from next-generation sequencing remains untapped for treatment.

Druggable Mutations

Of 750+ driver mutations, only ~50 are druggable with conventional FDA-approved precision oncology approaches.

Astron's Current Coverage

Astron's ever-evolving bioinformatic engine can already target 70% of known COSMIC-defined cancer genes

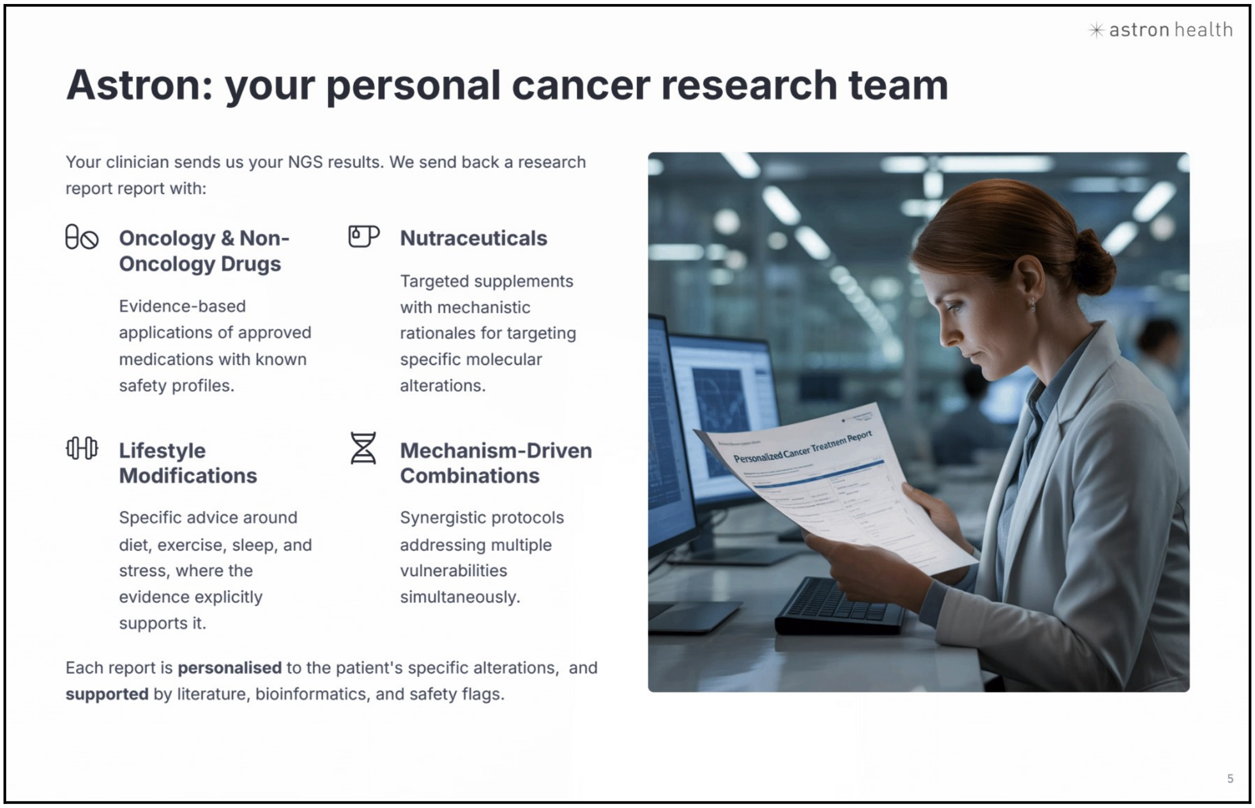
Many patients already using alternative strategies: lifestyle optimization, nutraceuticals, repurposed drugs, often without any proper clinical oversight.

What if they were mapped safely & precisely to each patient's unique molecular vulnerabilities, as adjunctive treatments to standard of care? That's why we created Astron.

We have made huge strides in understanding cancer genomics and molecular variations. There are not more than 750 identified cancer driving mutations, as defined by cosmic but unfortunately, only around 50 to 53 are currently druggable with FDA approved cancer therapies, and that's the core problem with precision oncology today, our ability to test far out paces, our ability to act creating a new precision drug takes somewhere between 10 and 15 years and costs somewhere between $1 and $4 billion and drug companies want to de-risk their R&D by creating drugs that hit molecular targets that are high ticket, and yet, there is a vast body of literature pointing us to ways to modulate many of the currently undruggable mutations using already available therapeutics. The data is there. It might not be there in the format that people need to see it. It's scattered across hundreds of 1000s of publications. There is a massive paucity of empirical outcome data.

The other part I wanted to address is that there is a lot of information out there in groups, curated by groups without full understanding of the scientific process, and that attracts patients, often to take anything and everything that has any putative anti cancer activity, and this can be really risky. I see this every day, patients taking different things. It's not the way to build evidence or credibility around these approaches. So we've built a strength to absorb the complexity, synthesize the research, and return something that clinicians can use in real time in the consulting room. Our approach is already moving the needle.Our bioinformatic approach can hit around 70% of cosmic defined cancer genes to some extent, and that will only improve as the database scales and more research is published.

Padman Vamadevan 9:19



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Astron: your personal cancer research team

Your clinician sends us your NGS results. We send back a research report report with:

Oncology & Non-Oncology Drugs

Evidence-based applications of approved medications with known safety profiles.

Nutraceuticals

Targeted supplements with mechanistic rationales for targeting specific molecular alterations.

Lifestyle Modifications

Specific advice around diet, exercise, sleep, and stress, where the evidence explicitly supports it.

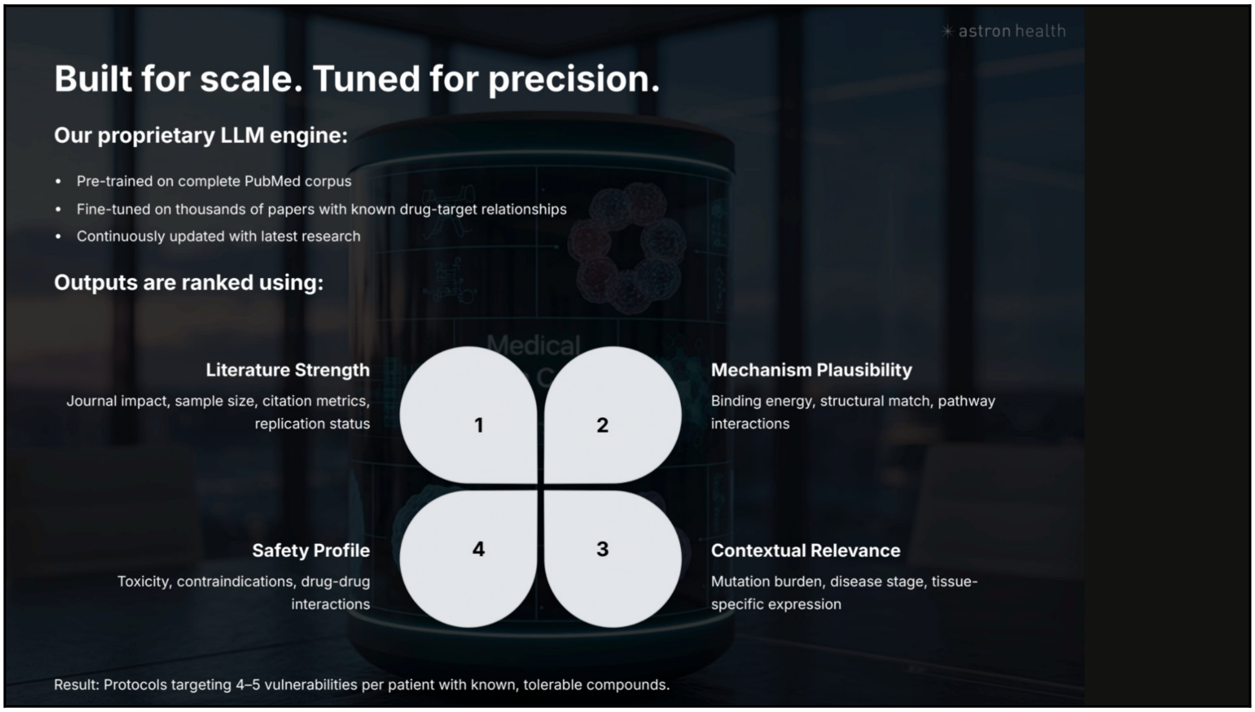
Mechanism-Driven Combinations

Synergistic protocols addressing multiple vulnerabilities simultaneously.

