Peter Attia MD Keypoints — Cancer: Prevention, Screening & Treatment

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Episodes in this pack: 19

412 The evolving science of cancer: emerging approaches to prevention and early detection, & more

Guest: Siddhartha Mukherjee
Date: 2026-10-19 · Duration: 2:04:53
URL: https://www.youtube.com/watch?v=xKB5GTsaKKs

KEYPOINTS

• Fifteen years after The Emperor of All Maladies, the picture splits into prevention, early detection and treatment—with real progress in each, but big gaps in prevention.

Mukherjee says overall US cancer mortality is falling, so 'cancer is exploding' is nonsense. But colorectal cancer in young people is rising, breast cancer's mortality gains have plateaued, and esophageal cancer is climbing. Endometrial cancer's rise is most likely obesity; the colorectal trend is 'a complete mystery.' Trends lag exposures by roughly 5–10 years.

• The 'bad luck' model of cancer is early, not wrong: the 5% hereditary figure is too low, and random mutations need a second push to become tumours.

Attia recalls Vogelstein's 2015/2017 Science papers: roughly 5% of mutations hereditary, ~30% environmental, ~two-thirds random. Mukherjee argues single-gene counts miss much of hereditary breast cancer—known single genes cover only about a third to a quarter of it—with the rest from hundreds of small-effect variants. 'Bert is not wrong. He is just early.'

• Think of hereditary risk as 'shove' mutations versus 'nudge' mutations.

BRCA1/2 are shoves: they push you off the cliff at roughly 9–10× baseline risk of early breast cancer. Polygenic nudges each add a little, combining with environment until you tip over. Because the categories overlap, quantifying where someone sits could route them into prevention programmes or trials.

• Healthy tissue is full of dormant 'sleeper' cells carrying cancer mutations; inflammation can be what wakes them.

Biopsy every lung cell in two non-smokers and you'd likely find thousands of cells with cancer-hallmark mutations, citing work including Charlie Swanton's lab. The real difference between people may be a particular inflammatory response converting one sleeper into a tumour. Mukherjee stresses 'inflammation' is still a loose word, like 'energy' before Newton.

• Chronic 'insulinemic tone' sustains cancers and their resistance to therapy—shown for treatment, hypothesised for causation.

His Nature paper with Lou Cantley found in animals that insulin and its downstream cascade, not obesity itself, drove resistance to therapy. He chooses words carefully: extending this to cancer initiation is an extrapolation and a 'fussy' but doable experiment nobody has run. Attia cites Mitch Lazar's two-by-two showing cardiometabolic disease tracked hyperinsulinemia rather than adiposity.

• Osteoarthritis is not simply an obesity or wear-and-tear disease; it reflects inflammation suppressing cartilage stem cells.

Mukherjee's lab discovered the first osteoarthritic stem cells. Cartilage is constantly made and destroyed; disease appears when genesis falls while destruction holds or rises. Lean women get it in non-weight-bearing hands and necks. In young mice, injecting an immune activator such as LPS into a joint stops stem cells making cartilage and almost exactly mimics osteoarthritis. Why stem cells respond this way is unknown—'teleology is not biology.'

• Tumours carry many recognisable neoantigens, but dozens of 'don't eat me' checkpoint flags keep T cells away.

Attia cites Steve Rosenberg: ~80% of solid tumours have neoantigens. Mukherjee argues the ~100 point mutations don't explain this; Tyler Jacks' lab shows dysregulated gene decoding produces cryptic proteins as the real source. Normal cells display many 'I'm normal' flags, which is why we don't have devastating autoimmunity; cancers that survive evolve the same flags.

• CAR-T works in blood cancers because it kills an entire lineage we can live without—so solid-tumour CAR-T needs an expendable tissue target.

CD19 CAR-T kills all B cells, not just malignant ones; humans tolerate that. The same logic could apply to ovary, prostate, endometrium or even pancreas, but not brain. Ovarian cancer (really fallopian-tube in origin) has known antigens and several CAR-T attempts. Pancreas lacks good unique antigens, and most KRAS sits inside the cell, making it a small-molecule target instead.

• Pancreatic cancer survival depends heavily on anatomy, and new KRAS drugs may be most valuable after surgery.

Tail tumours are often found incidentally and are anatomically separate; head tumours sit in 'the traffic intersection of everything,' presenting with pain or jaundice. Mukherjee has patients alive 10 years after tail cancers. The KRAS inhibitor daraxonrasib extends life in metastatic disease despite skin side effects; adjuvant trials after a Whipple are 'in the works in 1,000 ways.'

• Preventing the big killers may not equal longevity; the next frontier is 'regenerative failure.'

Supercentenarians tend not to die of cancer but of skin, bone, blood and immune failure. Attia counters that atherosclerosis can be made nearly an 'orphan disease' with known drivers—no smoking, insulin sensitivity, very low apoB, treated blood pressure—but cancer can't be eliminated that way. Both agree on a parallel strategy: remove proximal diseases while systematically studying regeneration.

• Aging science lacks its 'cholesterol'—a validated biomarker—and finding one is a decades-long Manhattan Project.

Cardiology moved fast once blood pressure and cholesterol served as proxies. A longevity biomarker study could take 15–30 years prospectively, perhaps 15 with AI; Attia suggests mining metabolomes and proteomes of Interventions Testing Program winners. Echoing David Sabatini, they argue funding must anchor in basic science rather than rushing to drug discovery, and likely sits outside the NIH's illness-focused mandate.

EXAMPLES

• Oxford's croton-oil mouse experiment (1950s)

Painting a carcinogen (DMBA) on a mouse's back produced about four tumours; adding an inflammatory agent, croton oil,

produced about 80. Mukherjee uses it to argue for publishing unexplained observations, as Osler urged.

- **Allan Balmain's staples**
  Genetically cancer-prone mice developed a few tumours; a simple cut did little, but wherever wounds were stapled—triggering ongoing inflammation—massive cancers grew.
- **AI reading of CT scans flagged the thymus**
  A Harvard group scanned tens of thousands of CTs and found people retaining a thymus had fewer autoimmune diseases and cancers. Correlative only; the next step is thymus transplants in older animals, then finding thymic growth factors. Attia calls a growth-hormone/metformin/DHEA regeneration study 'kitchen sink,' and Mukherjee agrees random cocktails are a mess.
- **Vogelstein's 'three zeros' on tumour burden**
  Cutting a billion cancer cells to a million lowers the odds of a pre-existing resistant clone a thousandfold—why debulking plus adjuvant therapy usually works better.
- **Low-cost CAR-T in India**
  Mukherjee co-founded one of India's first CAR-T companies, selling therapy at about 1/20th the US price and treating roughly 150–200 patients. Some US CAR-T patients are 15 years out.
- **Dennis Burkitt's fibre observation**
  Burkitt found virtually no colorectal cancer in fibre-rich African populations who evacuated about twice a day, versus once every 2–3 days in the US.
- **Manifold and the napkin trial**
  Manifold trains AI on medicinal chemists' rules to design 'keys' for wriggling protein 'locks.' Separately, a sushi-dinner napkin sketch with Cantley became Faeth Therapeutics, whose early metabolism-targeting trials in endometrial and breast cancer look promising.

OTHER RELEVANT

- **Mukherjee's colorectal advice**
  Double or triple fibre, cut exposure to 'forever chemicals,' and—by his own admission on no evidence—eat cheap live yogurt at least weekly. Attia argues screening should start at 40 for average-risk adults, earlier with hereditary drivers; guidelines moved from 50 to 45.
- **Use blood-based early-detection tests selectively**
  Applied to the general population they likely bring false positives and extra biopsies without lowering mortality; in high-risk people, such as gene carriers or survivors, they may be valuable.
- **A trial worth funding: GLP-1s as cancer adjuvants**
  Both endorse randomising patients with endometrial, ovarian or breast cancer to standard care with or without a GLP-1, tracking insulin versus weight effects. They prefer this over observational studies because of confounding.
- **Be sceptical of peptide 'hacks'**
  With 20 amino acids per position, the odds of finding the right peptide at the right dose randomly are effectively zero. Regenerative failure needs systematic science, not shortcuts.
- **Mukherjee's writing process**
  Spend 'dream time' on narrator, place, mood, reader, structure before writing; then write fast and edit slowly. He is now writing a book on death and longevity.

396 – Breast cancer screening: understanding risk, deciding when to start, and more

Date: 2026-06-15 · Duration: 0:50:44
URL: https://www.youtube.com/watch?v=_9mBlZXA1Lk

KEYPOINTS

• Screening works, but under-screening is the fixable reason women still die

About 1 in 8 US women develop invasive breast cancer and roughly 42,000 die each year. Stage 1 disease has over 96% ten-year survival versus about 30% five-year survival at stage 4, and regular screeners are up to 40% less likely to die of it. Peter estimates only ~7–10% of cases are biologically aggressive enough to evade even perfect screening; the bigger, solvable problem is that roughly a third of women over 40 haven't had a mammogram in two years and ~20% of 50–74-year-olds aren't up to date.

• The MRI gap is a pure execution failure

At least 9% of women meet guideline criteria for screening MRI, yet actual utilization is about 0.4%. Peter stresses MRI isn't controversial for these women — the high-risk group is identifiable and the tool exists; the system simply fails to connect the two, partly because insurance follows USPSTF guidance that doesn't address high-risk women.

• Guidelines disagree because they answer a population question

The composite from the American Cancer Society, NCCN and American College of Radiology: formal risk assessment by about 25, annual mammography from 40 for average risk, earlier MRI for high risk, and screening as long as you'd accept treatment. The outlier is the USPSTF — biennial mammography for ages 40–74 — which balances cost and false positives across millions. Peter's framework for individuals: know baseline risk, decide your false-positive tolerance, then pick modality and frequency.

• Risk is usually many small inputs, not one red flag

Beyond sex (1 in 8 women versus about 1 in 750 men) and age (median diagnosis ~62), factors include BRCA1/2 (only ~1 in 400 people, more in Ashkenazi Jewish ancestry), family history (which also captures low-penetrance variants and can show up as prostate or pancreatic cancer), ancestry (Black women diagnosed younger with more aggressive subtypes), prior high-dose chest radiation such as adolescent Hodgkin's treatment, density, reproductive factors and modifiable ones like alcohol, obesity and inactivity. Calculators such as Tyrer-Cuzick combine these; lifetime risk above 20% is generally 'high risk'.

• Breast density is both a risk factor and a blind spot

Dense tissue modestly raises risk and makes mammograms harder to read because tumors and dense tissue both appear white. About half of screening-age women are dense (BI-RADS C or D), and the FDA now requires centers to notify women. The catch-22 is you usually learn your density only once screening starts, but it is roughly 60–70% heritable, so a mother's or grandmother's density is worth asking about.

• False positives are real but mostly cost anxiety

About 10% of US screening mammograms trigger a callback, and only ~5% of callbacks end in cancer — roughly 95 of every 100 recalled women don't have it. More than half of women screened annually for 10 years get at least one false positive. The higher your baseline risk, the easier it is to justify that burden; for average-risk women it's a preference call.

• There is a clear hierarchy of imaging tools

Mammography — ideally 3D tomosynthesis (DBT), which detects more cancer with fewer recalls, especially in dense breasts — is the foundation and is best at calcifications like DCIS (25–60% of which may become invasive). MRI with gadolinium is the most sensitive tool and supplements rather than replaces mammography. Contrast-enhanced mammography is the backup when MRI isn't feasible. Ultrasound adds the least consistent value and is the most operator-dependent.

• Abbreviated MRI is the most underused tool

Peter says the abbreviated protocol keeps nearly all of full MRI's sensitivity in 10–15 minutes instead of 30–60, making it cheaper and more scalable. In women with extremely dense breasts, adding MRI after a negative mammogram halved interval cancers from 5 to 2.5 per 1,000.

• Screen annually if you're optimizing for your own survival

No RCT compares annual versus biennial screening on mortality; it rests on CISNET modeling. The 2009 analysis (film mammography) found biennial kept ~81% of the benefit with half the false positives — an efficiency argument. The 2024 CISNET analysis with digital and DBT showed annual screening from 40–79 cut mortality 42% versus 30% biennial. Per exam, false positives were actually lowest with annual screening, likely because radiologists have a recent comparison image.

• Starting age depends on risk more than the calendar

Only ~5% of diagnoses occur under 40 and cumulative risk to 40 is under 1%; registry incidence rises smoothly with no spike at 40, so low early incidence looks real. But younger women get more aggressive disease — about 20% triple-negative under 40 versus 6–12% after — and triple-negative tumors can double in under four months.

• Inflammatory breast cancer and symptoms bypass the screening logic

Inflammatory breast cancer (1–5% of cases) often has no lump — instead swelling, redness, warmth or skin thickening — and may not show on a mammogram, so a normal screen doesn't rule it out. Any new symptom, in women or men, warrants prompt diagnostic evaluation rather than waiting for the next screen.

EXAMPLES

• 2024 CISNET numbers: 230 vs 165 life-years

Versus no screening, annual mammography for women 40–79 gained 230 life-years per 1,000 women versus 165 for biennial. Peter's point: other cancer and radiology groups read the same CISNET data as favoring annual screening; the biennial case is about population efficiency.

• Interval cancers: 11% vs 38%

Observational data among women 40–84 who developed breast cancer: annual screeners had 11% interval cancers versus

38% for biennial, and 76% versus 56% were diagnosed at stage 1.

- **6-million-mammogram study under age 40**
  Among women 35–39 with at least one risk factor (personal history, first-degree family history or dense breasts), detection was 2.1 per 1,000 versus 0.59 for average-risk peers — about 3.5-fold — and higher than the 0.71 per 1,000 in average-risk women 40–44. Peter's takeaway: risk factors can shift a woman's screening profile forward by a decade.
- **Ultrasound depends on what it's added to**
  Physician-performed handheld ultrasound added to 2D mammography found 4.2 extra cancers per 1,000; technician-performed ultrasound added to DBT found only about 1.1 per 1,000.
- **BRCA1 risk is front-loaded**
  A BRCA1 carrier in her late 20s has roughly 100 times a non-carrier's risk, about 44 times in her 30s and about three times in her 60s — which is why MRI, not mammography alone, suits young high-risk women.

