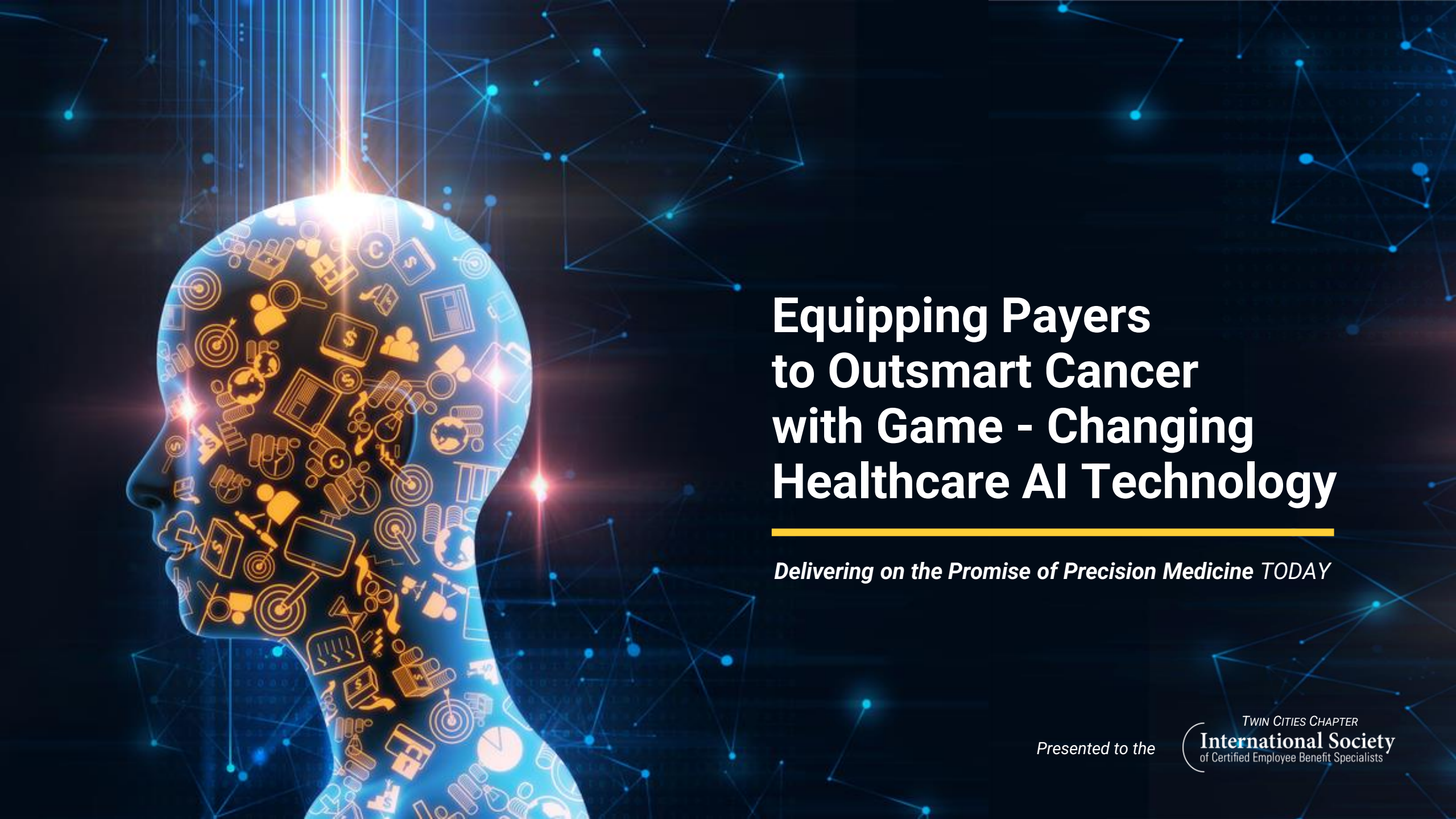


Equipping Payers to Outsmart Cancer with Game - Changing Healthcare AI Technology

***Delivering on the Promise of Precision Medicine** TODAY*

Presented to the

TWIN CITIES CHAPTER
International Society
of Certified Employee Benefit Specialists

International Society of Certified Employee Benefit Specialists

International Foundation of Employee Benefit Plans

Education | Research | Leadership

Wharton University of Pennsylvania

This presentation satisfies the requirements for continuing education credit as established by the International Society of Certified Employee Benefit Specialists.

For 45 years, the highly-regarded CEBS designation has delivered professional expertise supported by researched-based best practices. Established by the International Foundation of Employee Benefit Plans and The Wharton School of the University of Pennsylvania, the CEBS program was designed based on the latest proven business ideas and tools from world-acclaimed thought leaders.

RC Research Consortium

About the

TPA Network Research Consortium
a Healthcare-Focused Non-Profit Enterprise

Founded by healthcare industry veteran Richard Nicholas, the TPA Network Research Consortium is a healthcare-focused non-profit enterprise, created to help payers evaluate new, yet proven, medical technologies and healthcare innovations with translational research initiatives and comparative effectiveness analysis in real-world settings.

An entrepreneur, Richard Nicholas has four decades of executive-level domestic and international experience in the self-funded, managed care, outsourcing and mergers and acquisitions sectors. He testified as an expert at hearings before the US Congress; has been an advisor to the Mexican government; and is the author of a book on healthcare cost containment and several scholarly healthcare economics studies. Richard currently serves on the CDC-directed *ASTM International* workgroup that created the *Barrier Face Covering* standard that was adopted by the FDA, NIOSH. Mr. Nicholas earned a BA degree with distinction from Boston College and an MBA from Duke University.