Each report is **personalised** to the patient's specific alterations, and **supported** by literature, bioinformatics, and safety flags.

We are trying to build this platform in a practical way as we can plug into every clinician's workflow seamlessly. We want to be seen as a research partner. We're not a testing company. We are not the end prescribers. We're not trying to take anyone's place here. We're just trying to do the research that some of you were doing some of your clinicians could do if they had a spare 30 hours per patient to do it. And we're trying to do it in a really data driven, focused, robust way for each patient. So once we receive a patient's NGS report, we can run a deep analysis using our AI powered engine. It's not a black box, it's a transparent literature supported by a mechanistically scored recommendation engine, and the outputs are then manually curated by our scientific team thereafter. Within five to seven days of analysis, we deliver a research report to your medical team that prioritizes interventions based on the strength of the scientific evidence, the mechanistic plausibility, the disease context, the tissue, the stage, the mutational burden, the drug safety profile, tolerability, and known interactions. We don't just give people a list of molecules. We give doctors a treatment hypothesis, ranked by strength, supported by references contextualized to the individual's case. And the key to this is that we're really extending the breadth of interventions that we're exploring. We're looking across all drugs including oncology drugs, non oncology drugs, nutraceuticals, lifestyle modifications and anything that has data in a cancer setting. We are trying to really democratize access to precision oncology by being broad about this, so our methodology doesn't depend on inventing new drugs, but rather matching existing therapeutics intelligently to each patient's specific molecular vulnerabilities. In short, the challenge isn’t about pursuing niche science upfront which is that treating each cancer on an individual basis comes with immense difficulty and extremely high costs.

What we're really trying to do is to deliver public health impact at a global scale using technologies and therapeutics that are available now. I'm also going to brush over this one



Built for scale. Tuned for precision.

Our proprietary LLM engine:

- Pre-trained on complete PubMed corpus
- Fine-tuned on thousands of papers with known drug-target relationships
- Continuously updated with latest research

Outputs are ranked using:

1. **Literature Strength** — Journal impact, sample size, citation metrics, replication status
2. **Mechanism Plausibility** — Binding energy, structural match, pathway interactions
3. **Contextual Relevance** — Mutation burden, disease stage, tissue-specific expression
4. **Safety Profile** — Toxicity, contraindications, drug-drug interactions

Result: Protocols targeting 4–5 vulnerabilities per patient with known, tolerable compounds.

and I am also going to brush over this one.

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Why this works — and why now

1

Academic Partnerships

Collaborating in process with the largest surgical cancer unit in Europe to validate clinical outcomes in post-resection MRD-positive colorectal ca. Running translational outcome studies is vital to gathering the empirical data to optimise our algorithms and reach more patients.

2

Superior Coverage

Already matching >70% of driver mutations to actionable targets when conventional approaches cover only 6-10%.

3

Reduced Cost of Multi-Omic Testing & Universal Compatibility

NGS testing is becoming affordable - even when patients are paying out of pocket. In addition, the availability and maturity of computational tools and existing bioinformatic databases has accelerated our ability to act now. Works with Tempus, Boston Gene, Guardant, Caris, Datar, Foundation One and other leading NGS platforms.

Low-friction workflow:

- Initial onboarding call
- Secure data upload
- Comprehensive report in ~5-7 business days
- Full clinical support throughout

Example Case Report

GENE	TARGET TYPE	COMPOUND	REFERENCES
TP53 R273H	SL: CDK2	Lovastatin, Aspirin	1 2 3
TP53 R273H	Downstream inhibition	Metformin	1 2 3
NRAS	**SL: MEK1/2**	**Ursolic acid, Myricetin**	**1 2 3 4**
HMGB1	Downregulation	Ethyl Pyruvate, Glycyrrhizin, Guggulsterone, Chloroquine	1 2 3 4 5
ARID1A	SL: PIK3CA	Metformin, Caffeine	1
ARID1A	SL: EZH2	Simvastatin	1 2 3
ARID1A	SL: ATM/ATR	Caffeine	1 2
ARID1A	SL: PLK1	Scutellaria baicalensis	1 2
ARID1A	SL: AURKA	Hesperidin	1 2
ARID1A	SL: HDACs	Valproic Acid	1
APC	SL: Topoisomerase Poisons	EGCG	1 2
APC	SL: RAC1	Lipophilic Statins	1
PIK3CA	SL: PTGS2	Celecoxib	1

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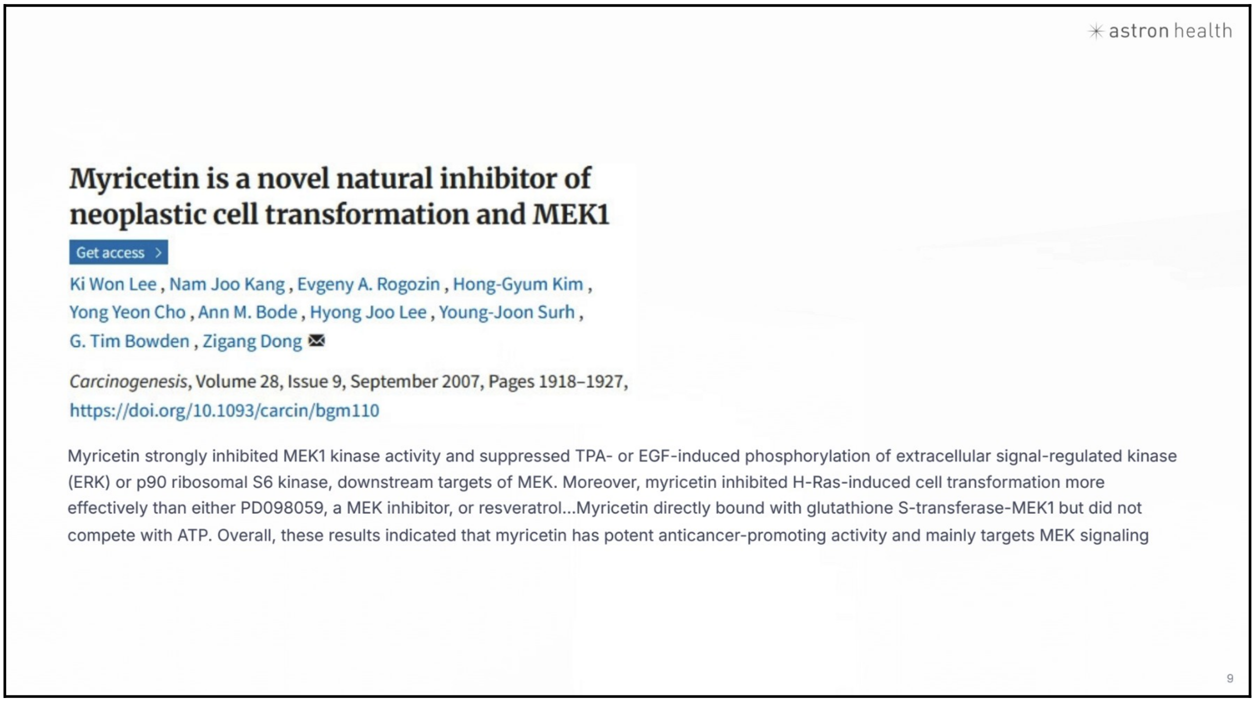
Travis Christofferson 11:50
This is a sample case report from a redacted patient with colon cancer. The genomic reports with this patient came from Tempest. I am going to give you an example of our methodology and as you can see on the left hand side, those are the gene mutations within this patient's cancer. We then identify, using a hierarchy of data, the most valuable target presented with each of these mutations from bioinformatic sources. We then expand that to drug repurposing and find compounds that will inhibit that target. We use a number of strategies you can see in the target type and go with down regulation of upregulated genes. We go with direct inhibition of activated oncogenes, or we use this concept known as synthetic lethality in which a mutated cancer cell particularly in tumor suppressors will rely on a compensatory pathway, and so if you target that compensatory pathway, it results in a non viable state for the cancer cell, where the healthy cell is fine because it doesn't have the mutations.

From the report, you can see this patient has an NRAS mutation, which forms a synthetically lethal relationship with MEK1/2.