OTHER RELEVANT

- **Do a formal risk assessment in your mid-20s**
  Use a validated calculator (Peter mentions Tyrer-Cuzick) early enough to change the plan; you don't want to learn at 42 that you should have started MRI years before.
- **Find out your density — consider a baseline mammogram in your 30s**
  Peter admits there's no direct evidence, but a single 30s mammogram mainly for risk stratification can reveal density that would change your strategy.
- **Match modality to risk and go to an experienced center**
  Average risk: annual mammography, preferably DBT, from 40. Elevated risk or dense breasts: add MRI (abbreviated is often enough), or contrast-enhanced mammography if MRI isn't possible. High-volume dedicated breast centers interpret more consistently, especially for MRI and ultrasound.
- **Alternating tests every six months is reasonable, not mandatory**
  Many high-risk women do mammography and MRI six months apart; evidence for alternating versus stacking is thin and inconclusive. Consistency matters more than scheduling.
- **Don't let a recent normal screen delay a symptom check**
  New lumps, skin changes, nipple discharge or persistent pain — in women or men — need in-person evaluation now.

343–The evolving role of radiation: cancer treatment, low-dose treatments for arthritis, & much more

Guest: Dr. Sanjay Mehta
Date: 2025-04-07 · Duration: 2:25:06
URL: https://www.youtube.com/watch?v=xtgQUiBuGVI

KEYPOINTS

• Only ionizing radiation damages DNA, so cell phones and microwaves can't cause cancer that way.

Houston radiation oncologist Sanjay Mehta (more than 25 years in practice) explains the spectrum: radio waves, microwaves and visible light are non-ionizing. They can heat tissue but can't knock out electrons, so 'fallacies about your cell phone giving you brain cancer are just that'. Ionizing radiation starts at UV and X-rays. Diagnostic radiology uses kilovoltage X-rays, while the linear accelerators used to treat cancer use megavoltage.

• Everyday exposures are tiny next to the 50 mSv annual limit.

A gray is joules absorbed per kilogram of tissue. A sievert is the equivalent exposure measure, and one gray is roughly one sievert. Living at sea level gives about 1–2 mSv a year, Denver two to three times that, and a polar flight perhaps 3–4 mSv per trip. A chest X-ray or mammogram is under about 1 mSv. Modern cardiac CT angiograms are about 1–3 mSv (once about 25), and a whole-body PET-CT is perhaps 50–100. By contrast, prostate cancer treatment delivers 70–80 Gy, but only to the gland, split into daily 1.8–2 Gy doses. Mehta never skimps on dental X-rays, mammograms or cardiac imaging: 'the risk–benefit ratio is so heavily in favor'.

• Mehta believes the linear no-threshold model overstates the harm of very low doses.

LNT extrapolates cancer risk downward from high-dose data (atomic bombs, Chernobyl). Mehta notes it rests partly on a Nobel laureate's 1940s fruit-fly work and argues there's effectively a threshold. He cites animal data suggesting hormesis at single-digit mSv (better bone healing) and reports of lower leukemia and thyroid cancer rates among people a few miles from Hiroshima and Nagasaki. He calls these controversial and not widely accepted, but thinks fear of low doses is 'overblown'. The ALARA principle (as low as reasonably achievable) still guides practice.

• Breast-conserving surgery plus radiation replaced radical mastectomy, and today's courses are shorter and gentler.

Trials in the 1980s (Fisher) showed lumpectomy plus radiation matched mastectomy for survival. Today a typical course is about 40 Gy in 15 daily fractions over about 3 weeks, roughly biologically equivalent to the old 50 Gy in 25–28 fractions, plus an optional 10 Gy boost to the tumor bed. CT-based 3D planning, molded body casts, angled beams and deep-breath holds for left-sided tumors keep dose off the heart and lungs. Even dosing has replaced the old cobalt-era hot and cold spots, which caused severe skin burns or missed areas. Sessions take about 15 minutes, and patients often ask 'when do we start?' after it's already done.

• Mehta considers prostate radiation now as curative as surgery, with fewer urinary and sexual side effects.

Radiation used to be reserved for men who couldn't have surgery, which made older results look worse. Precise beam shaping (IMRT/IGRT), a full bladder, an empty rectum and daily imaging now keep dose to the rectum, bladder and penile bulb very low. Mehta says he can't recall a continent patient leaving incontinent. The trade-off is hormone therapy (ADT) for higher-risk disease, with hot flashes and low libido. AI pathology (ArteraAI) and genomic tests (Decipher) now spare perhaps a quarter of Gleason 7 patients from ADT, and PSMA PET lets him treat isolated recurrences directly.

• In the brain, focused radiosurgery has largely replaced whole-brain radiation.

Whole-brain radiation (30 Gy in 10 fractions) caused memory problems years later in metastasis patients who now live longer. Its use is perhaps 10% of what it was. Radiosurgery targets individual metastases, and when the whole brain must be treated, IMRT spares the hippocampi. Small-cell lung cancer patients with a complete response still get preventive cranial radiation (about 20 Gy in 5 fractions), which Mehta says cuts brain recurrences by roughly 70–80%. Glioblastoma gets about 60 Gy, and proton therapy limits the dose beyond the tumor, which matters for children.

• Low-dose radiation for arthritis and tendinopathy is routine in Germany but rare in the US.

Mehta says Germany treats some 20,000–50,000 patients a year for osteoarthritis, tendinitis, bursitis and plantar fasciitis. The usual protocol is 0.5 Gy × 6 (Monday, Wednesday, Friday for two weeks; 3 Gy total, about one cancer fraction), with an optional repeat after 12 weeks. He describes a cortisone-like anti-inflammatory effect, quoting 60–80% response after one course and 90%+ after a repeat. He has treated about 70 cases, including his own Achilles. The evidence is mostly observational: the two randomized trials were small and, he says, poorly run.

• Benign treatments use large fields and very low total doses, the opposite of cancer treatment.

The goal is to calm inflammatory cells across the whole painful region, so Mehta treats generously: for an Achilles, from the calf down to the heel and onto the sole. For superficial joints like hands, knuckles or the elbow he can use electron beams with the target removed, so dose stays shallow. With no vital organs nearby, the body-wide dose is about that of a CT scan. Patients keep training through the two weeks. Spine results are less reliable because nerve compression can't be fixed this way, though facet and SI joints respond.

EXAMPLES

• US fear of radiation has historical roots.

Mehta points to the Radium Girls, who licked radium-paint brushes, though he says only about 50 of roughly 1,500 suffered toxic effects, along with Cold War fears and oil-industry lobbying against nuclear power. Meanwhile 0.5–2 million American children had nasal radium treatments in the 1920s–40s with few reported problems.

• A PSA of 1,900.

A symptom-free 65-year-old whose bone scan 'looked like a Christmas tree' responded to chemotherapy and ADT, then had his prostate treated. He was still active about 12 years later, with no fractures.

• Mehta treated his own Achilles.

His left side had two cortisone shots plus PRP. A year later he radiated the right side only. Relief took about two months, and

both sides are holding up. Surgeons with plantar fasciitis who couldn't stand to operate improved within about a week.

- **Keloids and Dupuytren's.**
  Keloids get about 12 Gy in 3 fractions starting the same day as surgical removal. Radiating an intact keloid does little. Dupuytren's and Ledderhose fibrosis take higher doses (about 3 Gy × 5, repeated).

OTHER RELEVANT

- **Don't avoid indicated imaging because of radiation fears.**
  Dental X-rays, mammograms and a modern cardiac CT add only a few mSv.
- **For prostate cancer, see both a surgeon and a radiation oncologist.**
  Ask about genomic or AI risk tests that could spare you hormone therapy, and choose a high-volume specialist in your type of cancer.
- **For stubborn tendinopathy or arthritis, ask whether low-dose radiation is an option.**
  The evidence is mostly observational, but Mehta says US insurers, including Medicare for osteoarthritis codes, often cover it.
- **Ask to see your treatment plan.**
  Mehta walks interested patients through dose–volume charts showing how much each organ receives.

310 - The relationship between testosterone and prostate cancer, TRT, and more

Guest: Dr. Ted Schaeffer
Date: 2024-07-22 · Duration: 0:48:20
URL: https://www.youtube.com/watch?v=fiVCsm4dNh0

KEYPOINTS

• TRAVERSE found no increase in prostate cancer with testosterone, but its limits matter.

TRAVERSE was designed mainly to test whether testosterone replacement raises cardiovascular risk, and it found it did not. Urologist Ted Schaeffer walks through its pre-specified prostate analysis. The roughly 5,300 men were symptomatic and hypogonadal, averaged in their 60s, and had a low median PSA of about 0.9, making them a low-risk group. Treatment raised testosterone only modestly, about 140 ng/dL, and more than 60% had dropped out by five years. Only about 23 prostate cancers were diagnosed, with no difference between testosterone and placebo. Peter notes the incidence curves diverged slightly, and both agree the trial was likely too small and short to rule out a small effect.

• In the trial, PSA kept working as a warning signal on testosterone.

Most men's PSA changed by less than half a point during the trial. The men diagnosed with cancer had higher PSAs at entry and larger rises over time. Ted's takeaways: men with low PSA have low prostate cancer risk, and PSA changes can be interpreted much as usual in men taking exogenous testosterone.

• The saturation model: prostate androgen receptors max out at low testosterone levels.

Androgens bind the androgen receptor, which moves to the nucleus and switches on androgen-responsive genes. Once a tissue's receptors are saturated, extra hormone does little more. Saturation thresholds vary by organ. Modeling by former Drive guest Abraham Morgentaler put prostate saturation at a serum testosterone of roughly 200–250 ng/dL, about the 10th percentile for adult men, according to Peter. Prostate and hair follicles are rich in 5-alpha reductase, which converts testosterone to DHT, about 10 times more potent, amplifying the effect. Muscle needs much higher levels for anabolic benefit. That's why raising a man from 300 to 800 ng/dL can visibly build muscle while barely moving PSA.

• Benign prostate cells are more sensitive to testosterone than cancer cells.

Benign prostate cells carry higher densities of androgen receptors. Ted says studies of testosterone supplementation more often show mild worsening of BPH (enlarged prostate) and urinary symptoms than any effect on cancer. He describes this as consistent with TRAVERSE and several smaller studies over two to three decades.

• Aggressive prostate cancers tend to rely less on androgen signaling.

An early-2000s New England Journal paper Peter and Ted discussed on Ted's first appearance linked lower testosterone to higher-grade cancer. Ted's lab built a nine-gene androgen receptor activity (ARA) signature from mRNA in tumor tissue. Larger signatures of 250 or 600 genes tell the same story: tumors with low androgen receptor output are more aggressive, spread more and resist standard therapy, using other pathways such as PTEN loss or MYC. Ted's garden analogy: high-AR tumors are big weeds with thin roots, while low-AR tumors look nothing like normal gland and are the dangerous ones.

• Genomic testing can sharpen treatment for higher-grade disease.

Ted collaborated on Decipher, a clinically certified mRNA test from biopsy or surgical tissue that scores aggressiveness from about 22 genes. A broader genomic panel from the same test reports the ARA score and tumor subtype. In low-grade (Gleason 3+3) cancer, Decipher flags an aggressive outlier only about 7% of the time, and surveillance usually catches those anyway. In phase 3 trial analyses, low-ARA tumors responded especially well when standard hormone therapy was intensified with drugs like enzalutamide, apalutamide or darolutamide. NRG radiation trials, fully enrolled, are testing this, with results expected in about two years.

• Ted rarely advises against testosterone replacement for symptomatic low testosterone.

For a cancer-free, symptomatic, hypogonadal man, Ted can't think of a case where he'd advise against it, because low testosterone threatens cardiovascular, bone, muscle and cognitive health. Strikingly, if a man on replacement at about 800 ng/dL is diagnosed with low-grade cancer on surveillance, Ted keeps him on it. He says there's no evidence it accelerates prostate cancer, and about 30% of men naturally run that high. He wouldn't encourage going above that, and he monitors both men the same way.

• Low-AR, intermediate-risk tumors may favor surgery over radiation.

Radiation for higher-grade cancer is paired with androgen deprivation, which takes testosterone to near zero, sensitizes cells and adds DNA damage. Ted calls that deprivation 'incredibly morbid.' Only about 50–60% of men recover normal testosterone after two years of it. Because benign tissue remains after radiation, restarting testosterone can create false-positive PSA rises. After surgery with favorable pathology, Ted can keep men on testosterone, perhaps around 400 ng/dL.

EXAMPLES

• Two men, same cancer.

Ted's thought experiment: one man naturally at 800 ng/dL and one supplemented to 800 both have Gleason 3+3 cancer. He would follow both identically and not force either to stop or have surgery.

• Testosterone as a differentiation factor.

In the normal prostate, testosterone pushes cells toward a mature, benign state. So high testosterone tends to accompany better-differentiated tumors, while tumors that arise in low-testosterone environments are more worrisome and harder to target.

• A sniper, not a bazooka.

After prostatectomy, men aren't routinely given preventive hormone therapy the way women with ER-positive breast cancer get anti-estrogens. PSA can detect recurrence from just a few hundred cells, so doctors can treat early recurrences only when they appear.

• A hope for breast cancer.

Peter and Ted hope cell-free DNA liquid biopsies can give breast cancer a similar monitoring tool, sparing the many women who don't need years of hormone suppression.

OTHER RELEVANT

- **Watch PSA trends on testosterone therapy.**
  A stable PSA is reassuring. Rising values warrant workup, typically MRI and possibly biopsy.
- **Ask about genomic profiling for higher-grade cancer.**
  Decipher and the ARA score are available through physicians and may inform surgery versus radiation and hormone-therapy intensity.
- **Weigh hormone-deprivation morbidity in treatment choice.**
  When surgery and radiation are equally effective, avoiding androgen deprivation can be a major quality-of-life advantage.
- **These are one expert's practices.**
  Ted's comfort with testosterone in low-grade cancer is his clinical approach. Individual decisions belong with a urologist.

290 Liquid biopsies for early cancer detection, the role of epigenetics in aging, and the more

Guest: Dr. Alex Aravanis
Date: 2024-02-19 · Duration: 2:21:31
URL: https://www.youtube.com/watch?v=9RaQyvI-Rgg

KEYPOINTS

• Genome sequencing costs have fallen faster than Moore's Law.

Alex Aravanis, Peter's medical school classmate, is an electrical engineer turned MD-PhD. He later became Illumina's chief technology officer and co-founded GRAIL. Sequencing one more genome right after the Human Genome Project would have cost a few hundred million dollars. By about 2012 it was in the low tens of thousands, and today it's a couple hundred dollars. The leap came from sequencing-by-synthesis chemistry developed by Cambridge chemist Shankar Balasubramanian and brought to Illumina through its acquisition of Solexa. Billions of DNA fragments are attached to a glass slide and read one base at a time, all in parallel.