To learn more visit www.ResearchConsortium.org or email Richard@ReseachConsortium.org or call (858) 395-4114

Learning *Objectives*

- Learn the *cancer basics* for non-clinicians
- Learn about *key oncology challenges* facing employers and commercial payers
- Learn about *comparative effectiveness research* and why reliance solely on the FDA and PBMs for guidance on medication selection … is ill advised
- Learn about *new approaches* to treating cancer
- Learn about how *new technologies* are being used to combat cancer
- Learn how *Healthcare AI* can be used in clinical *and* payer settings to improve outcomes, contain costs, manage utilization, and eliminate waste
- Case Study Deep Dive: CUREMATCH®

Presentation *Roadmap*

8 - 10 Mins

Cancer Basics for Non-Clinicians

- Today's improved understanding of cancer
- How cancer treatment is evolving and advancing

12 - 15 Mins

Unique Cancer Treatment Challenges Facing Payers

- Cancer's direct financial impact on payers
- Understanding *FDA approved*
- Aligning pharmaceutical industry incentives
- Distinguishing between waste and value

8 - 10 Mins

New Medical Technologies / Healthcare Approaches to Help Payers

- Precision medicine, NGS, genomic/multi-drug targeted therapies, drug-repositioning
- Clinical decision support systems, Healthcare AI
- (Real world) comparative effectiveness analysis

15 - 18 Mins

Healthcare AI Case Study: CureMatch®

AI and genomics power a comparative effectiveness approach to cancer treatment

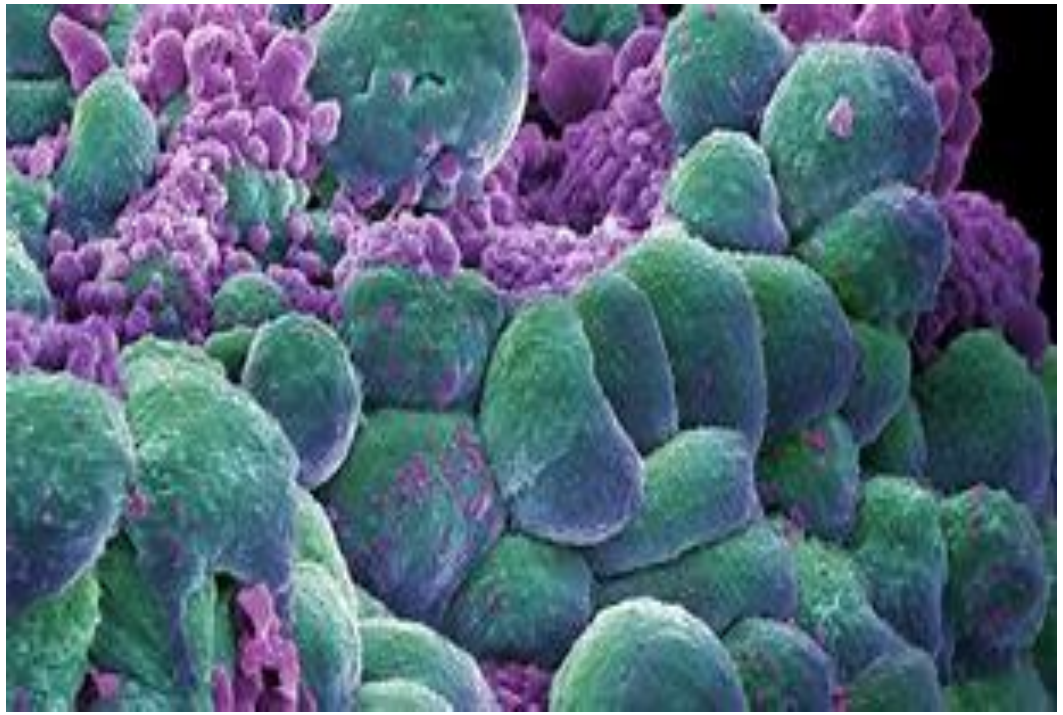
- What it does and how it works
- Scientific, clinical and real-world validation
- Payer waste-reduction and value-identification use cases

5 -7 Mins

Summary & Wrap Up

Cancer for Non-Clinicians: *Our Understanding of it Today*

- Our body is made up of trillions of cells that form tissues and organs
- Genes inside each cell instruct them as to when and how to grow, work, divide, and die
- Normally, cells follow these instructions, but when this process fails, cancer develops

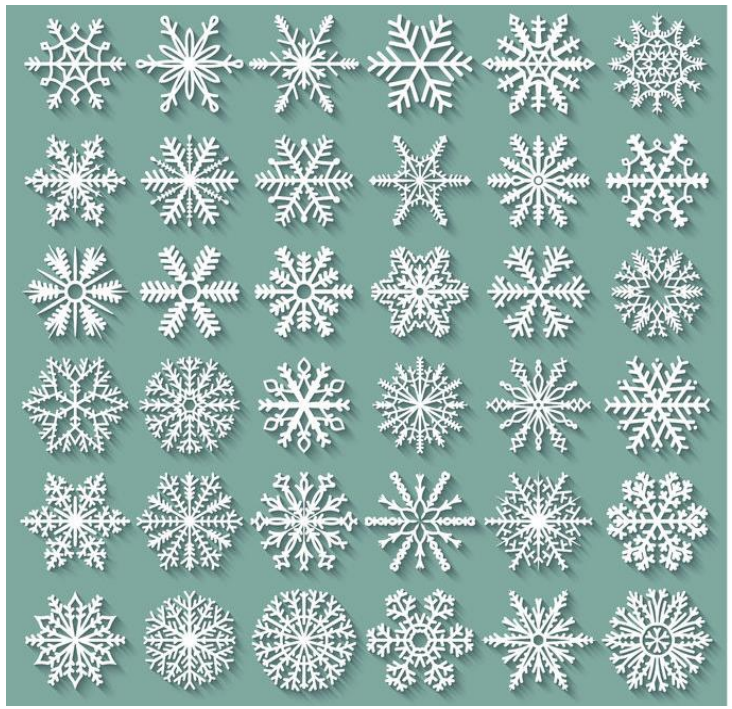


- Errant cancer cells are called *mutated cells*
- Cancer = uncontrolled, excessive cell growth
- Cancer appears as a tumor or in the blood
- Cancer cells hide from the immune system or trick it into helping them stay alive and grow
- As cancer cells don't stick together well, they can spread to nearby tissues (i.e., metastasis)
- With cancer, the organ impacted is secondary to a tumor's genomic / molecular make-up

All Cancers Are Different

Do Any of These Cancers Look Alike ?