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Myricetin is a novel natural inhibitor of neoplastic cell transformation and MEK1

Get access >

Ki Won Lee , Nam Joo Kang , Evgeny A. Rogozin , Hong-Gyum Kim , Yong Yeon Cho , Ann M. Bode , Hyong Joo Lee , Young-Joon Surh , G. Tim Bowden , Zigang Dong

Carcinogenesis, Volume 28, Issue 9, September 2007, Pages 1918–1927, https://doi.org/10.1093/carcin/bgm110

Myricetin strongly inhibited MEK1 kinase activity and suppressed TPA- or EGF-induced phosphorylation of extracellular signal-regulated kinase (ERK) or p90 ribosomal S6 kinase, downstream targets of MEK. Moreover, myricetin inhibited H-Ras-induced cell transformation more effectively than either PD098059, a MEK inhibitor, or resveratrol...Myricetin directly bound with glutathione S-transferase-MEK1 but did not compete with ATP. Overall, these results indicated that myricetin has potent anticancer-promoting activity and mainly targets MEK signaling

When you go to the bioinformatic drug databases, you can see that this natural product, Myricetin, is a strong inhibitor of MEK1/2, and it's been shown in lots of in vitro and animal studies to have anti-cancer activity. In this particular case, we're looking for direct, specific targeting of MEK, which does as good as the chemical compounds that you buy to be inhibitors of MEK1/2.

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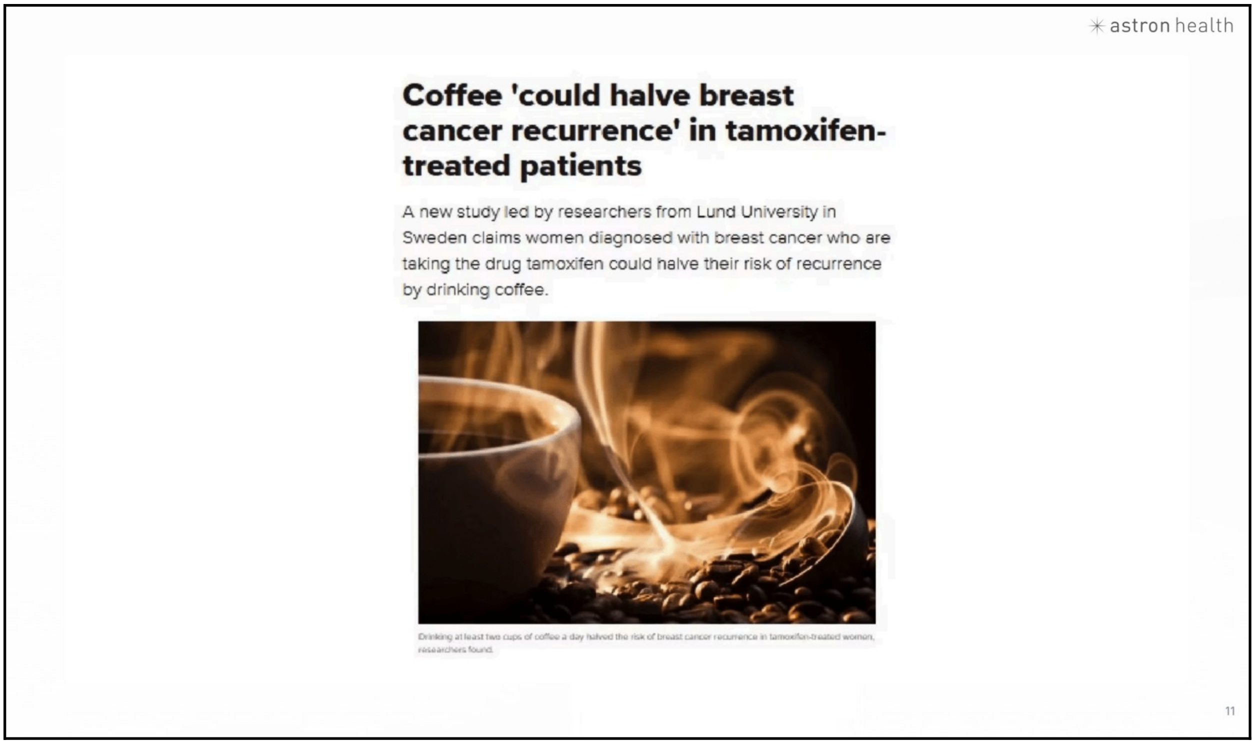
Example Case Report

GENE	TARGET TYPE	COMPOUND	REFERENCES
TP53 R273H	SL: CDK2	Lovastatin, Aspirin	1 2 3
TP53 R273H	Downstream inhibition	Metformin	1 2 3
NRAS	SL: MEK1/2	Ursolic acid, Myricetin	1 2 3 4
HMGB1	Downregulation	Ethyl Pyruvate, Glycyrrhizin, Guggulsterone, Chloroquine	1 2 3 4 5
ARID1A	**SL: PIK3CA**	**Metformin, Caffeine**	1
ARID1A	SL: EZH2	Simvastatin	1 2 3
ARID1A	**SL: ATM/ATR**	**Caffeine**	1 2
ARID1A	SL: PLK1	Scutellaria baicalensis	1 2
ARID1A	SL: AURKA	Hesperidin	1 2
ARID1A	SL: HDACs	Valproic Acid	1
APC	SL: Topoisomerase Poisons	EGCG	1 2
APC	SL: RAC1	Lipophilic Statins	1
PIK3CA	SL: PTGS2	Celecoxib	1

We see a relationship with PIK3CA, a very commonly mutated gene and cancer in general. For about 15% colorectal cancer, you have two options with Metformin, a downstream inhibitor. Caffeine is a direct and good inhibitor of PIK3CA and in the drug databases, caffeine is highly pleiotropic, and it's been known since the 70s. It inhibits ATM/ATR DNA repair genes and has been known as a radio sensitizer for a long time.

“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]

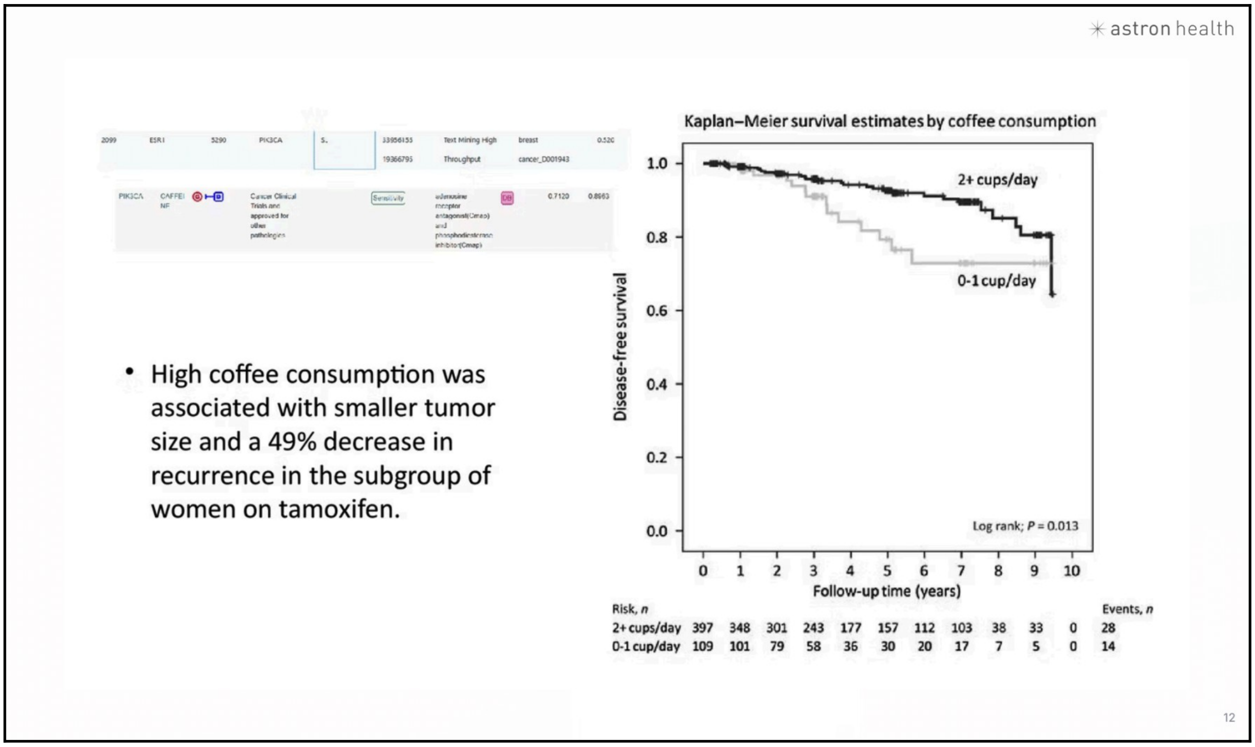


Coffee 'could halve breast cancer recurrence' in tamoxifen-treated patients

A new study led by researchers from Lund University in Sweden claims women diagnosed with breast cancer who are taking the drug tamoxifen could halve their risk of recurrence by drinking coffee.