• Tumors constantly shed DNA into the blood, which makes liquid biopsies possible.

Cell-free DNA was first seen in blood in the 1940s, and in the 1970s researchers noticed cancer patients had much more of it. Tumors grow chaotically, so their cells die at high rates and release DNA. Fragments are about 160 base pairs long because DNA wound twice around a nucleosome is protected from enzymes. Alex describes three uses: choosing targeted therapy without risky biopsies (lung biopsies can cause a collapsed lung), monitoring for residual disease after treatment, and screening people with no known cancer.

• Prenatal tests accidentally proved blood DNA could reveal hidden cancers.

Dennis Lo, and Stanford's Steve Quake, developed blood tests that detect fetal trisomies from placental DNA. Alex says these cut amniocentesis by about 80% in the US. At Verinata, an Illumina company, Meredith Halks-Miller and Daria Chudova noticed rare results with chaotic abnormalities across many chromosomes, which isn't compatible with a viable fetus. The mothers turned out to have undiagnosed invasive cancers. All of the roughly 10 women flagged, described in a 2015 JAMA paper, had cancer. That was no false positives, though most cancers in that population were surely missed.

• The key challenge for cancer screening is specificity, not sensitivity.

Alex notes that in 50 years nobody had built a broad blood test for cancer, and PSA's high false-positive rate cost it its USPSTF A or B grade. Proteins and metabolites rise in benign conditions too, giving false-positive rates of 5–10%. Population screening needs about 1% or less. GRAIL's CCGA study took nearly three years and hundreds of millions of dollars, using about 15,000 samples split into blinded training and test sets. It compared mutations, chromosomal changes, cell-free RNA and DNA methylation.

• Methylation, the 'dark horse,' won decisively.

Methylation adds a methyl group to cytosines at about 28 million CpG sites and controls which genes a cell uses. Alex calls it 'the software of the genome.' It's read by chemically converting unmethylated cytosines (bisulfite sequencing). Methylation detected the most cancers, reached a false-positive rate under 1%, and uniquely predicted tissue of origin. Adding other signals didn't help, because they weren't independent. His analogy: once you spot Ford's blue oval, also looking for 'F-150' adds nothing. Two tubes (about 10 mL) of blood suffice, since background biology, not blood volume, limits screening sensitivity.

• In PATHFINDER, about 40% of positive Galleri results turned out to be cancer.

In this interventional study of about 6,500 people at average or slightly elevated risk, with cancer prevalence just under 1%, about 40% of 'cancer signal detected' results were confirmed as cancer. By comparison, about 4–5% of abnormal mammograms lead to a cancer diagnosis. Specificity was above 99%, and the test caught about half of the cancers that emerged. Added to guideline screening, it roughly doubled the number of cancers found, mostly types with no existing screen. Alex notes that about 70% of cancer deaths come from unscreened cancers. The test predicts a top-two site of origin about 90% of the time, using a methylation atlas of healthy cell types built with Yuval Dor in Jerusalem.

• It's a functional test: it preferentially finds the dangerous cancers.

Sensitivity varies widely by type. Peter's review found roughly 20% detection of early-stage hormone-positive breast cancer versus about 75% for triple-negative. To shed detectable DNA, a tumor needs enough mass, cell turnover and blood access, traits linked to aggressiveness. In CCGA survival curves, people whose cancers the test missed did very well, while detected cancers carried substantial mortality. Low sensitivity for indolent prostate or hormone-positive breast cancer may therefore partly avoid overdiagnosis.

• Does earlier detection save lives? The two make their case, and NHS data are coming.

Peter states his bias that it does, noting that breast and colorectal cancers treated with the same adjuvant therapy fare far better when localized. Alex cites five-year survival of 70–80% for localized solid tumors versus under 20% for stage 4, and asks what surgeon would decline to treat a stage 1 pancreatic cancer found this way. The NHS is testing Galleri in about 140,000 people, using a reduction in stage 4 diagnoses as an earlier endpoint than mortality. Peter adds that single-cancer trials are rarely powered to show changes in all-cause mortality.

EXAMPLES

• 'Kiss-and-run' synapses.

In Richard Tsien's lab, Alex's PhD work helped explain how neuron terminals with only about 30 vesicles fire hundreds of times in seconds: vesicles briefly fuse, release transmitter and reseal.

• The airport metal detector.

Peter's analogy for the tradeoff. Turning sensitivity up stops everyone with a metal zipper. A 40% positive predictive value is excellent when the detector usually beeps thousands of times without catching anyone. GRAIL's algorithm has a similar dial.

• The insulin promoter.

Only pancreatic beta cells leave the insulin gene's promoter unmethylated. Every other cell type methylates it heavily, the kind of signal that lets the test infer tissue of origin.

- **Partial reprogramming.**
  Yamanaka factors can revert cells to stem cells but risk tumors. Juan Carlos Izpisua Belmonte's mouse work stopping partway reported improvements in eyesight and cognition. Alex hopes direct epigenetic editing could give more control.

OTHER RELEVANT

- **Discuss false positives before testing.**
  Peter tells patients up front that a positive may be false and will require follow-up imaging. Some reasonably decline.
- **Methylation may be the 'hallmark of hallmarks' of aging.**
  Smoking, exercise and obesity leave distinct patterns. The open question is whether restoring youthful patterns would restore youthful function.
- **Aged immune cells carry methylation signatures.**
  Exhausted T cells show distinct, largely shared changes that could become rejuvenation targets.
- **Disclosures.**
  Alex owns Illumina shares and now runs an epigenetics company in which Peter is an investor and adviser.

278 Breast cancer: how to catch, treat, and survive breast cancer | Harold Burstein, M.D., Ph.D.

Guest: Harold Burstein
Date: 2023-11-06 · Duration: 2:17:14
URL: https://www.youtube.com/watch?v=IdKIF28C1xg

KEYPOINTS

• Breast cancer is common, but most women are now cured

Harold Burstein, a Dana-Farber breast oncologist, gives a US lifetime risk of about 1 in 8 (12–13%). There are roughly 250,000–300,000 invasive cases a year (he first says about 275,000), plus another 50,000–60,000 cases of DCIS, and about 38,000 deaths. Assuming a steady state, about 80–85% of women are cured, while 15–18% remain at risk of recurrence and death. Outcomes depend on both stage and subtype.

• Three subtypes drive treatment

Estrogen-receptor-positive, HER2-negative tumours make up 70–75% or more. They are the type most often found on mammograms, peak around age 65 and, size for size, usually have the best prognosis. Triple-negative cancers (ER, PR and HER2 negative) are about 10–15%, skew younger and are more aggressive. HER2-positive tumours were once very aggressive but now have some of the best treatment results.

• Most risk factors move individual risk only a little

Early first period, late menopause, hormone therapy, fewer pregnancies and less breastfeeding all extend estrogen exposure and may raise risk 25–30%. Burstein says that only moves an individual from about 12% to about 15%. Postmenopausal women with denser breast tissue are at slightly higher risk, and not just because density hides tumours. He calls obesity a relatively weak risk factor, and smoking is not a major one.

• DCIS is a precancer, like a colon polyp

Ductal carcinoma in situ is cells building up inside a duct without invading the surrounding tissue. Seventy years ago it showed up as a lump, but today it is found on mammograms. In about 15–20% of excisions, a small invasive cancer turns up, so the diagnosis is upgraded. In the NSABP B-17 trial, about 25–30% of women treated with lumpectomy alone had a recurrence or new breast cancer within 10 years, and radiation cut that roughly in half. B-24 added tamoxifen. Burstein thinks the baseline risk for today's mammogram-detected DCIS is much lower.

• Radiation after DCIS is a trade-off in risk

For healthy women up to about 65–70, radiation after lumpectomy is standard. It lowers the risk in that breast to something like 1–2% with three to four weeks of treatment. Recurrence risk without radiation ranges from about 5–10% for low-risk lesions to 20–25% for higher-risk ones. Ongoing trials ask which low-risk women can safely skip it.

• LCIS signals higher risk rather than being a precursor that must be removed

Lobular carcinoma in situ and atypical hyperplasia raise the risk of future cancer by roughly 0.5–1% a year and warrant monitoring. In the NSABP P1 prevention trial, which enrolled many women with LCIS, tamoxifen cut breast cancer diagnoses from about 13 to 5–6 per 1,000 women per year. However, it did not improve survival, partly because it prevents the most treatable tumours.

• Stage, nodes and biology together predict cure

Burstein's ballpark 10-year cancer-free survival figures are about 90% or more for stage 1, 75–80% for stage 2 and 65–75% for stage 3. Peter cites 90–95% for tumours of 2 cm or smaller without lymph-node involvement. Risk rises steadily with size, with each additional lymph node, and with tumour grade, Ki-67 and receptor status.

• Genomic tests now spare many women chemotherapy

In 1999 the NCI said essentially every woman with a 1 cm cancer needed chemotherapy. Today, ER-positive tumours are scored with tests such as the Oncotype DX recurrence score or MammaPrint, which show that most low-scoring patients gain little from chemotherapy. Anti-estrogen therapy is advised for nearly all ER-positive patients, longer for high-risk cases, and oral CDK4/6 inhibitors are now added for very high-risk tumours.

• Screening plus better drugs each account for about half the mortality decline

Breast cancer mortality has fallen by about half over 30–40 years. Burstein credits roughly half of that to early detection and half to effective drug therapy, notably trastuzumab (Herceptin) for HER2-positive disease, with data emerging in 2005. Neoadjuvant therapy, meaning drugs before surgery, is increasingly used for larger tumours, and the tumour's response guides prognosis and later treatment.

• Hereditary mutations explain only about 8–10% of cases

BRCA1 and BRCA2 account for about half of hereditary cases, and PALB2, CHEK2 (also linked to colon cancer) and ATM for most of the rest. Clinical panels now test up to about 100 genes. Burstein doesn't rely on consumer tests like 23andMe for clinical decisions. Carriers may consider preventive mastectomy, ovary removal once childbearing is done (there is no good ovarian screening), or intensive screening: an annual MRI and an annual mammogram, staggered six months apart.

EXAMPLES

• Peter's case for aggressive screening

The same chemotherapy can cure early disease after surgery yet rarely cures metastatic disease. So Peter argues that finding cancers earlier, which shifts more of them to stage 1, must cure more women, despite overdiagnosis and lead-time bias. Burstein agrees. He notes that most screening trials ended in the late 1980s, before modern drugs, which partly reduces the advantage of early detection, though smaller tumours still need fewer or less toxic drugs.

• Hormone therapy after breast cancer

Burstein generally avoids systemic hormone replacement for survivors. Instead he uses non-hormonal treatments for osteoporosis and hot flashes (including a recently approved drug) and is fairly liberal with vaginal estrogen, which is absorbed very little into the body. A few women can't function without hormones, and that becomes an individual conversation with them.

• Male breast cancer

There is about 1 male case for every 200 female cases. Nearly all are ER-positive; triple-negative disease is very rare and HER2-positive uncommon, and treatment principles are the same. BRCA mutations in a family also raise men's prostate cancer risk.

• Where to get treated

Burstein says excellent breast cancer care is available at many centres. He thinks variation in care is greatest outside the top institutions, and that multidisciplinary teams combining surgery, radiation and medical oncology are the real test.

OTHER RELEVANT

• Get any lump checked

A palpable lump calls for an evaluation: a diagnostic mammogram, ultrasound and, if needed, a needle biopsy. Ultrasound and MRI supplement mammograms for high-risk or dense breasts but don't replace them.

• Know your family history and test for a reason

A strong history of breast or ovarian cancer warrants clinical genetic testing and counselling for relatives. A positive result changes screening and prevention options.

• Ask about genomic scores before agreeing to chemotherapy

For ER-positive, HER2-negative cancers, a recurrence-score test can show whether chemotherapy adds meaningful benefit.

273 Prostate health: common problems, cancer prevention, screening, treatment, and more

Guest: Ted Schaeffer
Date: 2023-10-02 · Duration: 3:46:39
URL: https://www.youtube.com/watch?v=poTcAm_rknw

KEYPOINTS

• Urinary symptoms are the norm with age, not the exception

Ted Schaeffer, a Northwestern urologist, says 50–60% of men over 50 have lower urinary tract symptoms, rising to 75–80% by 60, and these almost always involve the prostate. A normal prostate is about 20–30 g at 40–50 and grows with age. Size doesn't predict symptoms well: men can have severe symptoms with a 35 g gland.

• Waking at night to urinate is often about fluid handling, not just the prostate

Antidiuretic hormone normally rises in the evening to cut overnight urine production. That rhythm weakens with age, and alcohol inhibits the hormone. Fluid that pools in the legs during the day (look for sock marks in the morning) returns to the circulation when you lie down. Schaeffer says changing when you drink, plus knee-high compression stockings, can often cut nighttime trips from two to one without drugs.

• Medications: alpha blockers first, then 5-alpha-reductase inhibitors for large glands

Modern selective alpha blockers relax smooth muscle in the prostate to widen the urethra, without the steep blood-pressure drops of the first generation. Finasteride (5 mg) or dutasteride (0.5 mg) shrink the prostate by 20–30% over time. Their half-lives are long, so Schaeffer notes that a weekly 5 mg finasteride tablet roughly matches the 1 mg daily hair-loss dose.

• HoLEP has changed surgery for large prostates

TURP, still the gold standard, scrapes out tissue in roughly 1 g chunks. Holmium laser enucleation (HoLEP) shells out the gland along its natural plane. His colleague Amy Krambeck has removed 400 g from a 450 g prostate, about the size of a big grapefruit, and can operate on glands as small as 25–30 g. He estimates only about 10 surgeons in the US work at her level.

• Chronic prostatitis is often not an infection

The four-glass test cultures the first void, bladder urine, prostatic fluid and urine after massage. Bacteria found only in the prostatic fluid point to a true prostate infection. Many men instead have pelvic-floor tightness, which Schaeffer treats with transrectal myofascial release, which he says can change lives. He is wary of repeated 30–60-day antibiotic courses. In bed-bound or dementia patients, he warns that indwelling catheters drive urosepsis.

• Finasteride hides PSA, and that can kill

After about five years on a 5-alpha-reductase inhibitor, PSA falls about 2.5-fold. If patients and doctors don't adjust for this, a rising PSA gets missed. A UCSD study of veterans found markedly higher prostate cancer death rates in men taking these drugs, which Schaeffer attributes to this neglect. He also takes post-finasteride syndrome (lasting sexual and neurological effects) seriously and thinks young men at hair-loss clinics aren't properly warned.