Cancer is a general term for diseases that are similar but like snowflakes: *no two are quite alike*



Old Approach: A consistent drug between patients even in the presence of different molecular profiles

New Approach: A consistent (science-based molecular matching) strategy with access to the full range of drugs

Breast Cancer Mutations: *Malignant Snowflakes*

Tumor A	BRCA1	SOX2	TP53	FLT3
Tumor B	EGFR	CCND1	CDKN2A	FGFR1
Tumor C	*ERBB2*	PICK3CA	AURKA	ZNF213
Tumor D	*ERBB2*	MYC	CDK6	ESR1
Tumor E	GATA3	NF1	ATK3	MYCL1

Are We Expecting *Too Much from Our Drugs ?*

Drugs do not have the same utility for everyone: they are not designed to…and we should not expect them to. Yet, we do, as it relates to our traditional approach to the treatment of cancer.

- *Treatment Effectiveness*
- *Treatment Efficacy*
- *Number Needed to Treat*
- *Number Needed to Harm*

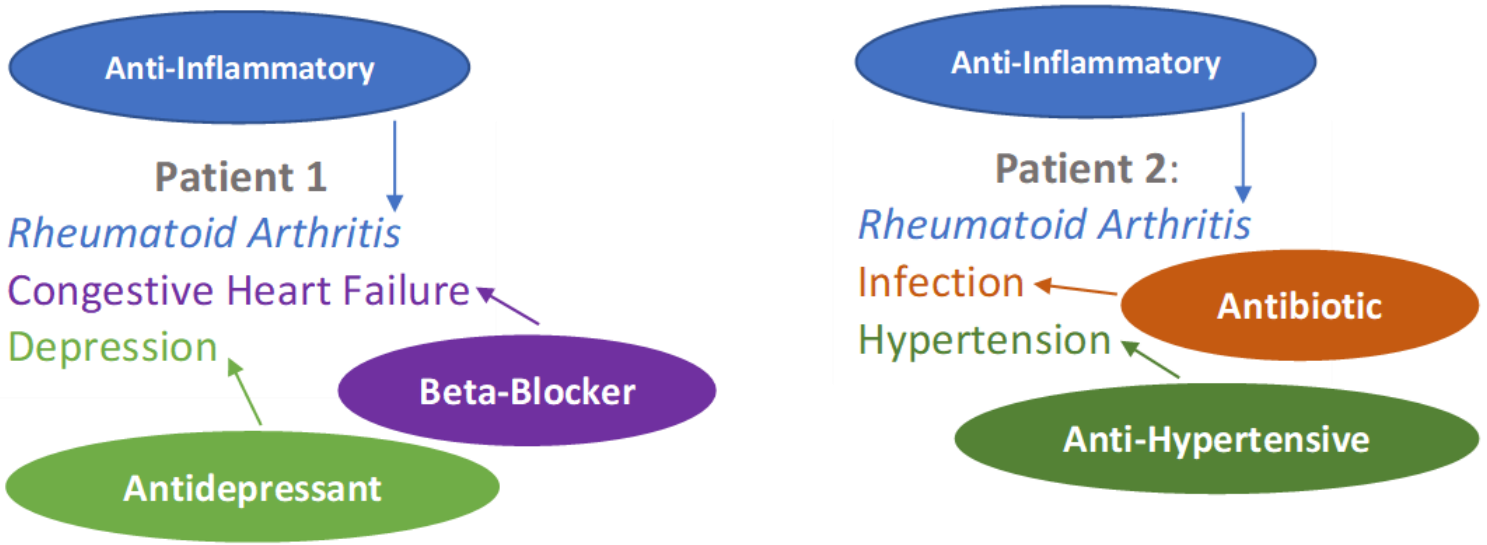
A medication can be 98% successful at treating a disease…but for only 2% of its intended patients.

- With settled science, *clinical trials solve math, not clinical, problems*: what percent benefited ?
- *The more Rx choices a doctor has, the higher the likelihood that the correct choice will be made.*

Do We Need a New Approach to *Treating Cancer ?*

Patient-Centric Practice (N-of-1) is Routine in Medicine

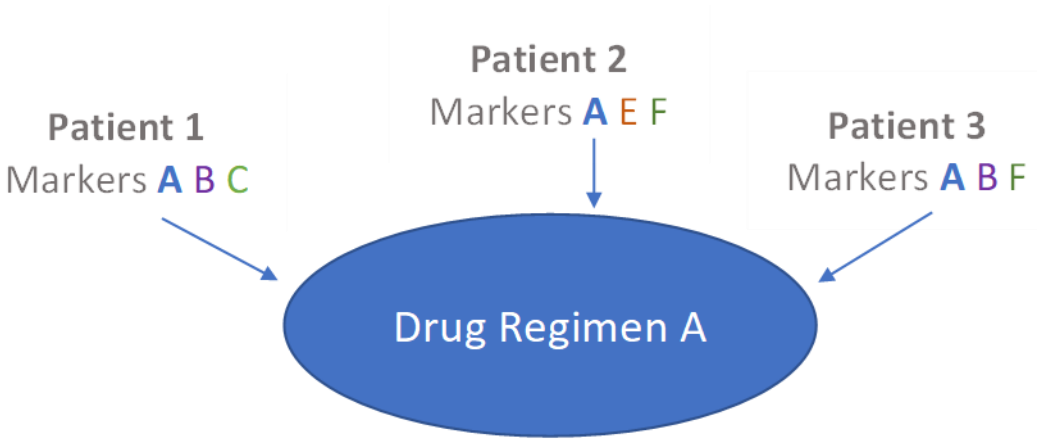
… EXCEPT for in the Treatment of Cancer



In the general practice of medicine, physicians develop customized therapy combinations — regimens — that are matched to address each of the patient's condition, *simultaneously.*

Our Approach to Treating Cancer is *Evolving…*

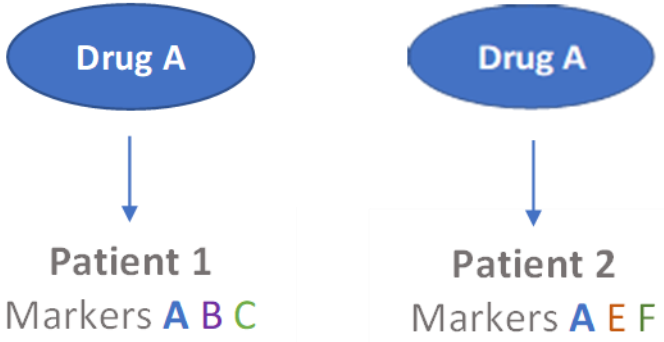
Traditional Drug-Centric Tx Approach



Logic:

Find a common feature among patients (e.g., type of cancer, molecular aberration, marker) and place all of them on the same drug

Novel **Drug-Centric Genomic-Based Tx Approach**



Logic:

All patients get the same medication(s) regardless of their molecular differences

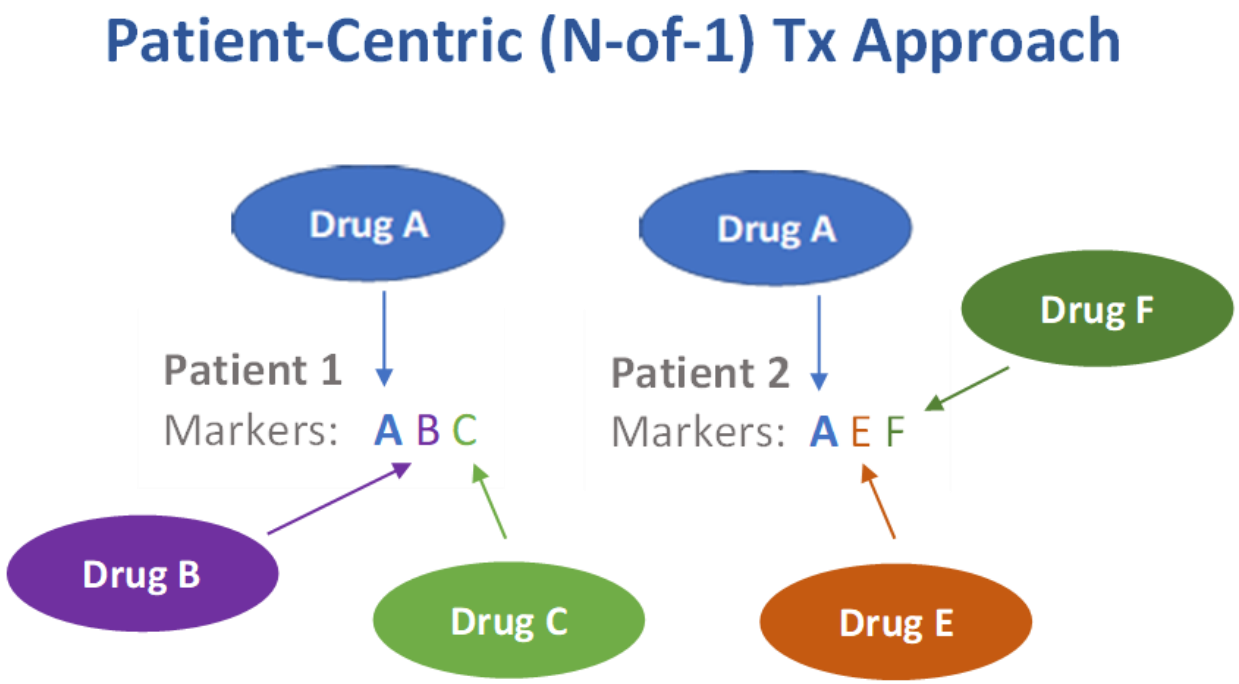
Your Cancer was Found to Have 13 Actionable Mutations

Would You be Okay with Starting Treatment to Address 3?

Even in the practice of precision medicine — where very targeted drugs are used to address specific tumor mutations — some doctors continue to follow a *whac-a-mole* approach where a single drug is used to treat 1 or 2 mutations at a time. This

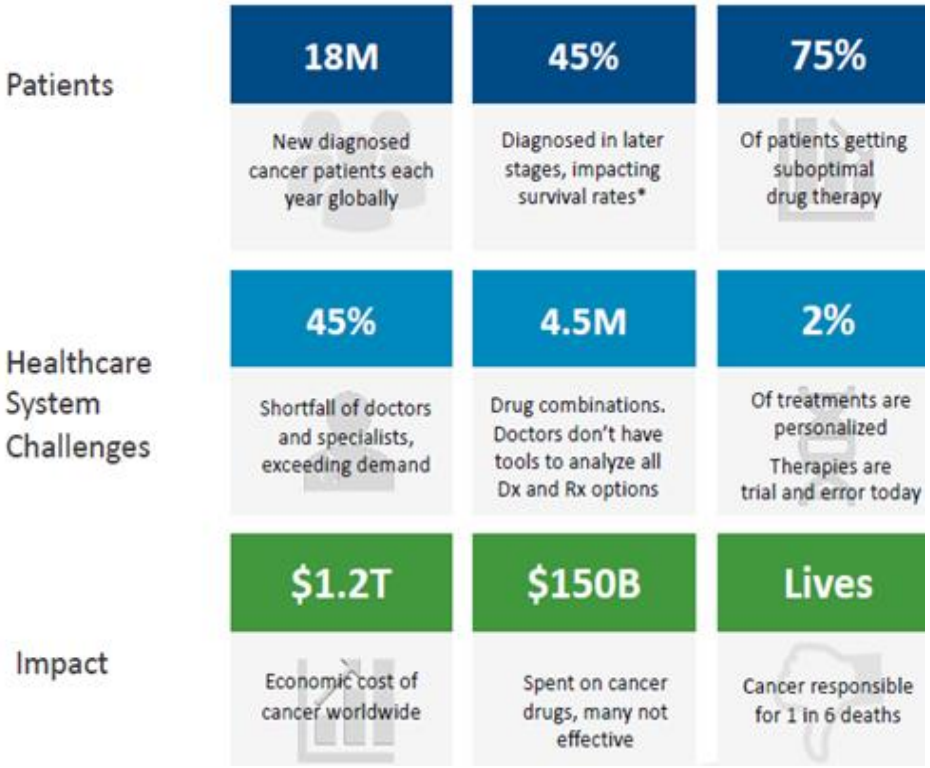
- leaves many potentially dangerous yet actionable mutations unaddressed, and
- enables mutations to develop resistance to certain Rxs over time, thereby making them more difficult to defeat.