Drinking at least two cups of coffee a day halved the risk of breast cancer recurrence in tamoxifen-treated women, researchers found.

To understand whether there's a strong relationship between PIK3CA inhibition and Estrogen Receptor (ER) inhibition in breast cancer, this presents a really good synthetic lethal relationship, so we wondered if there was any clinical data on that which really speaks to the predictive power of this approach. Around 2015, a headline published that coffee consumption could reduce the risk of recurrence in a certain subset of breast cancer patients by half.



2099	ESR1	5290	PIK3CA	S.	33956155 19366795	Text Mining High Throughput	breast cancer_D001943	0.520

PIK3CA	CAFFEINE	Cancer Clinical Trials and approved for other pathologies	Sensitivity	adenosine receptor antagonist(Cmap) and phosphodiesterase inhibitor(Cmap)	DB	0.7120	0.8963

- High coffee consumption was associated with smaller tumor size and a 49% decrease in recurrence in the subgroup of women on tamoxifen.

Kaplan–Meier survival estimates by coffee consumption

Risk, *n*	0	1	2	3	4	5	6	7	8	9	10	Events, *n*
2+ cups/day	397	348	301	243	177	157	112	103	38	33	0	28
0-1 cup/day	109	101	79	58	36	30	20	17	7	5	0	14

“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]

This data is coming from a study in Sweden on over 1000 women, and the question they were asking was, what is the impact of coffee consumption? They didn't have any mechanistic insight, because people are always curious about coffee consumption because it's so ubiquitous. The study initially found no response, but when they broke out this subgroup of the ER positive women on Tamoxifen. When they inhibit estrogen receptor and PIK3CA with caffeine, there is a dramatic reduction in recurrence and death. It is just a validation related to a clinical sort of study, that would suggest it is due to this mechanistic relationship.

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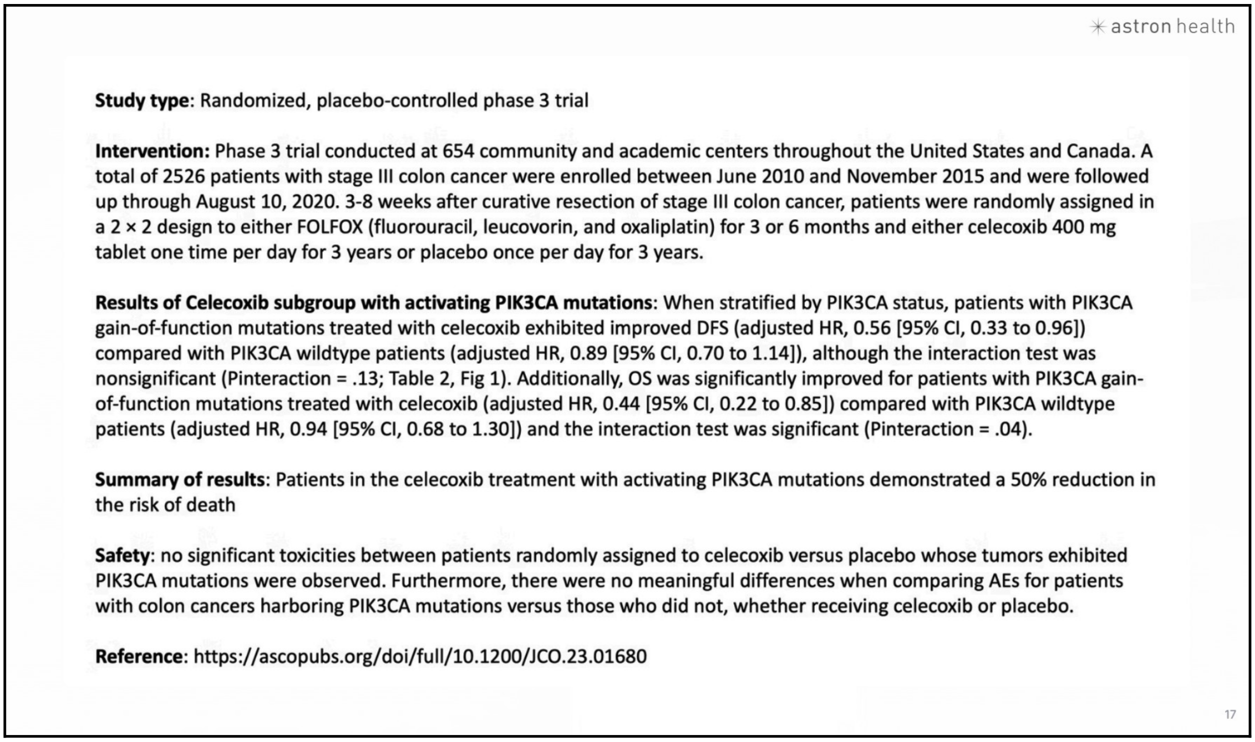
Example Case Report

GENE	TARGET TYPE	COMPOUND	REFERENCES
TP53 R273H	SL: CDK2	Lovastatin, Aspirin	1 2 3
TP53 R273H	Downstream inhibition	Metformin	1 2 3
NRAS	SL: MEK1/2	Ursolic acid, Myricetin	1 2 3 4
HMGB1	Downregulation	Ethyl Pyruvate, Glycyrrhizin, Guggulsterone, Chloroquine	1 2 3 4 5
ARID1A	SL: PIK3CA	Metformin, Caffeine	1
ARID1A	SL: EZH2	Simvastatin	1 2 3
ARID1A	SL: ATM/ATR	Caffeine	1 2
ARID1A	SL: PLK1	Scutellaria baicalensis	1 2
ARID1A	SL: AURKA	Hesperidin	1 2
ARID1A	SL: HDACs	Valproic Acid	1
APC	SL: Topoisomerase Poisons	EGCG	1 2
APC	SL: RAC1	Lipophilic Statins	1
PIK3CA	**SL: PTGS2**	**Celecoxib**	**1**

This is a relationship between PIK3CA and a gene called PTGS2 encoding COX-2. COX2 is the very famous inflammatory enzyme that all the NSAT drugs target like Ibuprofen, aspirin and so forth, and celecoxib falls in that class of NSAT. This is higher tier evidence that clinicians don't have access to.

“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]



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Study type: Randomized, placebo-controlled phase 3 trial

Intervention: Phase 3 trial conducted at 654 community and academic centers throughout the United States and Canada. A total of 2526 patients with stage III colon cancer were enrolled between June 2010 and November 2015 and were followed up through August 10, 2020. 3-8 weeks after curative resection of stage III colon cancer, patients were randomly assigned in a 2 × 2 design to either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) for 3 or 6 months and either celecoxib 400 mg tablet one time per day for 3 years or placebo once per day for 3 years.