• The deadliest prostate cancers may thrive without testosterone

In about 100,000 tumour gene-expression profiles (the Decipher database now has 140,000+), Schaeffer's group found luminal-like and basal-like cancers. Fewer than 10% of metastatic tumours are luminal. Basal tumours survive without androgens, which makes them most likely to spread and least hurt by androgen deprivation. That is why he is comfortable treating genuinely low testosterone in men diagnosed with or recovering from prostate cancer.

• Know your PSA relative to the median for your age

Median PSA is about 0.5 at 40 and about 1.0 at 50. Being above the median signals a much higher risk over the next 20–30 years and calls for closer follow-up. PSA density (PSA divided by prostate volume) refines this: he gets concerned above about 0.1–0.12 in men under 60 and 0.15 in men over 65–70. A free PSA above 18–20% is reassuring. Screening trials showed PSA cut prostate cancer deaths by 20–25%, yet about 35,000 US men still die each year.

• Use MRI to decide on a biopsy, and go through the skin

PI-RADS 3–5 lesions generally warrant a biopsy unless PSA density is very low (around 0.02). Transrectal biopsies carry about a 1–4% infection rate even with antibiotics. Transperineal biopsies go through the skin with buffered lidocaine and nearly eliminate infection. Schaeffer leads a 16-centre randomized trial comparing the two. A good biopsy takes 12 systematic cores plus targeted samples.

• Gleason 6 can usually be watched; pattern 4 changes the picture

Grade 3+3=6 is the least aggressive type. In the Johns Hopkins active-surveillance cohort started in 1996, about 30–35% of men were upgraded within five years, with roughly 2–3% added per year after that, about one in five overall over 10 years. Gleason 4+3, meaning more than 50% pattern 4, behaves worse than 3+4, and 3+5 behaves like 4+4. About 95–96% of prostate cancers are diagnosed while still localized.

EXAMPLES

• Prostatectomy outcomes at a high-volume centre

Schaeffer quotes a 95–96% chance that surgery succeeds against the cancer. He puts continence at about 66% at one month and 95% at three months. A 65-year-old with good erections before surgery has a 65–75% chance of recovering erections adequate for intercourse (with Cialis) within 24 months, as nerve recovery takes 24–30 months. Men who already needed Cialis before surgery do 10–20% worse.

• Inherited risk

BRCA2 carriers have a lifetime prostate cancer risk of about 60–70%, enough to warrant intensive screening. A USC polygenic study of about 235,000 men found that roughly 250–260 risk variants are enriched in Black men and in men diagnosed young.

• A PSA of 10 at 34

Schaeffer recalls a man from his Hopkins years who had workplace screening only to get a $250 insurance discount and was

found to have a PSA of about 10 at 34, not from infection. The median age at diagnosis is 68, and a diagnosis at around 50 or younger warrants genetic testing.

- **Advanced disease**

  For high-risk or lymph-node-positive disease, surgery debulks the tumour, typically followed by radiation and 6–24 months of androgen deprivation. In newly diagnosed metastatic disease, median survival without treatment is about 2–3 years. Traditional androgen deprivation alone extends this to about 48–50 months, at a real cost to metabolic health and quality of life.

OTHER RELEVANT

- **Get a baseline PSA early**

  The NCCN guideline says every man should have a baseline PSA by 45. Schaeffer sees no reason not to test earlier. Track your PSA against the median for your age and your prostate volume: if it's below 1, retest every 2–4 years; if it's above the median, follow it more closely.

- **If you take finasteride or dutasteride, tell every doctor**

  Roughly double the PSA value (Schaeffer's figure is about 2.5×) and watch the trend, since any rise matters.

- **Before a biopsy, ask for MRI and a transperineal approach**

  These cut unnecessary biopsies and nearly eliminate infection risk.

- **Choose a high-volume surgeon and ask for their numbers**

  Ask about continence and erectile outcomes, and how much nerve-sparing their approach allows.

267 The latest in cancer therapeutics, diagnostics, and early detection | Keith Flaherty, M.D.

Guest: Keith Flaherty
Date: 2023-08-21 · Duration: 2:05:39
URL: https://www.youtube.com/watch?v=hBrTtKmcg3k

KEYPOINTS

• Cancer's share of deaths peaks in midlife

By age band, cancer causes about 6% of deaths at 25–34, 13% at 35–44, 23% at 45–54, 30% at 55–64 and 31% at 65–74. The share then falls only because heart disease and neurodegeneration take over. Cancer ranks among the top three causes of death in every decade from the mid-20s and is number one in parts of midlife. Five cancers (lung, breast, prostate, colorectal, pancreatic) account for just over half of US cancer deaths.

• Hormone-driven cancers appear when the hormones are low

Peter points out that men have their highest testosterone and DHT in their 20s to 40s, yet prostate cancer appears when levels have fallen. Breast cancer likewise doesn't peak at peak estrogen. Low-androgen prostate cancers tend to be worse, as a New England Journal paper showed about 15 years ago. Keith Flaherty's takeaway is that the biology runs deeper than 'hormone in, cancer out'.

• Obesity is the second-biggest environmental cause of cancer after smoking

About 25–27 cancers have a tight link to obesity. Peter suspects the driver is not fat itself but insulin, probably IGF-1, and the inflammation that comes with it. These effects take years to kick in, so rising obesity rates today predict more cancer later.

• Survival with metastatic solid tumours barely moved for 30 years, and has only recently started to

Ten-year survival with distant spread was essentially 0% in 1970 and about the same in 2000. The only exceptions were the 10–15% of kidney cancer and melanoma patients who responded to high-dose interleukin-2. Flaherty thinks 15% is now a conservative estimate for durable survival, moving toward 20%. He notes that 52 FDA approvals since then cover only 19 unique mechanisms, and roughly half the gain comes from the PD-1 drug Keytruda.

• PD-1 does the heavy lifting in immunotherapy

Tumours display PD-L1, 'the foot that presses on the brake' of T cells. Blocking PD-1 gives roughly 10% of all cancer patients long-term, roughly 10-year-type benefit, by Flaherty's math. Adding CTLA-4 blockade helps about a fifth of tumour types but contributes only around 1% in addressable patients on top of that.

• Most epithelial tumours are visible to the immune system

Steve Rosenberg's finding that roughly 80% of epithelial tumours carry novel neoantigens means the immune system could, in principle, take most cancer deaths off the table. Spontaneous regressions are rare but real: Rosenberg's career began after seeing a patient who had been sent home to die with metastatic gastric cancer return 10 years later, needing his gallbladder out and cancer-free.

• Cell therapies work but are hard to scale

CD19 CAR-T is the poster child: every B cell carries CD19, so lymphomas arising from B cells can be targeted. Most solid tumours lack such a clean target, so researchers are engineering cells that require two markers. TIL therapy requires surgically removing tumour, for example a wedge of lung, then growing its lymphocytes to about 10 y cells and reinfusing them with interleukin-2. That is costly and bespoke, and it often fails against the tumour's defences.

• Tumours build a 'force field' that has to come down first

Flaherty uses a Star Wars analogy: you have to take out the shield generator before attacking the Death Star. Cancers recruit suppressive immune cells and fibroblasts (notably in pancreatic cancer) and alter their own metabolism. Lasting cures will need combinations matched to each patient, not one cocktail. Peter asks what it would take, over five years, to double long-term survival with these therapies from about 20% to 40%, a number he says he is making up for illustration.

• The same drugs cure microscopic disease but not visible metastases

Stage 3 colon cancer treated with surgery and chemotherapy gives about 60–70% five-year survival. Add liver metastases and give the same drugs, and five-year survival falls to somewhere between none and a few percent, with none alive at 10 years. Flaherty's explanation is clonal: drugs kill the dominant 99% of cells, but the remaining 1% contains about 10 subclones, one of which already carries resistance. Larger tumours hold more of them. Hence his view that early detection is the problem that 'wins the game'.

• Liquid biopsies are reasonable now and will get much better

Blood tests such as Grail's (ordered by a physician) detect tumour DNA and suggest the tissue of origin. Flaherty considers testing reasonable for early adopters who can tolerate uncertain results. Peter uses Grail selectively. Methods in development are 10–100× more sensitive from the same 10–20 mL blood draw, and repeated testing over 6–18 months may be needed to locate a cancer after a positive result.

EXAMPLES

• A friend with Lynch syndrome

Peter retells the case: stage 3 colon cancer at about 40, then advanced pancreatic cancer around 2012–13 with a 6–12-month prognosis. Because Lynch syndrome tumours carry many mutations, he received anti-PD-1 therapy and went into complete remission, but now needs insulin because his immune system destroyed his pancreas.

• Screening's limited reach

Colonoscopy and mammography cut deaths from those cancers by roughly 25–30%. Peter also notes that by using 4Kscore and multiparametric MRI before biopsies, none of his patients has had an unnecessary prostate biopsy in 10 years.

• P53

P53 is mutated in about 50% of cancers, with hundreds of variants, which is one reason mutation panels for blood tests need to be broad.

- **Expert access is a lottery**
  Peter can phone Flaherty about an unusual case; most patients can't. Flaherty argues AI decision support built on outcome data could handle the 95% of typical cases and leave experts free for the edge cases.

OTHER RELEVANT

- **Prioritize early detection**
  The same therapies are far more powerful against small numbers of cells. Combine standard screening with risk-appropriate extras.
- **If you use a blood-based cancer test, have a plan for a positive result**
  Do it through a physician who can manage serial testing and imaging, not as a standalone purchase.
- **Reduce the modifiable drivers**
  Don't smoke, and address obesity, high insulin and inflammation; their effects on cancer risk build over many years.

216 - Metabolomics, NAD+, and cancer metabolism | Josh Rabinowitz, M.D., Ph.D.

Guest: Josh Rabinowitz
Date: 2022-08-01 · Duration: 2:27:10
URL: https://www.youtube.com/watch?v=_kezGvY5bN8

KEYPOINTS

• Metabolism went from unfashionable to central.
Josh Rabinowitz, an MD-PhD who runs a metabolomics lab at Princeton, recalls a mentor saying that in the late 1990s metabolism researchers felt like the bottom 10th percentile because nobody found it interesting. Tools for measuring hundreds of metabolites and their fluxes have since made it a frontier in diabetes, aging and cancer.

• Concentrations hide flux.
Metabolomics measures levels; fluxomics measures how fast molecules are made and used. Attia's fasting glucose of 89 mg/dL represents only about 4–5 grams of glucose in the blood, roughly 20 calories and a few minutes of fuel, yet it stays in a tight 80–100 range overnight because production and consumption match. A static reading of 180 vs. 90 says little about which flux went wrong.

• Homeostasis is extraordinarily tight.
Attia uses pH as an example: the scale runs 0–14, but humans live at about 7.4 and can barely survive outside about 7.0–7.7, a narrow window on a logarithmic scale. Glucose is similar: Attia has seen his own range from about 50 to 240–250 mg/dL, a 5x span, while lactate ranges 60-fold.

• Glucose and fat compete for oxidation (the Randle hypothesis).
Rabinowitz thinks much of what sets blood glucose is competition between glucose and fat. In diabetes, underlying problems in fat handling mean more glucose is needed either to induce enough insulin to suppress lipolysis or to outcompete fat for burning in tissues, with ectopic fat in liver and muscle as part of the problem.

• Lactate is a fuel, not just waste.
Back to yeast, cells run glycolysis whenever needed and 'spit out' redox-balanced waste (lactate in humans, ethanol in yeast), then pick it up and reuse it in the TCA cycle. Attia has measured his lactate from about 0.3 mmol at rest to 20 mmol after an all-out two-minute effort. Rabinowitz's work helped establish lactate as a major circulating fuel.

• Fasting lactate may flag metabolic dysfunction.
Attia observes that insulin-resistant people often have fasting lactate approaching 2 mmol with no activity, while healthy people sit below about 0.5. Rabinowitz agrees the correlation is interesting and plausibly reflects impaired mitochondrial oxidation, though causation isn't settled.

• Metformin inhibits complex I, but that may not be the whole story.
It's not disputed that metformin inhibits complex I of the electron transport chain, where NADH is offloaded to make NAD+. The open question is whether that's the main effect at clinical doses of around two grams a day; 'five people who study metformin will tell you five different things.'

• NAD declines only modestly with age.
NAD+ levels fall perhaps 10–20% with aging, a percent change rather than a fold change, compared with much larger swings when tissues are stressed. NADH carries electrons for energy production, while NADPH supports biosynthesis and antioxidant defense.

• NAD supplements: plausible, unproven.
Oral NAD is broken down in the gut, and NR (nicotinamide riboside) largely enters the body as nicotinic acid or nicotinamide. People don't flush on NR or NMN at 500 mg–1 g because that doesn't produce enough niacin to cross the threshold of a few grams. Rabinowitz isn't convinced that boosting NAD by 20% in a 50-year-old helps, and says proper trials are needed; IV NAD has little supporting evidence.

• Cancer may become a chronic disease through metabolism plus immunity.
Rabinowitz admits he once doubted immunotherapy's promise. He now favors a 'stalemate' strategy that combines multiple modes of action, including metabolic and nucleic-acid targets, rather than hitting hard on one lever. Pancreatic cancer, his main focus, is the fourth leading cause of cancer death, with even stage 1 disease about 80–85% fatal.

EXAMPLES

• Ketogenic diet plus chemotherapy
In animal models, chemotherapy lowers tumor glucose, and adding a ketogenic diet that reduces insulin and glucose makes a powerful combination.

• SGLT2 inhibitor trial
Because patients can't be asked to give up the joy of food, Rabinowitz's group is starting a trial combining an SGLT2 inhibitor with a low-carbohydrate (not fully ketogenic) diet to induce ketosis while allowing some normal eating.

• Cahill's starvation studies
George Cahill's work showed that after 40 days of starvation people still had about 3 mmol of glucose, with ketones supplying up to about 60% of fuel.

• The Women's Health Initiative digression
Attia argues the WHI was misinterpreted: estrogen alone trended toward lower breast cancer risk (hazard ratio about 0.8), while estrogen plus MPA showed a barely significant hazard ratio of about 1.24, an absolute increase of about one in a thousand. He predicts a generation of women will be seen as having been harmed by fear of hormone therapy, though he grants a possible slight cardiovascular risk.

• Attia's insulin suppression test

During an insulin suppression test with Gerald Reaven at Stanford, Attia's glucose fell dangerously low ('I almost died') and, once corrected, rebounded to about 240 mg/dL. It's his illustration of how wide glucose swings can be even in a healthy person, and how hard the body works to restore the set point.