Today, We Approach Cancer with *Precision…*



Logic: Customized, patient-specific combination treatment developed based on matching the patient's unique molecular/immune markers to available on-/off-label drugs

Cancer's Direct Financial Impact *on Payers*



- Your chance of developing cancer are 1/200 each year
- Cancer remains responsible for *1 in 6 deaths*
- *Most* cancer patients get *suboptimal cancer therapy* as most cancer drugs are selected on a *hit or miss* basis
- Fewer than 2% of cancer therapies are optimized via personalization based on genomic information
- Much of the *$150B* spent on *high-cost, low-clinical-value cancer* Rxs can be avoided with evidence-based controls
- Medical knowledge doubles *every 73 days*

RC PA Network Research Consortium Healthcare-Focused Non-Profit Enterprise

Cancer's Direct Financial Impact *on Payers*

- Cancer remains the most elusive condition facing payers
- Representing *30%* of one ESL carrier's * reimbursements for claims for its *top 10* medical conditions

- *60%* of plan sponsors will have at least one cancer *shock loss claim,* each year
- Despite a lull in utilization due to the pandemic, cancer claims *have been increasing in frequency, severity and cost*

		From 2017–2020	
	Top five cancer conditions	Total spend up	Claim count up
1	Malignant neoplasm of the breast	80%	43%
2	Multiple myeloma	100%	64%
3	Malignant neoplasm of the trachea, bronchus and lungs	83%	44%
4	Malignant neoplasm of the brain	19%	10%
5	Malignant neoplasm of the skin	18%	15%

Total payments		Rank		Total
	Medical condition	2017–2020	2016–2019	Reimbursements 2017–2020
30.3% Top 3 conditions	Malignant neoplasm (cancer)	1	1	$842.6M
	Leukemia, lymphoma, and/or multiple myeloma (cancers)	2	2	$317.5M
	Congenital anomalies (conditions present at birth)	3	4	$173.7M
	Chronic/end-stage renal disease (kidneys)	4	3	$171.1M
50.7% Top 10 conditions	Septicemia (infection)	5	5	$144.9M
	Liveborn (with secondary complications)	6	6	$143.9M
	Complications of surgical and medical care	7	8	$125.0M
	Unspecified procedures and aftercare	8	9	$122.4M
	Transplant	9	7	$106.4M
	Diseases of the blood and blood-forming organs	10	12	$86.1M
	Stop-loss reimbursements for top 10 conditions			$2.234B

- Source: [2021 SUN LIFE STOP-LOSS & HEALTH RESEARCH REPORT: *High-cost claims and injectable drug trends analysis*]

Cancer's Direct Financial Impact *on Payers*

2020 Rank	Injectable drug	Total cost	Average cost	Most frequently used to treat
1	Keytruda	$28.8M	$139.1K	Cancer
2	Herceptin	$19.1M	$95.9K	Cancer
3	Opdivo	$18.1M	$136.3K	Cancer
4	Neulasta	$18.1M	$40.0K	Cancer
5	Perjeta	$16.7M	$94.3K	Cancer
6	Avastin	$12.6M	$67.0K	Cancer
7	Yervoy	$9.9M	$174.5K	Cancer
8	Truxima	$9.6M	$60.4K	Cancer
9	Darzalex	$9.1M	$141.8K	Cancer
10	Inflectra, Remicade	$8.9M	$85.5K	Other
11	Ocrevus	$8.8M	$112.3K	Other
12	Soliris	$8.4M	$420.1K	Blood disorder
13	Spinraza	$7.3M	$363.3K	Other
14	Adcetris	$6.4M	$221.9K	Cancer
15	Advate, Kogenate	$6.4M	$279.4K	Blood disorder
16	Alimta	$5.6M	$70.5K	Cancer
17	Gamunex-C, Gammaked	$5.4M	$84.2K	Immunodeficiency
18	Kyprolis	$5.1M	$118.4K	Cancer
19	Gammagard	$4.7M	$80.4K	Immunodeficiency
20	Ultomiris	$4.4M	$492.9K	Blood disorder
Totals	Top 20 by type	$159.1M	$89.0K	Cancer conditions
		$19.3M	$370.5K	Blood disorders
		$10.1M	$82.4K	Immunodeficiency disorders
		$24.9M	$123.3K	All other conditions
	Overall top 20	$213.4M		
	All injectables	$368.3M		

- In 2020, *9 of the top 10* high-cost injectable drugs for this ESL carrier* were for cancer
- The Rx part of cancer treatment averaged ≈ *$90,000*
- *27%* of the cost of cancer care is directly for drugs

% Medical	% Rx	Medical condition	Average cost
73%		Malignant neoplasm (cancer)	$188.2K
73%		Leukemia, lymphoma, and/or multiple myeloma (cancers)	$249.9K

- ≈ *80%* of adverse drug events are due to a drug's interaction with a patient's genomic makeup

* Source of Exhibits: 2021 SUN LIFE STOP-LOSS & HEALTH RESEARCH REPORT: *High-cost claims and injectable drug trends analysis*

What the FDA Does *and Does Not* Do

A survey* of physicians revealed substantial deficits in knowledge as it relates to the meaning of *FDA approval*: *> 70%* of physicians believe

- the FDA only approves new drugs *if they are at least as good as existing drugs*, and
- the FDA approves drugs *based on clinically meaningful benefits*

Neither is correct. To be approved by the FDA, a drug must only show

- *statistical* significance *(< 5% probability that trial results happened by random chance)* on
- *a* primary outcome *(not the most important outcome)*
- compared to a *placebo (not an active control, the standard of care…or an existing drug)*
- in a *small number* of studies *(>50% of all breakthrough Rxs are approved based on one trial)*

The FDA's low standard for obtaining approval *does not* include assessing how well they work

MDs overestimate the nominal evidence of efficacy required of new Rxs, and often mis-prescribe

- Study Source: Aaron S. Kesselheim et al. (2016) Physicians' Knowledge About FDA Approval Standards

FDA Expedited Pathways and Breakthrough Drugs

	Eligibility
Fast Track	• Drugs intended to treat serious or life-threatening conditions • Data demonstrate potential to address unmet clinical need
Breakthrough Therapy	• Drugs intended to treat serious or life-threatening conditions • Clinical data suggest more effective than existing therapies
Accelerated Approval	• Drugs that full unmet need for serious conditions
Priority Review	• Drugs that offer major advances in treatment or treatment for conditions with no existing adequate treatment • Priority review voucher