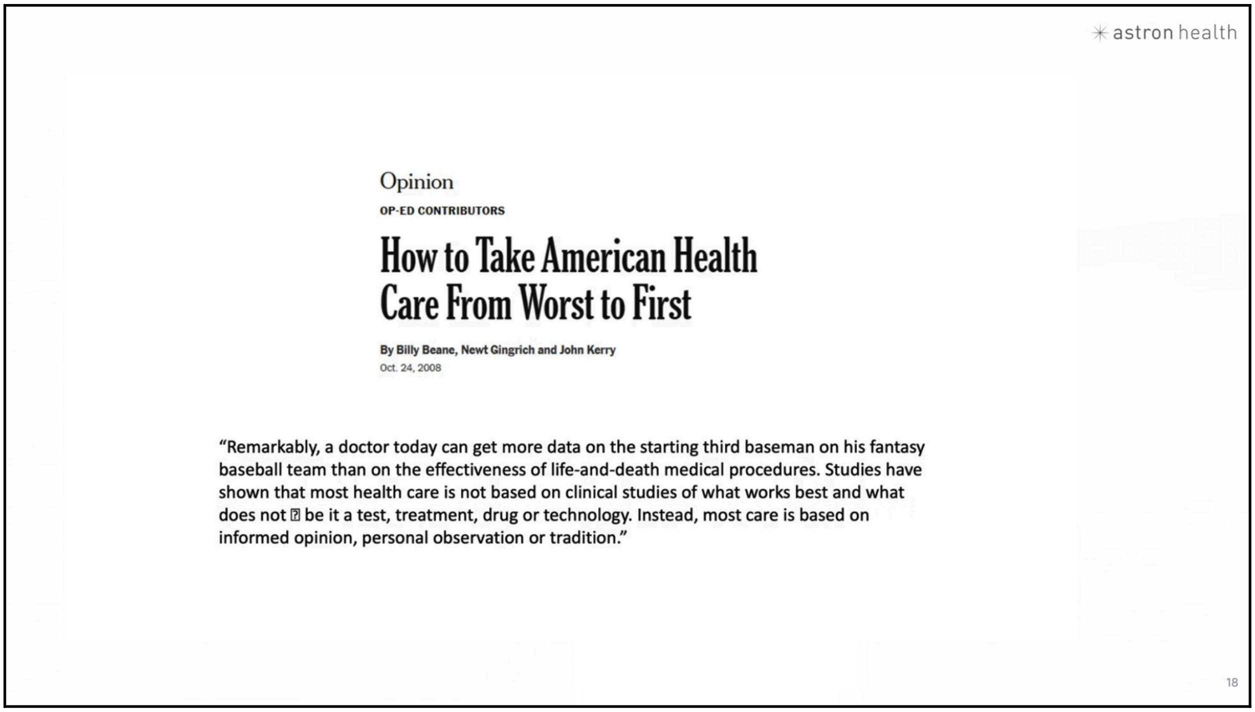
Results of Celecoxib subgroup with activating PIK3CA mutations: When stratified by PIK3CA status, patients with PIK3CA gain-of-function mutations treated with celecoxib exhibited improved DFS (adjusted HR, 0.56 [95% CI, 0.33 to 0.96]) compared with PIK3CA wildtype patients (adjusted HR, 0.89 [95% CI, 0.70 to 1.14]), although the interaction test was nonsignificant (Pinteraction = .13; Table 2, Fig 1). Additionally, OS was significantly improved for patients with PIK3CA gain-of-function mutations treated with celecoxib (adjusted HR, 0.44 [95% CI, 0.22 to 0.85]) compared with PIK3CA wildtype patients (adjusted HR, 0.94 [95% CI, 0.68 to 1.30]) and the interaction test was significant (Pinteraction = .04).

Summary of results: Patients in the celecoxib treatment with activating PIK3CA mutations demonstrated a 50% reduction in the risk of death

Safety: no significant toxicities between patients randomly assigned to celecoxib versus placebo whose tumors exhibited PIK3CA mutations were observed. Furthermore, there were no meaningful differences when comparing AEs for patients with colon cancers harboring PIK3CA mutations versus those who did not, whether receiving celecoxib or placebo.

Reference: https://ascopubs.org/doi/full/10.1200/JCO.23.01680

There was a study done for PIK3CA mutation which is a recent study involving a randomized placebo, controlled phase three trial. This was a huge study done at 654 community centers and hospitals over 2000 patients. The study was done in people with stage three colon cancer that had surgical resection followed by chemotherapy and were split into two groups. One received the standard of care, the other received standard of care in addition to Celecoxib. When they broke out the patients with PIK3CA mutations, they demonstrated a 50% reduction in death. So, when you look at this through the lens that we look through with the risk reward, if that adjunctive drug was adding a significant amount of toxicity, then you question whether the data has the veracity enough to go forward. However, there weren't any significant toxicities and adverse events from introducing it. So, it's a very safe thing. Through that lens of risk reward, we think patients and doctors should have access to this type of data.



Opinion

OP-ED CONTRIBUTORS

How to Take American Health Care From Worst to First

By Billy Beane, Newt Gingrich and John Kerry
Oct. 24, 2008

“Remarkably, a doctor today can get more data on the starting third baseman on his fantasy baseball team than on the effectiveness of life-and-death medical procedures. Studies have shown that most health care is not based on clinical studies of what works best and what does not ⍰ be it a test, treatment, drug or technology. Instead, most care is based on informed opinion, personal observation or tradition.”

This is to emphasize the problem that we are trying to solve. This is an article The New York Times from 2008 written by Billy Beane, Newt Gingrich, and John Kerry. Billy Beane is the manager for the Oakland A's. I don't know how many of you have seen the movie Moneyball, but what he did there was take a complete data approach to player selection. They had the second smallest budget in the league at the time, three times less than the New York Yankees, but they were able to take the team to win the championship, not the World Series, but their league championship. The way they did that was just simply sifting through data to see what was undervalued, what people were missing. And that's exactly what we're trying to do. The quote from that article that I'll leave you with, remarkably, a doctor today can get more data on the starting third basement of his fantasy baseball team than the effectiveness of life and death medical procedures. Studies have shown that most health care is not based on clinical studies of what works and what does not. It's not a test treatment, drug or technology. Instead, most care is based on informed opinion, personal observation or tradition. Most people give hippocrates know the Hippocratic Oath first does no harm. But the first quote from Hippocrates was, a doctor's judgment matters more than any external measurement, and that sort of ethos has carried through medicine, where doctors are viewed as sovereign entities upon their own. We've reached a time today where there's just too much complexity and too much being missed in the realm of data. And that's the void that we hope to fill.

Brad Power 20:18
From Russ in the chat: Have you seen this? There is a link to cell.com It looked like a nice genetic analysis using STAMPEDE as a basis. STAMPEDE being a clinical trial.

Padman Vamadevan 20:37

STAMPEDE is an interesting one because there was an arm of STAMPEDE, where they used Metformin as an adjunct. They use Metformin and recognize that Enzalutamide was going to cause all metabolic dysfunction and raise glucose and insulin. It was interesting in the slides that they talked about Metformin in an anti cancer as an anti cancer drug, as well as a metabolic optimizer for those patients. I'm not completely up to date with STAMPEDE, but when I last checked and looked at the subgroup analysis of that particular strata of the STAMPEDE, they didn't show a particular effect of just Metformin. When we look at some of the studies that are being done with Celecoxib, it was actually a Natera sponsored trial, which was a subgroup analysis of they were using signatera as an early detection tool. There was a study in colorectal cancer looking at all comers not stratifying by PIK3CA mutation.They found that adjuvant Celecoxib had no impact on overall outcomes at all. I've had lots of patients that have come to me taking Celecoxib, and their oncologist has said, there's no benefit for this at all. Here's the clinical trial, and what we're now doing is saying in this subgroup that it will benefit. It may well be in that STAMPEDE trial looking at Metformin or statins or whatever it might be as a particular subset of prostate cancer patients, and actually trying to work out what the biomarkers are that puts people into those categories, is what we're interested about. There are a lot of people in this field trying to use bioinformatics to gain the best predictive analytics at which treatments are going to work for which patients. And our commitment is getting the empirical data back from patients, both in terms of clinical outcomes such as imaging, tumor markers, overall prognosis, survival, etc, but also trying to collect longitudinal molecular data such as looking at how the genome, the transcriptome, the proteome, the immunome change over time. This is going to be critical for us which includes learning off every single patient, and understanding which subgroups benefit from which treatments.

Brad Power 23:15
How do you manage the complexity of all that? So first of all, you have all the omics data. You have to put it together into a comprehensive picture about what's the right thing. And then you have it looked like half a dozen or eight things. Is that a combination? And if so, how do you dose it? It just seems there's a great deal of complexity. Because you're exposing so much data. There's a great deal of complexity in all that.

Travis Christofferson 23:55
Pharmacologically, I will say we do have a lot of natural products that are small, planar molecules that bind a lot of things. We don't make any claim into the bioavailability, which is always a problem with natural products. However, there are a lot of patients that are taking supplements anyway, and if you can reduce that list of the ones that may be the most effective, we want to do that for their benefit, and then it falls to the clinician.