OTHER RELEVANT

- **Watch flux, not just levels.**
  A single glucose or lactate number is a snapshot; patterns across fasting, meals and exercise matter. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Consider fasting lactate as a clue.**
  High resting lactate may hint at poor metabolic health, an observation rather than a validated test. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Be skeptical of NAD hype.**
  Precursors are fairly safe, but benefits in humans remain unproven; IV NAD has little support. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Read relative risks with absolute numbers.**
  The WHI shows how a 25% relative increase can mean about one extra case per thousand women.

213 Liquid biopsies and cancer detection | Max Diehn, M.D. Ph.D.

Guest: Max Diehn
Date: 2022-07-11 · Duration: 2:26:07
URL: https://www.youtube.com/watch?v=rOU3rEHlhDo

KEYPOINTS

• Liquid biopsies began with a clinical frustration.
Diehn, a Stanford radiation oncologist, treats many early-stage lung cancers that haven't spread; targeted high-dose radiation cures most, but about 20–25% recur. Imaging can't tell after treatment who still harbours microscopic disease, and by the time a tumour is large on a scan — at 10×10×10 cm the tumour burden itself is fatal — options are worse. He wanted a blood test that could see cancer earlier.

• Older blood markers are limited by normal-tissue production.
PSA, CEA and CA 19-9 have long been used, but normal cells make them too — normal prostate cells make prostate-specific antigen — so they lack specificity for screening.

• Sensitivity and specificity must be read together, with prevalence.
Sensitivity is how many people with cancer test positive; a mammogram might be about 85% sensitive, missing 15 of 100 cancers. Calling everyone positive yields 100% sensitivity but useless specificity. Attia stresses that in a low-prevalence population, positive predictive value can be modest even for a test that sounds great.

• Low-dose CT is a proven lung-cancer screen.
Early chest X-ray studies showed no benefit, but the landmark National Lung Screening Trial randomized high-risk smokers to low-dose CT or chest X-ray and found about a 20% relative reduction in lung-cancer deaths. With a single-digit absolute benefit (say 5%), the number needed to screen is around 20. False positives were a concern in the original protocol; modern protocols reduce them. Radiation is low relative to the regulatory 50 mSv annual limit.

• The field moved from circulating tumour cells to cell-free DNA.
Early-2000s work focused on intact tumour cells in blood, filtered using markers like CD45 (a pan-white-cell marker). Attention shifted to cell-free DNA: double-stranded fragments of about 170 bases. Healthy people have roughly 1–5 ng/mL in plasma, so 20 mL of blood yields about 10 mL of plasma and 10–50 ng of DNA.

• Tumour DNA is a tiny fraction of the signal in early cancer.
In early-stage patients circulating tumour DNA is often well below 0.01% — sometimes 0.001% — of cell-free DNA. About 99.9% of fragments map to normal germline sequence.

• Tracking many mutations at once multiplies sensitivity.
If a patient's tumour has been sequenced, looking for 10 of its mutations instead of one raises sensitivity about tenfold, since you don't need to see all of them. Prior methods bottomed out near 0.01% (one in 10,000); Diehn's lab tackled this from around 2014, and newer methods go further.

• Filtering out white-blood-cell mutations is essential.
About 80–90% of cell-free DNA comes from white blood cells. With age, leukocytes acquire mutations through clonal hematopoiesis, which then appear in plasma. Diehn's team sequences both cell-free and leukocyte DNA to subtract them. Cancer-derived fragments are also a few bases shorter on average.

• Minimal residual disease detection is the near-term win.
After treatment, ultra-sensitive tests can detect microscopic residual disease with a very high positive predictive value: detectable ctDNA means the cancer will very likely return. This is easier than screening because the tumour's mutations are already known.

• Pan-cancer screening is far harder.
Without a known tumour, tests like Grail's look at methylation patterns of cell-free DNA. Specificity is above 99%, but presented stage I lung-cancer sensitivity is about 5% or less — and stage I is exactly where blood tests matter, since larger tumours show on CT.

• Diehn's target for a breakthrough.
He argues 50–75% sensitivity for true stage I cancers while keeping specificity above 99% would be a big step. Dropping specificity to 80% inflates sensitivity by luck — a trade some groups make.

• Cell-free RNA could add tissue-of-origin information.
Diehn says cell-free RNA exists in plasma and is a much more nascent field than cell-free DNA. Because RNA reflects which genes are active, it could in principle reveal what tissue a signal comes from and add information beyond mutations or methylation. His long-term vision is a single blood draw that detects cancer and points to where it is.

EXAMPLES

• The 50/99.5 thought experiment
Attia models a test with 50% sensitivity and 99.5% specificity at 1% prevalence: a negative result moves you from about 99% to roughly 99.5% confidence of no cancer, while a positive carries about a 40% chance of truly being cancer. Patients must understand both.

• Biased sensitivity
Including one stage I and 999 stage IV patients can make any test look highly sensitive; unbiased reporting by stage matters.

• Attia's own blood
Attia notes his small red cells (MCV in the 50s–60s) to illustrate individual variation in blood measures.

• Funding liquid-biopsy research
When Diehn began around 2012, grant reviewers were skeptical; liquid-biopsy proposals now score well and submissions have grown dramatically.

- **Liquid biopsy vs. tissue biopsy**
  In patients with known advanced cancer, blood-based mutation testing shows high agreement — in the high 80s percent — with tissue biopsy, and can sometimes find mutations a biopsy misses because a needle samples only one part of a tumour.

OTHER RELEVANT

- **Ask about low-dose CT if you've smoked.**
  Eligibility depends on pack-years; screening those unlikely to get lung cancer produces mostly false positives. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Interpret multi-cancer blood tests carefully.**
  A negative result doesn't rule out early cancer given low stage I sensitivity; discuss predictive values with your doctor.
- **Ask about ctDNA monitoring after treatment.**
  Residual-disease testing may flag recurrence earlier, though whether acting on it improves outcomes is still being studied.
- **Treat biomarkers as one input.**
  Combine blood tests with imaging and risk factors rather than relying on any single test.
- **Smoking history drives lung risk non-linearly.**
  Risk rises with pack-years and some studies suggest it plateaus around 20–30 pack-years; screening is targeted at people above a meaningful risk threshold so benefits outweigh false positives.

#187 - The Warburg Effect: Otto Warburg’s Cancer Metabolism Theory with Sam Apple

Guest: Sam Apple
Date: 2021-12-13 · Duration: 1:59:06
URL: https://www.youtube.com/watch?v=n6MjnI4vM7M

KEYPOINTS

• A journalist found his story in a single sentence

Sam Apple, a writer who teaches science writing at Johns Hopkins, was researching the clustering of metabolic diseases since the 19th century when he read that in 1923 a German scientist had made an important discovery about cancer metabolism. Googling Otto Warburg was a 'light-bulb moment'. He says he only writes about science when he has a central character, and Warburg became the subject of his New York Times Magazine piece in 2016 and then his book Ravenous.

• Warburg grew up among the titans of German science

Born in 1883 to Emil Warburg, a prominent physicist from a famous Jewish family who rose to the top of German physics at the University of Berlin, Otto grew up with Einstein, Max Planck and Emil Fischer visiting the house. Einstein called Emil his favourite physicist. Otto served in World War I in his early 30s, although Einstein had urged him not to go and wrote to him again in 1918. A friend described his devotion to science as a prophet's fervour, and Warburg said a scientist must be prepared to die for the truth.

• The Warburg effect: cancer cells ferment glucose even with oxygen available

Warburg had found that fertilized sea urchin eggs use more oxygen as they grow. In 1923 he expected cancer cells to do the same. Instead, they took up huge amounts of glucose and fermented it to lactate even when oxygen was present. Peter notes that fermentation yields about 2 ATP per glucose versus about 32–34 from full respiration, a roughly 17-fold difference, which is why the behaviour seemed so strange.

• Warburg insisted damaged respiration was the prime cause of cancer

He argued that fermentation compensated for defective mitochondria and occurred in 100% of cancers. Apple says today's estimate is perhaps 70% or more. Warburg distinguished a 'prime cause' (damaged respiration) from many 'secondary causes', such as carcinogens. He never had a good way to test the idea, and his own first experiments in the early 1920s showed respiration continuing.

• He won the 1931 Nobel Prize for respiration, not cancer

Warburg was nominated in 1926 for his cancer work, in what was apparently a tie that went to someone else. In 1931 he won for identifying the respiratory enzyme now called cytochrome oxidase, the last step of respiration. Apple and Peter discuss whether his later work on hydrogen transfer and coenzymes was his best science, research that ended up having a vast, mostly unseen influence on American life.

• A Jewish-descended scientist survived inside Nazi Germany

Of about 2,500 Jewish scientists at German institutions, Warburg was the only one who stayed to the end. He was useful for propaganda around the 1936 Berlin Olympics, but by 1941 that value was gone. On June 21, 1941, he was summoned to meet Viktor Brack, architect of the Nazi euthanasia killing programme, and was told he could live on one condition: that he work on cancer. Apple argues that Hitler, who lost his beloved mother to breast cancer when he was a teenager, was likely involved in that decision.

• Oncogenes eclipsed Warburg, until a 2009 rethink

After the war, Warburg feuded with critics such as Sidney Weinhouse in Science in 1956 and died in 1970. The discovery of oncogenes in the 1970s, recognized with the 1989 Nobel to Harold Varmus and Michael Bishop, pushed metabolism aside. Weinberg and Hanahan's 2000 'Hallmarks of Cancer' paper left Warburg out. The renaissance came with a 2009 Science paper by Matthew Vander Heiden, Lewis Cantley and Craig Thompson. They accepted the Warburg effect but argued the mitochondria are largely intact, and that the cells take up glucose to get building blocks for nucleotides and lipids rather than to make up for an energy shortfall.

• Apple's thesis: hyperinsulinemia may link obesity and cancer

In the late 1990s, just as labs such as Craig Thompson's and Chi Van Dang's returned to Warburg metabolism, epidemiology showed that elevated insulin and obesity both correlate with cancer. Apple thinks prevention should focus on hyperinsulinemia. Peter notes that insulin could only be measured in blood from the late 1960s. Even tumours with PI3K pathway mutations may remain responsive to insulin, he notes. Obesity's link is harder to untangle than tobacco's because its hazard ratios are far smaller.

EXAMPLES

• Fructose surprised the author

Apple assumed sugar mattered only by driving liver fat and insulin resistance. Lewis Cantley's work in colon cancer, along with Rick Johnson's ideas, suggests fructose metabolism itself depletes ATP in the cell and may directly feed tumour growth. Apple says sugar is still central, but this upended his idea of the mechanism.

• Prime versus secondary causes, using cholera

Peter applies Warburg's framework: in 19th-century London's cholera epidemics, the bacterium was the prime cause. With smoking, they agree tobacco is likely a prime cause through DNA damage, though Apple notes it comes down partly to semantics.

• How writing is taught

Apple did a two-year MFA in creative non-fiction at Columbia. Writing workshops of about 15 students critique each other's drafts several times a semester, a gruelling process of trial and error. When selecting science-writing students, he reads cover letters most closely.

• A 120,000-word gamble

Without biochemistry training or fluent German, Apple spent years on the book. He says finishing it taught him to trust himself as a writer.

OTHER RELEVANT

- **Separate the history from the conclusion**
  Warburg was right that cancer metabolism is distinctive and wrong to call damaged respiration the sole cause. Hold both thoughts.
- **Treat metabolic health as part of cancer prevention**
  Apple and Peter both see high insulin and obesity as plausible levers in cancer prevention. They frame this as a hypothesis with strong correlations, not settled causation.
- **Limit excess fructose**
  Excess fructose drives insulin resistance and may also have direct effects on tumour cells.
- **Be wary of single-cause stories**
  Warburg's certainty that he had found the one cause of cancer alienated colleagues. Apple's reporting suggests that both the mutation and metabolism camps hold part of the truth, with examples and counter-examples on each side.

181 - Viewing cancer through an evolutionary lens: a radically different approach to treatment

Guest: Bob Gatenby
Date: 2021-10-25 · Duration: 2:18:34
URL: https://www.youtube.com/watch?v=uR9i2aPD29s

KEYPOINTS

• Cancer is an evolutionary problem, and treatment selects for resistance.
Gatenby, a radiologist who trained in physics at Princeton, argues that oncology lacks the first principles that let physics make sense of messy data—as Newton did for planetary motion. His organizing principle is Darwinian: a tumor is a population of competing cells, and every therapy is a selective force that will eventually favor resistant variants unless it is managed strategically.

• Models don't need to predict ten years out to be useful.
Attia compared cancer modeling to economic models that can't forecast GDP a decade ahead, and Gatenby agreed that cancer sits toward the chaotic end of the spectrum (Attia rated it an eight or nine out of ten). The goal is not long-range prediction but answering 'what should I do next?' with models that are recalibrated to each patient's data as treatment proceeds.

• The pesticide lesson: maximum dose clears the field for resistant cells.
The diamondback moth has been hit with every pesticide developed and by the 1980s some populations resisted all of them. In Gatenby's illustration, a heavy spray kills the sensitive 80% and leaves the resistant 20% a whole field without competitors. Resistance mechanisms carry a fitness cost, so in a lower-pressure environment sensitive moths can out-compete resistant ones—potentially shrinking the resistant share over time.

• Adaptive therapy uses sensitive cells to suppress resistant ones.
In metastatic prostate cancer, his team gave abiraterone until PSA fell to 50% of its baseline, then stopped, letting drug-sensitive cells regrow and compete with resistant ones before restarting. The idea is to keep a controllable tumor burden rather than eradicate sensitive cells and release resistant ones from competition.

• The pilot trial roughly doubled time to progression.
Compared with patients on the standard maximum tolerated dose until progression, median time to progression went from about 14 months (consistent with the literature) to about 30 months with adaptive therapy, a 16-month difference—with less total drug. Some patients were still cycling about five years later. It was a small, non-randomized pilot, and models had predicted control would be lost somewhere between 2 and 20 cycles depending on the unknown starting fraction of resistant cells.

• The key surprise was a sevenfold fitness advantage.
The trial data implied that sensitive cells were about seven times fitter than resistant cells off-drug, versus the two- to threefold the team had assumed. Instead of plateauing, resistant populations declined, and modeling suggested three successive well-timed cycles could drive resistant cells toward extinction. They think competition for space and substrate, scarce in poorly perfused tumors, drives the differential.