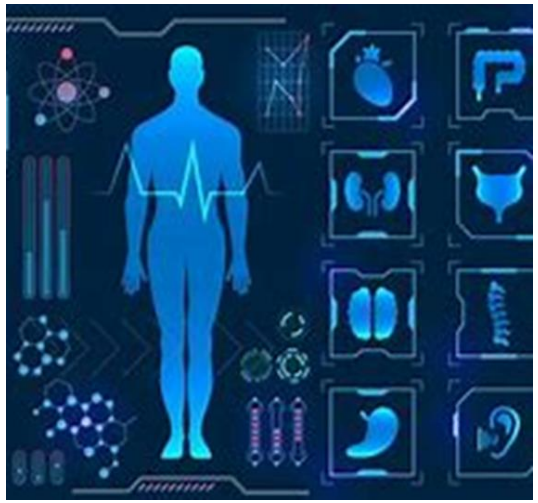
- Pathways exist to expedite approval for serious / life-threatening conditions, e.g., *breakthrough* status when preliminary evidence indicates that the drug *may* demonstrate substantial improvement on *a* clinically significant endpoint(s) over available therapies.
- Nearly *60%* of *breakthrough drugs* (≈ *125+*) have been for cancer.
- A Yale study* shows BTD approval is based on *shorter, smaller and fewer* trials, often w/o randomization, double-blinding, real endpoints.
- Many physicians *wrongly believe* that BTDs are supported by stronger evidence than the FDA requires, which often leads to over-prescribing.
- The term *breakthrough* often leads patients to be overly optimistic about a drug's true efficacy.
- Together, these *misconceptions* about BTDs often lead doctors to select them ahead of others.

- Study Source: Perceptions of the "Breakthrough Therapy" Designation. JAMA. 315(14): 1516–1518. doi:10.1001/jama.2015.16984

Evergreening and
High-Cost, Low-Clinical-Value Drugs

- *Evergreening:* tweaking an existing Rx via new release forms, dosages, combinations or variations
- It extends an Rx's patent, and artificially high price, with no added therapeutic advantage/efficacy
  - ≈ *75%* of new drug patents are not for new drugs, but for existing ones
  - ≈ *60%* of the best-selling drugs over the past decade had their patents extended at least once
- Evergreening may endanger patients who participate in unnecessary clinical trials
- High-cost, low-clinical-value drugs represent great waste for payers, financial toxicity for patients

That evergreening continues to occur is evidence that we must revisit how we assess a drug's value



How Reliable are
Clinical Practice Guidelines

Many doctors rely on *clinical practice guidelines* from professional organizations to help them with their complex treatment decision-making, e.g., for advice on which drugs they should use vs. others

- Most CPGs are created by *consensus*…e.g., expert elicitation, collective opinion or educated guess
- The evidence upon which CPGs are based is often *not subject to an exhaustive systematic analysis*
- *Conflicts of interest*, among CPG contributors, can (un)consciously influence their decision making
- Unfortunately, in practice, the CPG process does not always support *true evidence-based advice*

We Understand the Pharmaceutical Industry

… its Complex Operation and Evolving History

Some *20 years ago*, circa 2003, we* authored some of the very first white papers and health economics studies that detailed the then largely unknown inner workings of the drug industry…

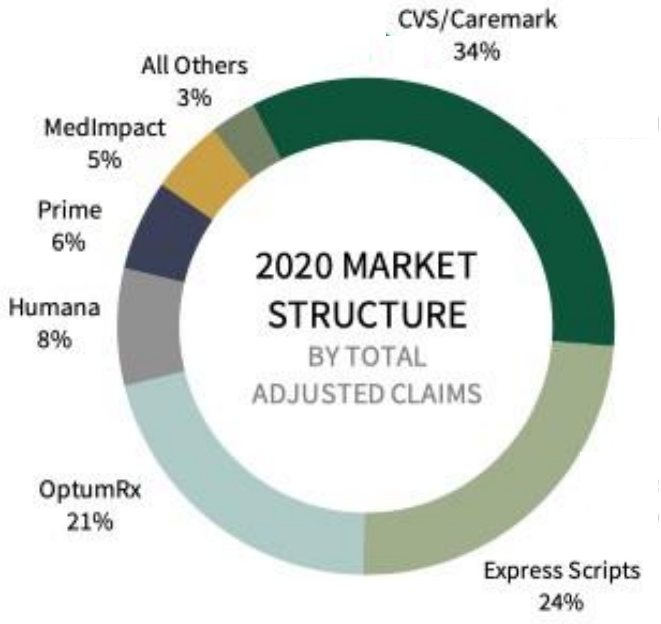
Since then, the pharmaceutical industry has evolved to adopt a more transparent, efficient and cost-effective business model.

Today, it is committed to achieve the best clinical outcomes at a fair cost by supporting patients, pharmacists, doctors and payers.

** With the assistance of one of the federal government's leading forensic PBM and drug company auditors*

The Rise of Pharmacy Benefit Management

… into an Integral Part of our Healthcare System



- Pharmacy benefit managers emerged in earnest in the ’80s when they enabled insurers to extend coverage to include drugs by automating pharmacy claim processing
- Over time, PBMs morphed to represent the interests of payers / plan sponsors in negotiations with Big Pharma
- PBMs then began to *manage* the Rx formulary and plan design to improve patient quality and reduce payer cost
- Today, the top 3 PBMs control ≈ *80%* of the drug market

Payer, Patient and Pharmaceutical Industry
Alignment is Critical

Critics argue that our pharmaceutical system can only work *if everyone's incentives are re-aligned*