Padman Vamadevan 24:32
Yeah. I think the important thing for me as someone who's crossing from the research into the clinical world and does both is that the clinicians judgment is really important. We have patients that will prepare a report for and the clinician will say, Well, that's all well and good. I understand your point, but for example, I’ve treated my lung cancer patients with this combination of drugs, so I’ll incorporate some of your research, but I’m also still going to give them this drug, or

recommend this lifestyle intervention or whatever it may be. That’s actually really important for us, because we’re trying to uncover the truth both at the individual patient level and overall. The science is incomplete. Peer-reviewed science is incomplete. The empirical data is far from complete as well. So the fact that we could give the same report to three different clinicians and end up with three completely different intervention strategies is actually crucial for building the strongest algorithms. Otherwise, if we had set ourselves up as a clinic, doing the research and then essentially marking our own homework by treating people in a very specific way, it would take much longer to improve our algorithms. By contrast, divergence, which is having different doctors use different protocols and dosing strategies is valuable, even though, as you say, Brad, there’s a lot of noise in that. I completely recognize that. But one of the things we are working on now is a longitudinal registry study with a defined group and a large number of clinicians, so we can limit the amount of divergence while still allowing individual doctors to make individual decisions.

Brad Power 26:21
I'm a process consultant, and just understanding how this works at a process level, at a workflow level, timing could be really important here. When I sit down with my clinician, which I will be doing tomorrow, we have a consultation. Things that come into that conversation are valuable. If it takes five to seven days to order your report, and then it gets into the next conversation, but a decision may have already been made about what the treatment protocol is. So how have you found that integration of your advice takes five to seven days from getting the inputs, how does that fit into the flow of the decision making of the patient working with their medical team?

Padman Vamadevan 27:08
It has taken us a year of optimizing the bioinformatic pipeline to get where we are, and there's still a manual part of this process. Our scientific team sits down with a long list of everything that's come out and curates them with the large language model and that takes some time. It takes probably 8 to 10 hours per patient to do that. As we build the bioinformatics out, and we get more quality data, and we're able to stratify by different measurements. We are very confident that we'll get to a process that is almost completely automated, and at that point we'll be able to use this as a clinician interface. The hope is that the clinician will be able to use this in real time without having to have the clunky process of getting an NGS report and sending it to us and getting the report back and dealing with it. This is what we ultimately want, Brad. We want you as a patient to turn up often. We don't even need to know about what Astron is doing. What we really want is the data so that the clinician can use our software, use our technology, and very much as a peer to peer research tool, not as a software, as a medical device tool as yet, but in order to make the right decision for the right patient at the right time.

Brad Power 28:34
Rick Davis from the chat asks: do you request patients list of medications to check contraindications, frequently overlooked by HCPs, and an important aspect of a personalized report?

Padman Vamadevan 28:45
You're 100% right, Rick. This is something that we are absolutely going to be doing. The issue with that at the moment is if we start getting into the realms of absolute dosing, we are producing a kind of Pharmacopoeia encyclopedia, which is a list of all the potential drugs, supplements, nutraceuticals, lifestyle interventions, potential dosing, etc. But if we get into the realms of directly getting a patient's blood test results, drugs that they're already on, etc, and this could be interpreted as software as a medical device right now. This is what we are looking to build, but there is a process and a structure to get there in terms of the regulatory side of things. The way we're getting around that for now is by really handpicking clinicians working with people that are already doing this and are used to prescribing some of these drugs already, and have experience in doing this, but that responsibility at present falls on the clinician.

Richard Anders 29:59
Aside on the nutraceutical front, it's very hard sometimes to know which particular nutraceutical actually is meaningful or precisely calibrated. It's really hard to know you could have five versions of a compound you want in a nutraceutical. One of them actually delivers and three of them have wildly variable doses. Does that might be a service that would be useful for you to help people figure out because I don't know if they have good ways of doing that. It's a really interesting problem that you're dealing with in terms of what you predict. When you're in the world of large predictions of lots and lots of stuff, you're going to get a lot of noise. And if you’re in a situation where there aren’t many options, even something without statistical significance might still be a reasonable choice. But earlier in the process, many of these findings like the one you mentioned that didn’t seem to show statistical significance in part of the study raise the question: do you have a way to help patients or clinicians decide which results to pay attention to when there are so many potentially interesting ones? For patients, this likely varies: early-stage patients with plenty of strong treatments may be better off sticking with the standard of care, while late-stage patients with very few choices might consider more. What should they think about this? How would you suggest they approach it? And how do you refine or adjust your results over time so that some findings rise to the top as ones to definitely consider, while others may be less strong but still worth noting?

Padman Vamadevan 31:57
You’re absolutely right. There’s a tremendous amount of noise, and that’s why the very first thing we’re trying to do is control as much as possible. Patients come to us with every type of cancer, at every stage of disease, and with a wide range of sequencing tests such as genome, some exome, transcriptome, immunome, and so on. It can be overwhelming.

So, in our first study, we’re working with the largest surgical cancer unit in Europe on a very specific clinical problem: MRD in colorectal cancer. These are patients with stage I–III colon cancer who have had curative surgery and possibly chemotherapy, but show no macroscopic evidence of disease. Many of you are familiar with Signatera or other circulating tumor DNA tests used in this setting. Patients who still have circulating tumor DNA in their blood face a very high risk of recurrence. The challenge is, we’re spending billions on this testing particularly in the US but there’s currently no actionable path forward. As a surgeon, three months after an operation, you may have to tell a patient they have circulating tumor DNA and a high recurrence risk, but you can’t reoperate without a lesion, you can’t irradiate for the same reason, and chemotherapy shows no real added benefit with current data. This leaves a big gap. In fact, from our discussions, it feels like we’re a few years ahead of where the field is, because many haven’t fully recognized this problem yet. But our study is attempting to directly address MRD as a clinical setting where the data can be more homogeneous. These patients may have different genes or transcriptomes, but they share the same tumor type and stage of disease. This gives us the opportunity to test whether precision oncology such as drugging genes, pathways, proteins in a safe, tolerable, and proportionate way can extend time to recurrence or even eliminate MRD altogether.

Richard Anders 34:30
What you have here is a trial that isn’t set up with multiple different endpoints, but rather with a single endpoint and a black box in the middle. The black box is where you take the genomic data, and out of that black box without meaning it negatively comes to the treatment. And what the clinical trial is really measuring is whether that treatment impacts the endpoint, such as survival, time to recurrence, or something similar, even though the black box in the middle is very heterogeneous?

Padman Vamadevan 35:03
Yeah, so in our view, it’s not really a black box, we would call it a molecular tumor board. The intervention itself is the molecular tumor board, and that’s where the major point of difference lies. It brings together our software and technology with clinicians, forming a tumor board of scientists and doctors who decide on the best course for that patient, and then the patient proceeds with that treatment.

Richard Anders 35:27
But the challenge is, with all those different variables in the middle, it becomes very difficult to control exactly what’s happening. It might end up being more about the doctor’s judgment than the capability of the computer program.

Padman Vamadevan 35:42
But the approaches will be structured. For example, if a patient has a PIK3CA mutation, there will be defined options. it’s not simply Doctor X choosing something based on an article they happened to read last week. There will be a clear process behind it. Still, as with everything, until we’re approved as software as a medical device, we can’t just state that our software alone is the intervention. That wouldn’t work.

Richard Anders 36:08
But of course, once you start stratifying, say, midway through the trial you conclude, “We perform well for the PIK3CA group but not so well for the PTEN group”, then the trial becomes compromised. It gets very hard to draw meaningful results, because you’ll uncover endless subsets, some that respond and some that don’t. You really have to preserve the integrity of the

trial. It needs to be either universal, or clearly defined by subtype from the start. You can’t just switch between them as you go.

Padman Vamadevan 36:40
It really depends on what your endpoint is. In this case, it’s almost a proof-of-concept study. Going forward, you may well be right that we’ll stratify, for example, saying in patients with TP53 or APC-deficient colorectal cancers, we’ll try an intervention generated from our research and engine to see if it extends time to recurrence. That may absolutely be the direction, but at this stage, the approach is so novel. Another important point is measuring the data longitudinally not just MRD status or circulating tumor DNA status, but also mutational burden and transcriptional burden. For instance, if someone has a PIK3CA mutation, what’s happening to PI3K or AKT at the transcriptional level. That layer of information is critical. Too often we focus only on clinical endpoints like recurrence or overall survival, which are of course paramount, but it’s also vital to ask: what was the intervention’s molecular effect? Did two patients with the same dose see different responses on PIK3CA? Did we fail to drug it strongly enough? And if so, why?

Richard Anders 38:11
It's ambitious and really neat. I wish you the best of luck. It sounds very interesting.