• Small populations are vulnerable—hit them with a sequence, not a single strike.
Small populations can go extinct from minor shifts in birth and death rates (stochasticity), and tumors may show an Allee effect, where cells benefit from numbers, for example to build blood vessels. Gatenby favors an 'extinction' strategy borrowed from ecology: after a first strike shrinks the tumor, follow-up therapies attack the remnant before resistance emerges, as in pediatric leukemia regimens.

• Probability math explains why one drug rarely cures large tumors.
A 100-gram tumor holds on the order of 100 billion cells, so some pre-existing resistant cells are near-certain. Knocking a population down to millions and then adding a second and third drug changes the odds dramatically. Attia's analogy: the US could survive a 90% population loss in theory, but a nation of 33 million under ongoing attack would be a very different, vulnerable entity.

• Immunotherapy may work best on minimal disease.
Response to anti-PD-1 drugs is best in people with relevant mutations; first-generation interleukin-2 had perhaps 10–20% response in melanoma, but always in full-blown metastatic disease. Gatenby suggests immune approaches might perform very differently in patients with no visible disease, when the cancer population is small.

• Most cells that spread die; metastasis is about the soil.
When cancer cells are injected into mice, nearly all die at distant sites. Around 30–40% of women undergoing mastectomy for apparently localized breast cancer may have cancer cells in their bone marrow, yet not all relapse. He and Attia discussed few cancers that kill without spreading, such as glioblastoma.

EXAMPLES

• Physics under Feynman's shadow
Gatenby studied physics at Princeton in the late 1960s and early 1970s before medicine, and found medical school's rote memorization—like Catholic catechism—at odds with his search for first principles.

• Hospital antibiotics
He compared standard dosing to a fixed 10-day antibiotic course continued after the patient recovers; overuse breeds superbugs, much as maximum-dose chemotherapy breeds resistant tumors.

• The p53 vaccine
A p53 vaccine in heavily treated lung cancer patients failed on its own, yet subsequent chemotherapy produced 60–70% response rates, versus an expected under 5%—perhaps because cells downregulated p53, an evolutionary trade-off that made them vulnerable.

• Darwin's finches

With billions of genomic data points but no observation of the beak matching the seed, Gatenby doubts Darwin could have derived evolution; measuring tumors' environments matters as much as sequencing them.

- **The trial's oncologist**

He credited oncologist Jingsong Zhang for running the trial against the grain; a European philanthropic fund wants to support a phase 3 trial in prostate cancer.

OTHER RELEVANT

- **Ask about treatment strategy, not just drugs.**

For metastatic cancer, discussing intermittent or adaptive dosing and the sequence of therapies with an oncologist may matter alongside drug choice.

- **Monitoring frequency affects outcomes.**

Gatenby's team found infrequent scans (every three months) delayed decisions; patient-specific modeling needs frequent biomarker data like PSA. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Prioritize early detection.**

If small cancer populations are the most vulnerable, finding cancer early—Attia's argument for aggressive screening—gives therapies the best odds.

- **Being told you've 'failed therapy' isn't the end.**

Gatenby dislikes the phrase; patients interested in adaptive approaches need an oncologist willing to try them, ideally in trials, since he isn't a treating oncologist himself.

177 - The development of cancer immunotherapy and its promise for treating advanced cancers

Guest: Steven Rosenberg
Date: 2021-09-27 · Duration: 2:11:34
URL: https://www.youtube.com/watch?v=pVMl0LgdnOU

KEYPOINTS

• Metastatic solid cancers are the real problem

Rosenberg says about 600,000 Americans died of cancer in the past year, and roughly 550,000 of those deaths came from solid epithelial cancers (colon, breast, lung, pancreas, prostate and similar). Blood cancers are about 10%. Surgery and radiation cure many localized tumors. Once epithelial cancer has spread, cures are rare, which is why he has spent his career on the immune system.

• A spontaneous regression set the course of his career

As a young resident, Rosenberg found a patient whose gastric cancer had spread to his liver and lymph nodes 12 years earlier and been left in place after a palliative operation. The cancer had disappeared without any treatment. Rosenberg concluded that the body had some way to reject cancer, and that the immune system was the likeliest candidate.

• Chemotherapy has hit diminishing returns for common metastatic cancers

Chemotherapy came out of mustard-agent research during wartime around 1942. It cures some leukemias, lymphomas and testicular cancer. For most metastatic epithelial cancers, Rosenberg says progress has been incremental. Median survival in metastatic colorectal cancer rose from about 8–10 months to about 2.5 years. Some newer drugs add weeks of life at high cost and toxicity.

• IL-2 produced the first immune-driven cures

T-cell growth factor (interleukin-2), discovered in 1976 by Morgan, Ruscetti and Gallo, let researchers keep lymphocytes alive outside the body. Before that, they died within a day or two. Rosenberg's team treated dozens of patients with IL-2 or IL-2-grown cells and saw no responses. After they changed the schedule and raised the doses, a patient with widespread melanoma treated in 1984 had a complete, lasting regression.

• Only certain cancers responded, and mutations explain why

High-dose IL-2 caused regressions in about 15–20% of patients with metastatic melanoma and kidney cancer, and some of those were durable cures. Melanoma carries an unusually high mutational burden. Rosenberg's view is that mutated proteins (neoantigens) are what T cells actually recognize.

• Mutations are the antigens, and they're almost all unique

In a series of 195 patients with common epithelial cancers, his lab found T cells recognizing mutations in about 80% of them. There were 393 distinct antigens, and almost none were shared between patients. The exception was a KRAS mutation on a rare HLA type. Only about 1.3–2% of a tumor's mutations are immunogenic. He calls this good news: after decades, 'we finally understand what a cancer antigen is.'

• Tumor-infiltrating lymphocytes improved results, then lymphodepletion jumped them

Growing TIL cells from tumors in IL-2 and infusing them raised melanoma response rates from about 15% with IL-2 alone to 30–35%, though responses were often short. Wiping out the patient's inhibitory regulatory T cells before infusion pushed response rates to about 55%, with roughly 25% durable complete remissions.

• CAR T cells were engineered from a gene-insertion idea

His team inserted receptor genes so T cells could recognize CD19 on B cells. A 2009 patient with chemotherapy-refractory lymphoma, who had a kilogram-sized chest tumor after four failed regimens, was disease-free 12 years later. Losing normal B cells turned out to be survivable.

• Checkpoint inhibitors release the brakes, but most solid cancers need more

Anti-CTLA-4 and anti-PD-1 drugs (James Allison later won a Nobel Prize for his checkpoint work) unleash existing immune responses. Rosenberg says most patients with the epithelial cancers that cause 90% of deaths respond poorly, because taking off the brakes does nothing if there aren't enough reactive T cells.

• The frontier is personalized T cells against each tumor's mutations

His lab published the first mutation-targeted T-cell treatment in 2014, in a woman with metastatic bile-duct cancer. All of his work now goes into turning these unique reactivities into treatments. He also isolates libraries of T-cell receptors against recurring mutations such as p53 and KRAS, which he calls 'almost an engineering problem.'

EXAMPLES

• Kite and the path to approval

Urologist Arie Belldegrun, a former fellow, visited in 2011 and founded Kite. A 2012 cooperative research agreement (CRADA) funded the work. After more than 50 patients, over half had durable regressions. A multi-institutional study reproduced about a 70% response rate with roughly 50% durable complete regressions, and Kite was sold to Gilead in 2017 for roughly $11.9 billion.

• Operating on President Reagan

In 1985 Rosenberg was called to Bethesda Naval Hospital, partly because he already had a security clearance from an emergency medical team role. At the press conference he said plainly that the president had colorectal cancer, which displeased Nancy Reagan. The episode later cost him consideration for the NCI directorship.

• Persistence through dozens of failures

Peter compares the 1984 IL-2 breakthrough to Thomas Starzl's early liver transplants, where many patients died before success came. By Peter's recollection the 1984 responder was about the 67th patient treated, after a long run of patients who didn't respond. He reworks Pasteur: 'Chance favors the prepared mind only if the mind is at work.'

• Why he stayed at the NCI

He took over as NCI chief of surgery on July 1, 1974, the day after finishing residency, and has held the post for 47 years. He turned down offers including Johns Hopkins, where it came down to John Cameron and him, because the NIH let him research rather than 'practice today's medicine.'

OTHER RELEVANT

• Ask about immunotherapy and trials for metastatic disease

For melanoma, kidney cancer and B-cell lymphomas, immune-based treatments can cure some patients. For most epithelial cancers, checkpoint drugs help a minority, so clinical trials of cell therapies are worth exploring. Rosenberg's results come from highly selected NCI patients.

• Expect cell therapies to become practical

Critics said CAR T could never be delivered at scale. Rosenberg's view is that if something cures people, 'the genius of modern industry will figure out ways to make it available.'

• Stay present with patients who aren't saved

Peter recalls that eight or nine of every ten 'Hail Mary' patients at the NCI died. Rosenberg taught him not to retreat from them out of a sense of failure. Rosenberg still remembers individual patients, such as a 25-year-old newlywed, after more than 20 years.

#133 - Vinay Prasad, M.D., M.P.H: Hallmarks of successful cancer policy

Guest: Vinay Prasad
Date: 2020-10-19 · Duration: 2:12:04
URL: https://www.youtube.com/watch?v=1CO7Ya7FAMc

KEYPOINTS

• Medical reversal: widely used practices that turn out not to work

Prasad, a haematologist-oncologist and meta-researcher at UCSF and author of Ending Medical Reversal and Malignant, came to the idea as a resident. He noticed practices that ran against the best evidence. As a resident he managed stent patients after the procedure and saw the complications. Meanwhile the large COURAGE trial had found that stents in stable disease didn't reduce heart attacks or extend life. He and colleagues called this pattern 'medical reversal': plausible biology plus observational data, later overturned by randomised trials.

• Sham-controlled trials separate the procedure from the ritual

Arthroscopic knee surgery beats physical therapy or ibuprofen, but not a sham operation in which the surgeon inserts the scope and does nothing. The same holds for cement injections into osteoporotic vertebral fractures, some shoulder procedures and, Prasad believes, stenting for chronic stable angina (the ORBITA trial). Much of the benefit comes from reassurance and the patient's belief that something was fixed.

• Stents are 'seductive' because both patient and doctor feel rewarded

Patients come back grateful, convinced their life was saved and that shovelling the driveway hurts less. That feedback reinforces the procedure even when trials show no hard benefit. Prasad says this disconnect between what patients think a treatment does and what doctors know it does recurs across medicine.

• Structural problem 1: huge costs for small gains

In an analysis by Fojo and colleagues, 71 consecutive drugs approved for solid cancers improved survival by an average of 2.1 months. Prasad says two months can matter a great deal to someone, but the result should come with a lower price. Attia recalls a drug that added 0.7 months, about 20 days, at roughly $38,000. Compared with 1960 or 1970, someone with metastatic breast cancer in 2020 is not dramatically better off, Prasad argues, while surgical outcomes like the Whipple procedure and the move away from radical mastectomy have improved.

• Structural problem 2: approvals rest on weak surrogate endpoints

Progression-free survival and response rate often stand in for living longer or better. 'Progression' means the tumour has grown 20% from its smallest size. At 19% the disease is 'stable', at 21% it has progressed: an arbitrary cut-off that often doesn't track how patients feel. The 30% shrinkage needed to count as a 'response' goes back to a 1976 Mayo Clinic exercise in which doctors measured marbles through foam rubber. Prasad questions why so much weight is put on drugs with 10–20% response rates.

• Structural problem 3: the people choosing don't pay

Patients and doctors decide while insurers, governments and employers pay. Prasad compares it to a Saudi friend who left his air conditioning running all summer because energy was subsidised. When someone else pays, cost stops affecting choices. In the UK, NICE declined drugs above a cost-effectiveness threshold, which Attia recalls as about £100,000.

• Hallmark 1: independence from industry money

Patient advocacy groups are often heavily industry-funded. The most common employer for staff leaving the FDA is industry. Prasad calls expert oncologists, many of whom take payments, 'probably the biggest offender'. He thinks the profession won't police itself, because the most influential doctors receive the most payments. He would have guidelines written by experienced oncologists with no financial ties.

• Hallmarks 2–3: evidence and relevance

Drugs should prove they help patients live longer or better, against the right control group. Trials should also enrol patients who look like the people who will actually get the drug. Trial participants tend to be younger and fitter, so real-world success rates are lower because the drug is less tolerable and response is poorer.

• Hallmark 4: affordability

Prasad groups possible fixes into buckets. One he highlights is letting Medicare decline to pay for drugs. At the moment it must cover drugs recommended at level 2A or above by guidelines such as the NCCN's, whose authors are often industry-funded. He notes that some states asked HHS for permission to experiment with not covering every drug.

• Hallmarks 5–6: possibility and agenda

Possibility means funding more bold science. The NIH budget of about $30 billion a year is 'not nearly enough', grant cycles favour incremental work, and Prasad suggests running randomised experiments on how grants are awarded. Agenda means looking at the whole trial landscape. Many trials test 'Coke, Pepsi and 18 other Cokes', near-identical low-promise drugs, and at $p<0.05$ some will come out positive by chance.

EXAMPLES

• Hormone replacement and the Women's Health Initiative

Observational data from Harvard found that nurses on hormone therapy had less heart disease. Plausible biology and heavy promotion by Wyeth followed, and it became a multibillion-dollar treatment. The randomised Women's Health Initiative, around 2001–2002, was halted for more blood clots and cardiovascular events: the opposite of what was expected.

• The CAST antiarrhythmic trial

Antiarrhythmic drugs suppressed post-heart-attack arrhythmias, and cardiologists felt it was unethical to withhold them. When a randomised trial (CAST) was finally run, the drugs increased the risk of death, and class 1C agents were largely abandoned. Prasad's lesson: smart, well-meaning people with sound biology and observational data can still be wrong.

• POLO in pancreatic cancer

Patients whose disease was controlled on chemotherapy (FOLFIRINOX) stopped it and got either a targeted drug costing

about $12,000 a month or a placebo. Progression-free survival improved but overall survival did not. Prasad argues the control arm should have continued the chemotherapy that was working, not a placebo.

• Real wins exist

Gleevec for chronic myeloid leukaemia, which targets the single driver fusion, took median life expectancy from three to four years to near-normal in Swedish data. Prasad also calls treatments 'no-brainers' when the benefit is clear and the toxicity low or reversible. Attia notes that Avastin's first approval (around 2000–2002) was in colon cancer, at roughly $100,000 a year.