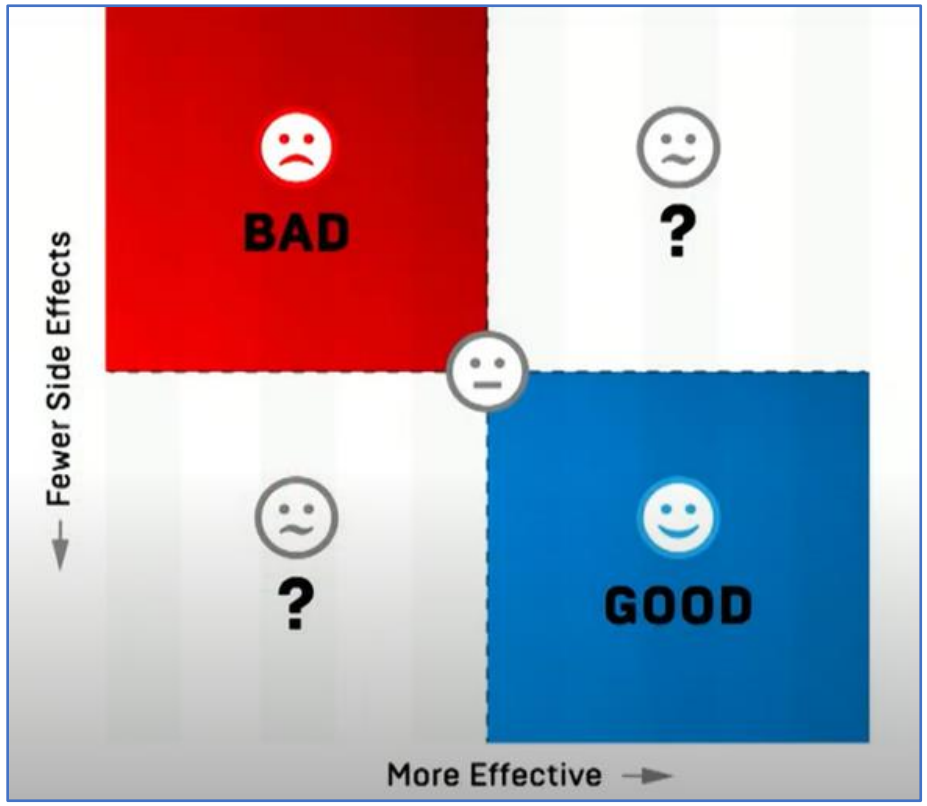
- PBMs heavily influence drug prescribing and dispensing with their e-Prescribing, network, formulary and prior authorization processes
- The 3 largest PBMs own mail, retail and specialty pharmacies and collectively dispense more pharmaceuticals than any other entity
- Some 80% of PBM revenue comes from Rx sales as they benefit directly from the volume sold
- Payers often unknowingly design their Rx plans and formularies in ways that disadvantage them

Lowest Net Drug Cost …
or Most Appropriate Drug ?

- Manufacturers pay PBMs large (≈ *40%)* rebates on brand Rxs to influence formulary placement; this model can often favor high-cost vs. low-cost drugs
- Payers negotiate to have all rebates passed on to them; though it is estimated that few get > 40%
- Payers often design their drug plans, or enter into PBM contracts, that work to their disadvantage
- Creating a formulary to optimize net drug cost — *by limiting placement to only those Rxs having high rebates* — is a clinically / financially unsound policy

Distinguishing Between Waste and Value

Is Comparative Effectiveness Research the Solution ?



This case study involves anti-clotting drug thinners

Drugs are measured and compared as to their

- *effectiveness* (horizontal), and
- the incidence of associated *side effects* (vertical)

Red zone drugs (more side effects, less effectiveness)

Blue zone drugs (more effective, fewer side effects)

Red zone Rxs should be avoided in favor of Blue zone Rxs

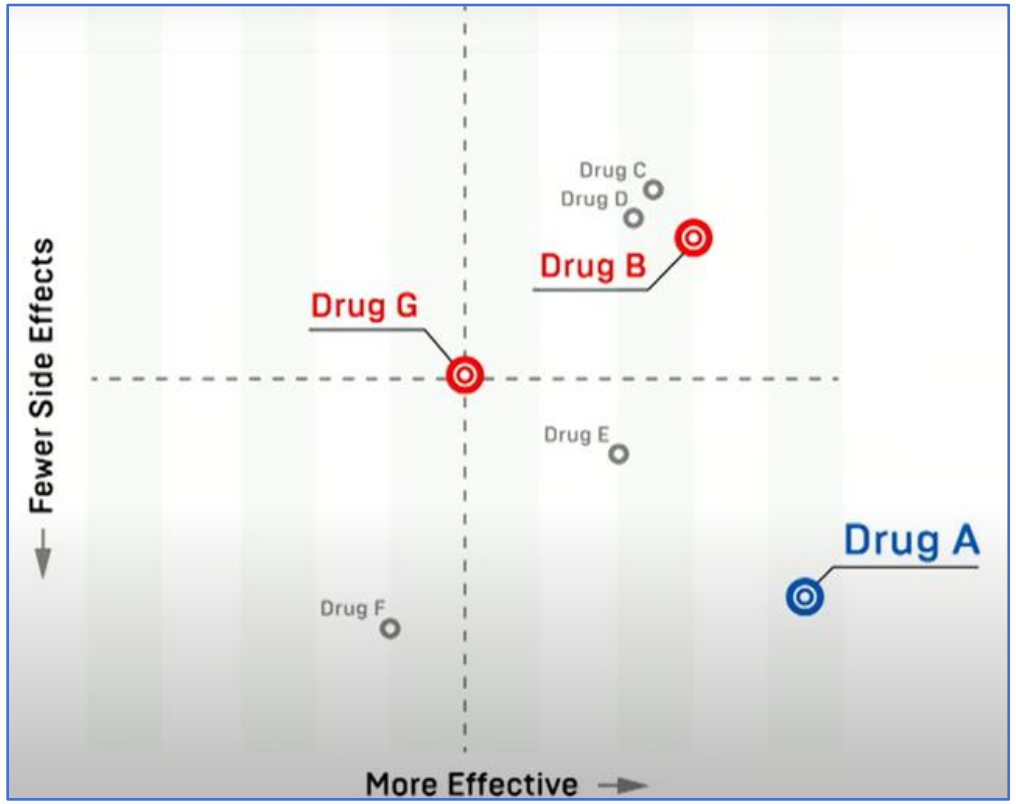
The *standard of care* is found at the center of the exhibit

Trade-offs must be made when considering drugs that fall into the other zones

Case studies, illustrations and analysis furnished by: trudataRx

Is Comparative Effectiveness Research the Solution ?