Travis Christofferson 38:19
Yeah, Richard, your first question really gets to the core of what I think about constantly. The best way to put it is the rigidity of the system. As we know, there are very strict criteria for which drugs make it into an oncologist’s toolkit. But patients often have a very different calculus. As you pointed out, especially with things like nutraceuticals, the thinking shifts down the evidence chain to, “What have I got to lose if something is extremely safe?” We want to make that option visible, even if it’s lower on the evidence chain, so patients and their clinicians can decide together. But when it comes to higher-tier evidence, like the Celecoxib study, those will absolutely be ranked more prominently and highlighted as ones that deserve close attention.

Brad Power 39:12
Some recommendations you might feel very confident in, while others less so. Do your recommendations include a way of showing how much confidence you have in each one?

Travis Christofferson 39:31
Right, as we keep iterating on this product, what we have now is tied to references so the clinician can directly see the supporting data, and it’s flagged if it’s from clinical trial evidence. But it’s hard for us to assign a confidence score, because the reality is, we just don’t know. You see this often with trials that there have been hundreds looking at things like Metformin or Beta blockers as adjuncts in oncology. Sometimes you expect results and don’t see them, and we don’t know why the complexity of the human body about the immune system interactions. That kind of evidence is top tier precisely because of that uncertainty. Still, as you move down into the risk–reward profile, with 200 or so repurposable drugs, we aim to highlight the ones that present the strongest chance, that is, those we can have more confidence in.

Padman Vamadevan 40:25
I think another key point is that we’re putting a lot of emphasis on the empirical data we’re collecting. It’s one thing to have scientific confidence from a clinical trial, but as you know, many of those trials weren’t stratified in the ways we’d like, or in ways we may discover are more powerful in the future. That’s why the empirical data, and the way we’re gathering it, is so important. Also, our use case for molecular testing is different. Typically, a patient sees their oncologist, gets a molecular test, and even if cost wasn’t a barrier and they could repeat that test every three months, the oncologist might still only be checking for three or four genes relevant to a particular cancer type. That doesn’t change very often, so frequent testing isn’t routine. For us, though, because we can act on many more changes at the genomic, transcriptomic, and proteomic levels, frequent testing has real value. What we’re missing in cancer today is the dynamic picture of cancer evolution. If you look at CBioPortal or TCGA, and study something like colorectal cancer or lung adenocarcinoma, you see disease progression, KRAS at diagnosis, then TP53, then APC, and so on. But that data comes from thousands of patients who happened to get molecular testing at different times in their disease. That introduces huge heterogeneity and noise. What we’re aiming to do is build a solid use case where we map longitudinal data from thousands of patients within each cancer subtype. For example, colorectal cancer has seven or eight subtypes. We want to track what happens at various “omic” levels in each one. That would give us predictive analytics to anticipate what’s likely to happen next in disease evolution, so we can intervene earlier and drug the pathway one step ahead. That’s where we see the real value.

Brad Power 42:53
Russ has a question about your testing inputs: Are you using whole genome sequencing, whole exome sequencing, targeted like a Guardant 360, or all the above? Do you ever go back to the patients and the doctors and say, “There's a hole here? You really should get this kind of test to fill out the picture.”

Padman Vamadevan 43:17
We are not a testing company ourselves right now, so we work with whatever results the patient already has. There are a few important factors to consider, and one is temporal. For example, I recently had a patient with a Guardant report from January showing a PIK3CA mutation, CDH1, and ESR. She hadn’t done anything except follow a strict ketogenic diet for six weeks. By the time we repeated both a Guardant and a Data report, those mutations had disappeared, and when we checked the transcriptome, PI3K and AKT were also downregulated without any other treatment. That really highlights the power of longitudinal analysis. The timing of tests is critical. If someone brings a report that’s two years old, but in the meantime has had multiple rounds of chemotherapy or immunotherapy, the data may no longer be relevant. Another point is scope: many doctors assume “more is better” and order whole genome or whole exome sequencing, but sometimes the read depth isn’t sufficient, so you miss mutations at lower variant allele frequencies around the 3–5% range and that might have been picked up with a focused pan-cancer panel. From my perspective, I like as much breadth as possible with genomic, transcriptomic, proteomic data because it paints the clearest picture. We often see patients without an obvious druggable KRAS or EGFR mutation at the genomic level, but when we

examine the transcriptome, there’s massive KRAS overexpression that we would have otherwise missed. That information is critical for guiding decisions. At the same time, we’re very mindful of cost. I’m based in the UK, and all of this is out-of-pocket for patients. So it’s a careful balance which is getting the most comprehensive and up-to-date data to support the best clinical or research decisions, while recognizing that cancer care is already extremely expensive.

Brad Power 45:44
Russ asks from the chat: Are your suggested therapies validated options or emerging mechanistic? I haven't found enough of the validated options. We've been forced to look into non validated predictions.

Padman Vamadevan 46:01
It really depends on what you mean by “validated.” If you define validated as FDA-approved, then yes, we do consider FDA-approved therapies. But in practice, if someone has next-generation sequencing, say a Tempest, BostonGene, or Guardant report and it shows a mutation or fusion with an FDA-approved therapy, that information will already appear on their report. So that part is covered. Much of what we focus on is either oncology drugs used off-label or other strategies. For example, if a patient has a HER2 mutation but in a cancer type where no studies have tested Herceptin or another HER2 blocker, we may still consider it. That wouldn’t be FDA-approved for that indication, but scientifically, there is validation for blocking HER2 with Herceptin or similar drugs in other tumor types.

Brad Power 47:02
Allen Morris has a question that’s really more about competition. He says: I have the following somatic mutations in my bone metastatic prostate cancer—CDKN2A, CDKN2B, MTAP, PTEN, FASN, MAP3K1. How is your approach different from me simply asking ChatGPT or another clinically focused AI engine to point me to the most promising phase II or observational studies, like the “Coffee study” you mentioned on ER+ tamoxifen-treated breast cancer?

Travis Christofferson 47:42
You absolutely can, and at a basic level, that is essentially what we’re doing. But we have a team, a methodology, and an approach. We work hard to ensure nothing is missed, and there’s a lot of depth that goes into it. ChatGPT is good, but you have to be very careful. As was said at the beginning, any clinician could do this with enough time for each patient. The advantage of our database, though, is that it keeps improving and becoming more refined and more powerful over time.

Padman Vamadevan 48:16
The way we approach this really matters. The technology exists for you to do it yourself, but it’s taken a long time to build because at the core is a bespoke LLM, currently trained on more than 100,000 peer-reviewed papers drawn from various open-source datasets. On top of that, we use a weighted evidence system that pulls in many inputs such as disease specificity, study design, quality, preclinical binding affinity, and clinical validation. It integrates all the omics we

can, and we apply named entity recognition to extract meaningful associations like drug–gene, drug–pathway, gene–pathway, gene–stage. Then we run it through a multi-dimensional scoring system: literature quality, mechanistic plausibility, disease context, and a safety overlay. If there’s anything negative, we flag it. For instance, if you’ve got a PIK3CA mutation, we might recommend Celecoxib or a ketogenic diet, but if there’s evidence that fat metabolism plays a critical role in your case, we’d also flag that a ketogenic diet might not be the best fit across your disease profile. That’s what sets this apart. I’ve seen plenty of patients who’ve uploaded their whole exome or NGS reports into GPT and asked it to generate a repurposed drug protocol. And while it’s easy to make something look convincing on paper, some of the results have been genuinely alarming but not just risky in terms of liver function or side effects, but potentially harmful to the disease itself.

Brad Power 50:19
Russ follows up on the testing question: if price were no object, would you recommend WGS, WES, proteomics, RNA? You mentioned several omics. Are there particular ones you’d prioritize if cost wasn’t a limitation? From what you said about breadth, it sounds like you’d focus on filling in gaps if someone already has WGS but not RNA, for example. So what principles guide you in deciding which tests people should get?

Padman Vamadevan 50:45
As we know the non-coding regions you get from whole genome sequencing are very important, but with that breadth you sacrifice read depth. So while you capture more of the genome, you might actually miss a mutation that’s driving the next step of the cancer simply because of sensitivity limits. From where we are now, I usually favor a pan-cancer panel in the range of about 500–650 genes, regardless of cost, combined with full RNA sequencing and, if possible, proteomics or at least immunohistochemistry with the standard markers like PD-L1, MMR, CLDN18, and so on. When it comes to highly specific immunogenomic assays, I think the field isn’t quite ready yet. We don’t have enough data to handle such large-scale inputs effectively. My recommendation would be a 500–650 gene panel, full transcriptome, plus proteomics or immunohistochemistry. There are already tests out there that deliver that kind of package. I know you’re strong advocates of things like TumorPortrait, Tempus, and others. There are a number of excellent companies doing very good work in this space.