• Press release before data on dexamethasone

When the UK announced that dexamethasone helped hospitalised COVID patients needing oxygen, Prasad pointed out that the published protocol showed a well-run trial. He was willing to act on it before the full paper and took criticism for doing so. His point was that the quality of the trial matters more than its format.

OTHER RELEVANT

• Ask what a treatment does for survival and quality of life

With any new cancer drug, ask whether it helps people live longer or better, by how much, and compared with what. A hazard ratio of 0.7 in a press release says nothing about how long people lived or the side effects.

• Be skeptical without being contrarian

Prasad's clinical stance is to do everything that adds something for the patient in the room, while being honest about weak evidence. When asked about expensive add-ons like hyperbaric oxygen protocols, his first question is how much they cost.

• Watch for conflicts of interest

Ask whether an advocacy group or expert is funded by the companies whose products they recommend. Prasad admits that as a resident, sleep-deprived, he didn't see through drug-rep perks such as fancy branded pens.

• Be cautious about 'game changers'

CAR-T and checkpoint inhibitors produce real, sometimes dramatic responses in some people. The open question is how much they help across all the conditions they are now being tried in.

#121 – Azra Raza, M.D.: Why we’re losing the war on cancer

Guest: Azra Raza
Date: 2020-07-28 · Duration: 1:54:55
URL: https://www.youtube.com/watch?v=3GcP75TXEfM

KEYPOINTS

• Raza argues that age-adjusted cancer mortality is essentially where it was in 1930

Peter usually says cancer mortality hasn't changed since about 1970. Raza goes further. She says the roughly 27–30% decline over the last 30 years followed a 30-year rise driven by smoking, so the fall mostly tracks the drop in smoking. In her words, 'otherwise we are really at square one.' She compares herself to Nietzsche's man with a lamp at noon, except she is 'looking for an adult in the room.'

• Most cures still come from 'slash, poison, burn,' and only in early disease

Raza's breakdown: of newly diagnosed cancers, about 68% are cured, overwhelmingly with surgery, chemotherapy and radiation. The 32% who present with advanced disease mostly can't be cured with those same tools. She takes this as the best evidence that the only reliable lever is catching cancer early. Some of the first chemotherapy agents came out of chemical weapons research, and she gave all three of the original drugs to her own husband.

• Real breakthroughs are real but rare

Gleevec for CML and GI stromal tumors proved targeted therapy can work, but those are rare cancers, and Peter doubts it has moved overall mortality even 1%. Melanoma survival is dramatically better with checkpoint inhibitors. Still, Raza estimates all such successes together account for under 10% of cancers. Her question is whether they reflect the 'quarter of a trillion dollars' invested. She is clear that this research should continue.

• 95% of experimental cancer drugs fail, and Raza says many of the 5% shouldn't have passed

In her account, the 'winners' often extend survival by a few months in only 20–30% of patients. Approvals often rest on progression-free survival: if the tumor isn't seen to grow for an extra two and a half months but the patient dies at the same time, the drug can still be approved and earn billions. Peter adds that a 'partial response' has a somewhat arbitrary definition and that durability is rarely discussed.

• The core scientific problem, in her view, is the preclinical model

Raza blames the failure rate on reductionist testing platforms such as cell lines, 2D and 3D cultures, and genetically engineered or immune-compromised mice. She says she supports animal research for biology, but not for drug development, because what a drug does in a mouse is only true for mice. She would not even rely on animals for safety. She points to the FDA's phase zero design, which starts humans at 1/500th of a dose and escalates.

• New drugs often cost far more for small gains, with ruinous consequences for patients

Her figures: 42% of newly diagnosed cancer patients will be financially ruined by the second year, and 50% of women with breast cancer are pursued by collection agencies. Peter recalls that Avastin in metastatic colorectal cancer added about four months of median survival at roughly $100,000, which led some publicly funded systems to rely on quality-adjusted life years. Peter flags that his Avastin details may not be exact.

• Good intentions slowly produced a broken system

Raza uses the frog-in-slowly-heating-water image: each step began with good intentions. Peter adds that publication as a promotion metric fuels a 'cottage industry' of low-quality journals and irreproducible studies. He also says that by his own analysis from about five years earlier, slightly more than half of global oncology research money ran through the NCI after Nixon's war on cancer, though he notes he could be a little wrong.

• Her proposed solution is aggressive early detection, monitored continuously

Raza argues that mammograms and PSA failing on their own doesn't prove early detection fails. She wants genomics, transcriptomics, proteomics, metabolomics and imaging combined with AI, with up to '50 tests if we have to,' read continuously rather than once a year. Peter frames it as three rules: don't get cancer, screen smartly, and treat when tumors are in the millions rather than billions of cells. He estimates lifestyle changes could cut cancer risk 30–50%, based on his reading of the literature.

• Powerful late-stage therapies should move earlier

She calls current treatment 'paleolithic,' quoting the line about beating a dog with a baseball bat to get rid of its fleas. She notes that whole industries exist just to manage CAR-T side effects. She says such therapies should be developed, but used when tumor burden is low.

EXAMPLES

• Andrew, 22, and the book The First Cell

Her daughter Shahzad's best friend developed arm weakness, was quadriplegic within hours, and had a 9 cm unresectable glioblastoma. His first words were 'just call Azra… she will cure me.' Their helplessness pushed her to write after years of turning down literary agent John Brockman.

• 'Seven and three' for AML since 1977

Raza still uses cytarabine plus daunorubicin. Five-year survival rose from about 10% to about 26%, which she credits to better antibiotics and transfusions, not new drugs. A liposomal version for patients aged 60–75 costs $45,000 versus $5,000, approved on a 3.7-month median survival gain in selected patients.

• Karachi in the early 1970s

Raza was born and raised in Pakistan and entered science through medicine. She saw patients arrive by donkey cart with fungating tumors. Her first patient, a young woman with AML and a large spleen, made her favor studying liquid tumors, which can be sampled repeatedly.

• Harvey Preisler's acceptance

Her husband, head of the Roswell Park leukemia program, died in 2002 after a five-year battle; their daughter was four at diagnosis. On hearing his diagnosis he said, 'I'm glad it's me and not you or Shahzad.' Raza admits kicking doors and crying

while he called it 'the luck of the draw.'

• A 60,000-sample tissue bank

Since 1984 Raza has collected serial blood, marrow and germline samples, doing every marrow herself. She hopes to trace pre-leukemia to leukemia, find early biomarkers, and find the 'first cell.'

OTHER RELEVANT

• Read 'approved' and 'progression-free survival' skeptically

When a new drug is touted, ask about median overall survival, what fraction of patients benefit, and whether the gain is weeks or months. Raza's 3.7-month example shows how far headlines can outrun benefit.

• Smarter screening beats single tests

Peter points to PSA velocity, PSA density and 4Kscore over PSA alone, citing his Ted Schaeffer episode, and to his Raj Attariwala episode on mammography's limits. Raza highlights an FDA-approved fingertip-blood PSA chip and Toshiba's claim of 13 cancers from one drop of blood for $180 in four hours.

• Treat liquid biopsies as promising but early

Both are optimistic about multi-cancer blood tests such as Grail, which Raza says was in phase 2 with about 30 cancers. Peter avoids predicting a timeframe and wants regulatory milestones first.

#114 – Eileen White, Ph.D.: Autophagy, fasting, and promising new cancer therapies

Guest: Eileen White
Date: 2020-07-09 · Duration: 1:58:54
URL: https://www.youtube.com/watch?v=93U__YRR-aU

KEYPOINTS

• Eileen White found autophagy by accident, through apoptosis

Eileen White, of the Rutgers Cancer Institute of New Jersey, did her postdoc with Bruce Stillman at Cold Spring Harbor. She was given an adenovirus oncogene and found it was a viral version of BCL-2, a human oncogene that blocks apoptosis (programmed cell death). Cells that couldn't commit suicide survived even in buffer with no nutrients. Explaining how led her lab, in the early 1990s, into autophagy, then barely studied in mammals.

• Apoptosis is a tidy, tumour-suppressing death

Unlike necrosis, where cells burst and inflame surrounding tissue, apoptosis breaks a cell down in a controlled way and packages it into apoptotic bodies. Macrophages clear these, which limits inflammation and may help antigen presentation. p53 activates apoptosis-promoting proteins such as PUMA and NOXA, which antagonise BCL-2. Common hotspot mutations of p53 can both disable it and actively promote cancer, so the old 'loss versus gain of function' teaching is too black-and-white.

• Autophagy is the cell's recycling system

Under stress such as starvation, cells engulf their own components in autophagosomes and send them to lysosomes to be broken down for fuel and building blocks. Exercise induces autophagy strongly, and muscle needs it because exercise damages muscle. White points out that much of a cell's mass is protein, a point David Sabatini has made, so recycling proteins is a major supply route.

• Autophagy is essential to life

Mice lacking the autophagy genes ATG5 or ATG7 are born but die in the newborn period. When White's lab deleted autophagy in adult mice, they died of neurodegeneration within two to three months. If those mice were fasted, they were all dead within 16 hours. The brain and liver depend on autophagy for long-term protection.

• Tumours depend on autophagy more than the host does

In mice with lung cancer driven by RAS, deleting an essential autophagy gene throughout the body killed the tumour before the mouse. A newer model from a former trainee and a UK lab can switch autophagy off and back on, and normal tissues show a remarkable capacity to recover. That suggests treatment could use a temporary window.

• Some cancers are especially autophagy-dependent

RAS-driven cancers, BRAF V600E lung cancers and melanomas, and homologous-recombination-deficient breast cancers appear particularly sensitive. Lung cancers that have lost LKB1, the tumour suppressor that activates AMPK, can't turn on this protective response to low energy, a mouse model made by Jessie Guo, now at Rutgers.

• The paradox: autophagy prevents cancer yet feeds established tumours

By clearing damaged components, autophagy buffers the stress that can lead to cancer. Once a tumour exists, it uses autophagy to survive. White cautions against equating caloric restriction with autophagy. Caloric restriction may limit tumours partly through other routes.

• No one knows the dose of fasting

Attia is sure that after about seven days of water-only fasting, autophagy is 'fully cranked', and that a 12-hour gap does nothing. Where between those it switches on is unknown. That leaves his own protocols (3 days monthly, 5 or 7 days quarterly) as guesses. Measuring autophagic flux requires blocking lysosomal breakdown with bafilomycin or hydroxychloroquine and tracking the conversion of LC3-I to LC3-II, so blood-cell measurements in fasting people only give clues. George Cahill's classic 40-day fasting study showed that the first, second and third 24 hours are metabolically very different. The open question is whether 48–72 hours gets you 80% of the benefit or only 20%.

• Metabolic tracing could answer this

White proposes labelling mice with carbon-13 or nitrogen-15 tracers to see how different tissues use nutrients during fasts of different lengths. That could define the roughly 50 metabolites or proteins that track autophagy, and later test them in humans. It's possible now, she says, in a way it wasn't 20 years ago.

• Delaying chronic disease is the real target

Attia argues that the animal and centenarian data point to delaying the onset of chronic disease, which by his analysis accounts for 82% of US deaths over 50. He notes that for solid tumours, median survival has improved by less than about a year since 1970.

EXAMPLES

• A Lynch syndrome patient on Keytruda

A friend of Attia's with Lynch syndrome developed unresectable pancreatic adenocarcinoma wrapped around his mesenteric vessels. A paper in the New England Journal of Medicine on mismatch-repair-deficient tumours led Attia to push for the anti-PD-1 drug Keytruda through a trial. Five years later he was disease-free.

• Mutation burden and immunotherapy

Melanoma responds well to CTLA-4 and PD-1 blockade because it carries so many mutations. Yet some high-mutation tumours don't respond. White's NIH grant builds mouse models with low, medium and high mutation burden to test how blocking autophagy affects the response.

• The 2016 Nobel

The Nobel Prize for autophagy went to work in yeast that White's field then extended to mammals.

• The Warburg debate

Attia cites the 2009 Science paper by Matt Vander Heiden, Lewis Cantley and Craig Thompson, which argued that cancer cells' heavy glucose use serves biosynthesis, not just energy.

OTHER RELEVANT

- **Exercise as an autophagy inducer**
  Exercise is a potent, low-risk trigger. White says it's less of a dosing problem than fasting, since most people just need more.
- **Treat fasting protocols as unproven**
  The duration and frequency of fasts are educated guesses until autophagy can be measured in humans. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Inherited risk still matters**
  Good health practices don't erase a BRCA mutation. Screening still matters. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch for autophagy-blocking cancer trials**
  Combining autophagy inhibition with targeted drugs or immunotherapy is an active research direction, but still experimental. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#61–Rajpaul Attariwala, M.D., Ph.D: Cancer screening with full-body MRI & a masterclass in radiology

Guest: Rajpaul Attariwala
Date: 2020-01-12 · Duration: 2:13:15
URL: https://www.youtube.com/watch?v=ZYviNY8xpes

KEYPOINTS

• Radiation dose varies by orders of magnitude across imaging tests

Attariwala puts a mammogram at roughly 0.05 millisieverts, which he calls negligible, while a whole-body PET-CT stacks the CT's x-ray dose on top of radioactive fluorine-18 glucose and can easily total 30–40 millisieverts. Attia notes the US regulatory ceiling is 50 millisieverts a year and that simply living at sea level contributes about 2–3, more at altitude or with radon. His rule: if you are going to irradiate someone, extract as much information as possible from that exposure.

• A CT is an x-ray done in three dimensions, calibrated so tissues are comparable anywhere

CT uses Hounsfield units, with water fixed at zero and air and bone at the extremes. Because the eye cannot see the whole range at once, radiologists 'window' the image, centring it on lung, bone or soft tissue. Attariwala says that for non-moving organs such as the pancreas, slice count matters less than people think; 256-slice machines mainly help with fast-moving structures like the heart.

• Ultrasound is fast and radiation-free but depends heavily on the operator

High-frequency sound waves bounce back from tissue boundaries, which makes ultrasound ideal for quick bedside answers and, through a window that avoids lung air, for watching heart valves move. Attariwala stresses that the skill of the person holding the probe can't be replaced, which is the main reason results vary so much.

• Mammography accuracy depends on breast density

Attia recalled all-comer figures of about 84–85% sensitivity and 90–91% specificity, while acknowledging the numbers may be dated. Attariwala said averages hide the real story: in fatty breasts sensitivity can exceed 95%, but a single mammogram in dense glandular tissue may be only about 55% sensitive, because low-energy x-rays don't penetrate that tissue well. That is why some women are told they also need an ultrasound.

• Sensitivity and specificity measure two different failure modes

Using 100 women with cancer, 80% sensitivity means 20 are missed (false negatives). Using 100 women without cancer, 90% specificity means 10 are wrongly flagged (false positives). Attia pushes listeners to ask which error a test makes, and in whom, rather than accepting a single accuracy number.

• MRI uses strong magnets to align hydrogen in water and fat

Field strength is measured in tesla (one tesla is 10,000 gauss), and scanners commonly run at 1.5, 3 or 7 tesla. Higher fields align more hydrogen nuclei, which gives more signal. Contrast-free 'dry' MRI is usually described as harmless, but Attariwala described a patient with severe migraines whose headache was triggered by the scanner.

• Diffusion-weighted imaging finds cancer by how freely water moves

DWI, or DWIBS with background suppression, compares water motion at two points within microseconds. Tumours are densely packed with cells, so water diffusion is restricted. Attariwala compares this to how a surgeon feels a hard lump. Pairing this functional signal with anatomical detail approaching 1×1×1 mm is his version of PET-CT's 'one plus one equals three', without ionising radiation.

• The main harm of screening is the false positive, not the scan itself

Attia calls whole-body cancer screening a very personal decision that isn't for everyone. Outside of rare issues like a magnet-triggered migraine, the harm is what a false alarm sets off: anxiety, extra imaging, biopsies and the small but real risks of each procedure.

• MRI quality isn't standardised, so 'a DWI MRI' isn't one product

Unlike Hounsfield-calibrated CT, MRI signal varies with vendor, coils and protocol. Attariwala calls it buyer beware. The Quantitative Imaging Biomarkers Alliance (QIBA) at the Radiological Society of North America is pushing standards organ by organ, starting with prostate and liver, with breast following. Attia admits that even he couldn't judge differences between scanners in another city.

• Machine learning helps most where the problem is narrow

Algorithms are already being tested as a second reader for mammograms, especially for comparing a woman's current images with her previous ones. Attia floats 97–98% sensitivity and specificity as the level needed for confidence. Attariwala thinks that will be hard to reach because breast compression and positioning differ each time. In whole-body images, even telling which organ is the liver or the kidney is still unsolved for machines.

EXAMPLES

• Two false positives in roughly 1,000 scanned people

One was a man with breast tissue on one side only. Because gynecomastia is usually on both sides, he was sent for an ultrasound, which also couldn't rule out cancer, and the biopsy came back as normal tissue. The other was a woman in her late 50s, who had never had a mammogram, with a fluid-trapping scar from a seatbelt injury.

• Prostate: MRI plus a 4K blood test avoided biopsies

FDG-PET is close to useless for the prostate: the gland gets little blood flow, and tracer pools in the bladder next to it. Attia described two of his patients with high PSA and high 4K scores who, instead of the biopsy they would once have had, got a DWI MRI that came back clean. Attariwala said MRI is becoming the de facto prostate screening tool in places like the UK, Scandinavia and Australia.

• A cycling friend's fatal aneurysm

Attia recalled a riding partner, six or seven years older than him, who got a sudden headache at Disneyland and died of a congenital aneurysm. Attariwala put mortality after rupture at roughly 93–95%. Aneurysms found early can be electively coiled or

clipped, and his non-contrast MRI shows brain vessels with angiogram-like detail.

• From robot eye surgery to building his own MRI

Attariwala trained in chemical and then biomedical engineering (PhD, Northwestern), helped build a robot for keyhole eye surgery, then went to medical school, radiology and nuclear medicine, training at Memorial Sloan Kettering, UCLA and USC. In Vancouver he bought an MRI 'so I could play with it', which led to the AIM clinic and later Prenuvo. A brain scan there is fully isotropic and a whole-body scan takes about 55 minutes.

OTHER RELEVANT

• Ask about your breast density

If you have dense breasts, a normal mammogram is far less reassuring, because sensitivity may be near 55%. Ask whether supplemental imaging such as ultrasound or MRI makes sense, and keep earlier images so they can be compared over time.

• Weigh radiation against the information you get back

A mammogram or chest x-ray adds little to your yearly exposure. Repeated PET-CTs at 30–40 millisieverts each add up quickly against a 50-millisievert annual limit. Ask whether a non-ionising option like MRI or ultrasound would answer the same question.

• Before screening, plan how you'll handle a false positive

Decide in advance how you would respond to an ambiguous finding, including follow-up imaging, a possible biopsy and the wait in between. Attia treats this as the real cost of screening and the reason it should be an individual choice.

• Ask exactly how an MRI will be done

Because protocols aren't standardised, ask whether diffusion-weighted sequences are included, what the resolution is and who reads the scan. Two 'full-body MRIs' can differ enormously in quality.

#32–Siddhartha Mukherjee, M.D., Ph.D.: new frontiers in cancer therapy, medicine, and writing

Guest: Siddhartha Mukherjee
Date: 2020-01-07 · Duration: 1:05:16
URL: https://www.youtube.com/watch?v=iWWTMdEGan4

KEYPOINTS

- **Sid combines Pulitzer-level writing with practicing oncology and lab science.**
  Peter calls out how rare that triad is in one person. The Emperor of All Maladies made cancer's history readable without sanding off scientific teeth, and Sid's later books continue that translation project while he still sees patients and runs research. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **They first bonded over science-on-a-napkin energy.**
  A Japanese-restaurant brainstorm—energetic teams, multi-site ideas—became a friendship before The Gene even landed. Peter had already been reshaped by Emperor and wanted the craft behind it as much as the oncology. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Writing craft: braid personal story with dense science.**
  Sid's method toggles intimacy and mechanism so neither tourists nor experts feel abandoned. Peter, struggling with his own book, presses him on how to do science justice without turning chapters into review articles. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Cancer therapy's frontier is smarter targeting, not only harder chemo.**
  They survey how genomics, immunology, and cell therapies are changing who survives which diseases. Sid is careful to separate durable remissions from hype cycles that outrun evidence. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **History literacy prevents false novelty.**
  Emperor's long arc—from radical surgeries to chemo to targeted drugs—shows each era declaring victory early. Knowing that pattern makes today's press releases easier to handicap. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Medicine needs storytellers who will not lie about uncertainty.**
  Sid argues narrative is not the enemy of rigor; bad narrative is. Patients already live inside stories—clinicians should offer accurate ones. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Research teams beat lone genius mythology.**
  Even napkin-born ideas require 'very energetic teams' across sites. Sid's praise of collaborative infrastructure matches how modern oncology trials actually run. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Reading cancer changes how you read risk in ordinary life.**
  Peter notes even non-cancer listeners gain a template for evaluating medical claims: mechanism, history, effect size, and human cost. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **The physician-writer must protect clinical humility.**
  Seeing patients keeps Sid's prose from floating into abstraction; writing keeps his clinic from drowning in unspoken fear. Each practice disciplines the other. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Translation is a moral act when stakes are mortal.**
  Clear public explanation of cancer biology can reduce both nihilism and magical thinking. That is why Sid keeps doing mass-audience books instead of only papers. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

EXAMPLES

- **Pulitzer for The Emperor of All Maladies**
  Proof that rigorous cancer history can win both scholars and general readers. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Napkin dinner origin with Peter**
  Friendship and project sparks before The Gene—science as social and intellectual sport. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Peter's own book struggle**
  Sid's craft advice lands on a listener mid-manuscript, making the meta-conversation concrete. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Era-by-era false peaks in cancer care**
  Historical pattern that disciplines excitement about any single new modality. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

- **Multi-site team science**
  Modern oncology progress as choreography, not solitary heroics. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

OTHER RELEVANT

- **Read Emperor (or equivalent history) before the next cancer headline.**
  Context turns press releases into placeable moves on a long board. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Demand effect sizes and durability, not just mechanisms.**
  Beautiful biology still has to move survival or suffering. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **If you write about science, braid scene and citation.**
  Sid's toggle is learnable craft, not mystic talent. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Keep patient contact if you theorize about care.**
  Clinic is the bullshit filter for elegant ideas. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

#30 – Thomas Seyfried, Ph.D.: Controversial discussion—cancer as a mitochondrial metabolic disease?

Guest: Thomas Seyfried
Date: 2020-01-06 · Duration: 2:48:21
URL: https://www.youtube.com/watch?v=6PJfOFTaYow

KEYPOINTS

• Seyfried argues cancer is primarily a mitochondrial metabolic disease, not a genetic one

Following Otto Warburg, Seyfried, a Boston College professor, says there is 'only one primary cause' of cancer: chronic damage to cellular respiration. Mutations are downstream effects. Peter frames the episode as controversial and repeatedly presses for experiments that could settle it. Seyfried notes estimates that only about 5–6% of cancers stem from inherited germline mutations.

• His interest in cancer grew out of epilepsy research and calorie restriction

At Yale, Seyfried studied glycolipids, epilepsy and lipid storage diseases, and an internal grant to study ketogenic diets was rejected. Years later, a student pointed him to a ketogenic diet meeting connected to Jim Abrahams' Charlie Foundation. In his mouse work, seizure control and tumor shrinkage tracked with calorie restriction: lower blood sugar plus higher ketones. He says children on ketogenic diets can get breakthrough seizures when blood sugar spikes, a visible signal that tumors don't give.

• Seyfried says the 'Warburg effect' everyone cites is only the secondary feature

Warburg saw tumor slices produce lactic acid even in 100% oxygen. He concluded respiration was defective, so cells had to ferment. Seyfried says Warburg himself called aerobic glycolysis a secondary, environment-dependent phenomenon. He argues that cell-culture findings of 'normal' oxygen uptake mislead, because uptake in tumor cells is uncoupled from ATP production.

• His proposed 'missing link' is mitochondrial substrate-level phosphorylation fueled by glutamine

Substrate-level phosphorylation makes ATP by moving a phosphate directly from a molecule onto ADP, for example at the succinyl-CoA step of the TCA cycle, without the electron transport chain. Seyfried argues most cancer ATP comes from this pathway inside the mitochondria, driven by glutamine, with glucose fermentation in the cytoplasm. The heart can do this briefly under stress, he says, but normal cells can't sustain it. Warburg couldn't have known about it.

• He points to structural defects: abnormal cristae and cardiolipin

Seyfried says cardiolipin, the signature lipid of the inner mitochondrial membrane, has been abnormal in every tumor his lab has examined. He cites Peter Pedersen's lifetime of work showing abnormal mitochondria and accuses top journals of ignoring it. He compares this to the Church refusing to look through Galileo's telescope. Peter pushes back that this looks like a stalemate between bodies of literature and calls for collaborative new experiments.

• Metastasis may come from macrophage–cancer cell fusion

Seyfried cites early observations of tumor cells fusing with immune cells and becoming more aggressive. He also cites John Pawelek's Yale work suggesting malignant melanoma behaves like a macrophage. He offers this as why some plant tumors with damaged respiration never metastasize: plants have no immune system.

• His 'press-pulse' strategy: press glucose, pulse glutamine

Press means steadily lowering glucose with a calorie-restricted ketogenic diet, drugs, and stress reduction, since anxiety raises corticosteroids and blood sugar. Pulse means intermittently targeting glutamine, with DON (6-diazo-5-oxo-L-norleucine) working best in his hands. It is pulsed because T cells, macrophages and other immune cells also depend on glutamine and are needed to clear dead tumor cells. He also proposes hyperbaric oxygen at about 2.5 atmospheres as an oxidative-stress 'pulse' to replace radiation.

• The 'therapeutic ketosis' target is a glucose-ketone index near 1.0 or below

His group published the GKI, a ratio of blood glucose to ketones. He adds that in his experience women reach the target more easily than men, and that Dom D'Agostino's ketone supplementation can help.

• Seyfried claims a 50% drop in cancer deaths within 10 years, and Peter calls it bold

Seyfried says stopping 'half of the stuff we're doing' and treating cancer by its metabolism could cut deaths by more than 50%. Peter notes age-adjusted mortality had fallen only about 3% in 50 years by his figure. His dream trial adds the missing arm: metabolic therapy without standard of care, compared against standard care alone and standard care plus metabolic therapy. Peter notes a practical barrier: GBM usually presents with mass effect that requires urgent surgery or steroids.

EXAMPLES

• Peter's near-blackout at Stanford

After three years on a ketogenic diet, Peter underwent an insulin suppression test, which in roughly 400 non-diabetic subjects had produced steady-state glucose no lower than about 79 mg/dL. Peter's glucose fell to about 31, and his ketones dropped from about 2.5–3 mM to under 1. He drenched in sweat, nearly seized, and the IV dextrose infiltrated his arm. His wife didn't even know he'd flown there.

• Sequencing tumors with no pathogenic mutations

Seyfried says his lab sequenced the whole genomes of five independently derived mouse cancers and found no pathogenic mutations. He uses this to argue cancer can exist without driver mutations.

• Mouse fasting isn't human fasting

Mouse metabolism runs about seven to eight times faster. One day of water-only fasting in a mouse roughly equals seven days in a human, and 35–40% calorie restriction in mice approximates therapeutic water fasting in humans.

• A GBM case and radiation necrosis

A glioblastoma patient in a published case report spent three weeks in therapeutic ketosis before debulking surgery and deferred standard care for three months. He lived 30 months, far longer than typical, but at his death the tissue showed radiation necrosis rather than tumor. Seyfried argues against brain radiation. He also cites Andrew Scarborough, a stage 3 astrocytoma patient who refused radiation and chemotherapy, and admits these are anecdotes.

• Avastin in brain cancer

Seyfried calls the roughly $100,000-a-year anti-angiogenic drug 'despicable' for GBM. He argues starving vessels worsens hypoxia, which fermenting cells tolerate, so scans look better while survival stays 'abysmal.' He says GBM survival resembles the 1926 Bailey and Cushing paper.

OTHER RELEVANT

• Don't try extreme glucose lowering alone

Seyfried insists 'our goal is to kill the tumor cells,' not ourselves. Drugs must be used strategically by people who know what they're doing. Peter's hypoglycemic episode shows the danger.

• Treat this as a hypothesis awaiting trials

Peter's stance throughout is curiosity plus a demand for rigorous head-to-head trials. The only setting where mainstream medicine accepts ketogenic diets as legitimate first-line therapy is drug-resistant epilepsy.

• Question both camps' evidence

Seyfried notes that up to 50% of papers in top journals can't be reproduced. Peter counters that both sides can explain away each other's data, which is why new collaborative experiments matter.