Brad Power 52:30
Let me ask a quick one on keeping your data current. We had Mark Taylor and Gabriel Gavaxian, who are working on something similar, and they said they review around a thousand research papers a week and feed that into their decision-making system. How does it work for you when it comes to staying on top of the constant stream of new studies being published?

Padman Vamadevan 52:53
That is actually the biggest part of our spending right now as the GPU costs for doing exactly that. On top of it, we manually check to make sure it’s happening robustly and that the model keeps iterating and improving. But as a clinician, I’d say the real foundation is how we pre-trained the LLM in the first place, and the people behind it. Our team includes former Sanger

and COSMIC scientists who really understand this space. That’s our core and we’re not a group coming in without experience in cancer. We know the heterogeneity, the complexity, and we respect both the disease and the fact that we’re still far from having complete certainty.

Brad Power 53:48
Rick Davis raised a question about access and costs. If someone is convinced by Astron Health and what you’re offering, and they want to go to their physician and ask to have this incorporated into their care plan, how would they actually do that? And what would it cost?

Padman Vamadevan 54:07
Yes. In the US it works a bit differently because of regulatory requirements. We sell only through clinicians that could be your primary oncologist, another doctor with genomics expertise, or even metabolic or integrative physicians and some MDs we partner with. If your current physician isn’t willing to make the referral, we can connect you with one of our partner clinicians. Once that’s set up, we schedule a free call with me to walk you through the process and review your reports, explain the research behind it, what we aim to achieve, and how long it will take. Right now, the cost is £950 in the UK. In the US, it’s about $1,250 direct-to-consumer. As we scale and automate more of the report generation, two things will happen: the cost to patients will drop, and we’ll be able to semi-automate at the clinician level, so the report becomes part of their workflow. That way, patients could receive the report as a benefit of working with that clinician, without bearing the direct cost.

Raphael Leong 55:39
It’s actually closer to $1,150 now as it’s come down from $1,250, and the aim is to bring it down further toward $1,000. If you’d like to sign up, just visit **astron.health** and book a call with me, Travis, or another member of the team. We’d be delighted to walk you through the process personally. We’re still a small team, but one of the advantages of being a software-based business is that we can stay lean while keeping things very personal, and we’re more than happy to do that.

Brad Power 56:05
How would you characterize the types of providers you’re selling to? For example, I imagine an oncologist at an academic research medical center might feel they already know everything and don’t need additional input. But a community oncologist, treating many different cancer types, might be more open and see real value in your service as a tool to keep current and ensure they’re not missing anything. So how do you describe the different provider personas you’re targeting, and what kinds of objections or openness are you encountering from them?

Padman Vamadevan 56:52
The first thing to recognize is that many conventional oncologists, be it academic or not, have a set toolkit. Even if you show them compelling data for a repurposed drug, some will hesitate to prescribe it because it falls outside their usual practice. And that’s completely understandable. But in a clinical study context, it’s often the academic doctors who see this as a huge opportunity. It’s really about framing like if you talk about “drug repurposing,” interest is limited.

But when you frame it as “synthetic lethality or drugging MRD”, suddenly everyone pays attention. They get excited, because it’s something actionable that hadn’t been on their radar before. From our experience, some of the most engaged have actually been academic professors and assistant professors. Many of them have lost access to research funding especially post-COVID and with recent governmental changes so they’re open to new approaches that allow them to stay at the cutting edge. That said, the majority of doctors we work with directly are “Integrative cancer specialists”. These are oncologists who practice conventional oncology but also run clinics where they incorporate adjunctive approaches such as repurposed drugs, supplements, dietary interventions alongside standard of care. They have the expertise, awareness, and willingness to explore beyond the conventional toolkit, which makes them very receptive.

Brad Power 58:47
I posted the meeting summary from our session with Will Lavalley where he was discussing molecular integrative oncology, many of the same molecular pathways and algorithmic approaches you’ve been describing. He’s really working in the same space. If you don’t know him yet, you should, and I’d be happy to connect you outside of this.

Will LaValley 59:17
I'm glad to be here. Very interested in and absolutely the field is emerging, and there is a newer openness to the understanding that these repurposed drugs are multi-purpose drugs, and that we have data that can support their use in addition to conventional oncology treatment.

Brad Power 59:46
I always like to close by giving the discussion leaders a chance to share any final thoughts like key takeaways, words of wisdom, or concluding messages. Would each of you like to take a moment to do that?

Padman Vamadevan 1:00:12
We want to make precision oncology equitable. We want to make it scalable. And we want to make it as impactful as we can today, across the globe. We don't want to wait for future drugs or future technologies. Those will come, and those will be absolutely vital. The patients I'm seeing are getting younger and younger. We're not talking about, or we shouldn't be talking about, 5-year survival anymore. We need to be talking about 20-year survival. The opportunity and the data that we have at our fingertips gives us a massive opportunity, a massive public health opportunity, to scale precision oncology right now.

Our two core values are patient-centricity and collaboration. We really want to build an infrastructure that groups like yours, theory makers, the Mark Lintons of this world, etc., can use the data that we have to go further. We don't claim to have all the answers, but we want to try our best to enable smarter people than us to get there.

Travis Christofferson 1:01:28

“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]

When I look at the healthcare system within this realm of oncology, what you notice is a vast underutilization of the Pharmacopeia (the list of drugs and the ways they can be used). It comes to pharmacology, where, on average, these small molecules affect a dozen relevant cellular pathways, but due to financial reasons, they will never get FDA approval.

There's a perfect case of that recently with statins, where they've noticed a linkage between APC mutations and colon cancer with a protein called Rac1, which downregulates this incredibly important oncology pathway, Wnt. They are developing de novo statins to do this, which will cost again, billions and then be typical drug biases where we have statins existing today.

It's a problem. It's a systemic failure in the system the way the system is structured. It’s the same thing with these genomic reports, which are vastly underutilized. From a patient-centered view, we're trying to fill that void.

“Target Your Molecular Vulnerabilities with Personalized Cancer Treatment" (Padman Vamadevan, MD, and Travis Christofferson, MS) [#159]

CHAT DISCUSSION

00:26:01 Russ: Have you seen this: https://www.cell.com/cell/fulltext/S0092-8674(25)00864-5
Looked like a nice genetic analysis using STAMPEDE as a basis.
00:27:06 Rick Davis: Do you request patients' list of medications to check contraindications? Frequently overlooked by HCPs and an important aspect of a personalized report.
00:33:31 Russ: You mentioned the clinician sends you NGS results. I might have missed it. Which NGS results? WGS, WES? Targeted like Guardant360?
00:34:50 Russ: Are your suggested therapies validated options or emerging/mechanistic? I haven’t found enough of the validated options. We’ve been forced to look into non-validated predictions.
00:39:03 Allen Morris: I have the following somatic mutations in my bone metastatic prostate cancer: CDKN2A, CDKN2B, MTAP, PTEN, FAS, MAP3K1 ---- How is your approach better than me asking ChatGPT or other more clinical medicine centric AI engine for the most promising phase 2 or other for example observational studies such as the coffee study you presented regarding ER+ tamoxifen treated breast cancer?
00:43:26 Helen: Can I ask which European hospital you are working with? And thanks for this presentation.
00:44:45 Alexander Lalov, Pendleton, IN: Reacted to "Can I ask which Euro..." with 👍
00:54:57 Raphael Leong: Replying to "Can I ask which Euro..."

University Hospitals Birmingham NHS Foundation Trust
00:58:30 Russ: So, back to the WGS vs WES question line, which would you recommend as the best? WGS and proteomics RNA, etc? Assume price is no object.
01:02:37 Russ: So, hate to hog all fhe time, guardan360 (2025 version), proteomics, foundationone rna?
01:02:47 Russ: natera to track?
01:03:27 Richard Anders: On the paper front, do you follow retraction watch and other such information?
01:03:33 Rick Davis: No one has asked ... cost??
01:04:58 Raphael Leong: Replying to "So, hate to hog all ..."

Yes we can work with these WGS tests. We are WGS test agnostic so we can work with Tempus, Datar Exacta tests, Caris etc as well!
01:10:03 Rick Davis: Think about approaching ACCC to make a package for all community cancer centers.