A Case Study to Illustrate Real-World Rx Tradeoffs

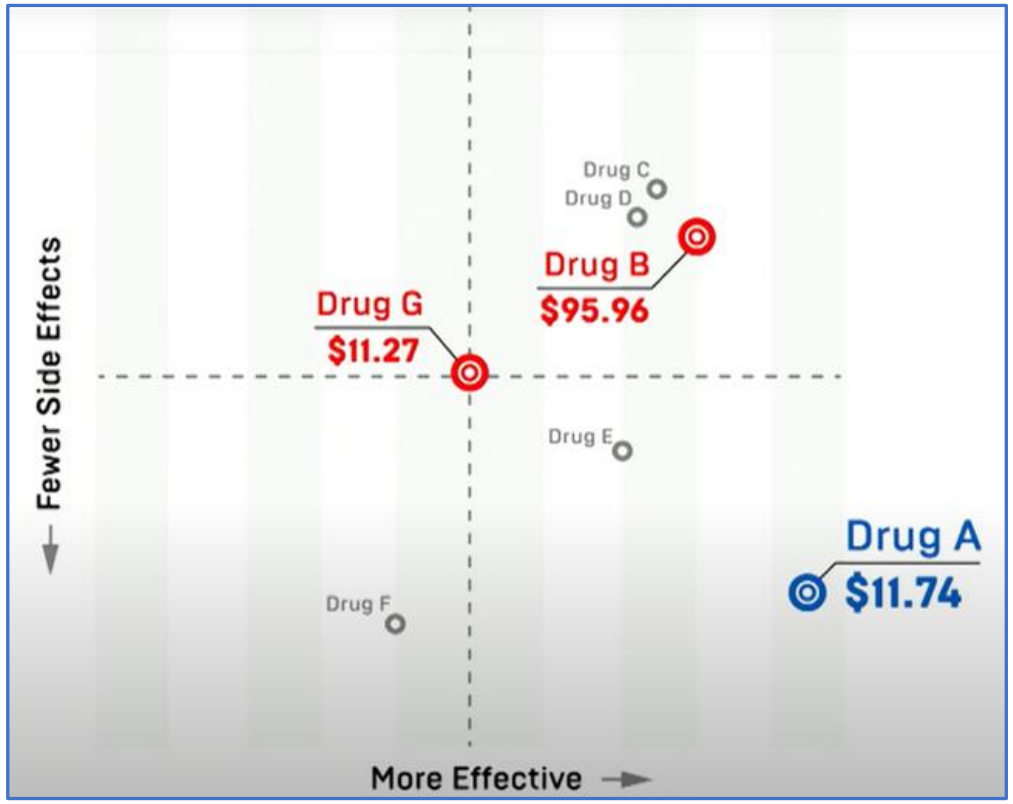


- Sophisticated and unwitting buyers alike can fall victim to the practice of *formulary manipulation* and the *rebate / net brand pricing fallacy*
- Each of the 7 drugs shown treat blood clots in legs
- Only the 3 highlighted drugs are on the (*PBM-designed*) formulary and covered by the plan
- 4 drugs were purposefully left off the formulary
- Drugs in *b*lue are *b*rands; drugs in red are generic
- Note that Drug G is the standard of care

Case studies, illustrations and analysis furnished by: trudataRx

Comparative Effectiveness Research *Case Study*

Adding Cost Data Exposes High-Cost, Low-Clinical-Value Rxs



Drug A, a *brand* drug, is about the same cost as the standard of care (Drug G) yet it is *far more effective* and causes *far fewer side effects*

Drug B, a generic, is less effective, causes more side effects, and costs *8 times* more than Drug A

A drug's cost tells you nothing about its clinical value

Why is expensive Drug B on the formulary with a low generic drug co-pay, and low-cost, high-clinical-value Drug A on the formulary with a high brand co-pay ?

High-cost, less effective Drug B *was FDA-approved last*

Only though *comparative effectiveness analysis* is this clear…despite being counterintuitive

Case studies, illustrations and analysis furnished by: trudataRx

PBA Network Research Consortium
Healthcare-Focused Non-Profit Enterprise

The Deck is Stacked *Against Payers*

- Cancer claims are increasing in frequency, severity and cost
- New cancer drugs are expensive and not always better
- Medical knowledge is increasing faster than humans can uptake and process it (without machine assistance)
- Confusion about *FDA approval* and *breakthrough drugs* often results in faulty prescribing assumptions
- Industry consolidation and unaligned payment incentives confound the free-market operation of the drug industry
- Traditional methods to assess the cost-effectiveness, ROI and value of drug treatments are obsolete

New Medical Technologies and Healthcare Approaches *to Help Payers*

- Next-Generation (DNA) Sequencing - NGS
- Precision (Personalized) Medicine
- Genomic-Based Targeted Treatments
- Novel (Multi-Drug) Combination Cancer Therapies
- Off-Label Drug Use / Repositioning
- Advanced Clinical Decision Support Systems
- Healthcare AI
  - *Deep Dive Case Study*: CureMatch®

Next-Generation *(DNA)* Sequencing - NGS

NGS is a revolutionary, new form of DNA analysis that has changed cancer testing and treatment

Commercially available for clinical use only since 2005

NGS enables the *reading of the full human genome* to

- fully determine its unique molecular code
- *identify hundreds of bio-markers*/mutation drivers
- permit the interrogation of normal/abnormal genes

NGS provides *the basis* upon which a genomic profile of a person, or malignant tumor, can be created

NGS support the practice of precision medicine and enables the design of *tumor-specific therapies*

Precision **Medicine**

Precision medicine (aka *personalized medicine*) refers to any set of strategies that use a patient's *unique genetic/genomic information* to guide clinical actions that are tailored specifically to them

- Precision medicine is based on the premise that the right treatment, provided at the initial discovery of a disease, will lead to *quicker, better, more definitive outcomes*
- Proponents believe that precision medicine will result in *lower total long-term healthcare costs*
- In large part, this is owing to *fewer, and less resource intensive*, diagnostic episodes and therapeutic regimens

Off-Label Drug Use / Drug Repositioning

Drug repositioning, aka *off-labe*l drug use, is a therapeutic approach whereby current drugs, that are primarily used to treat one indication, are used to treat a different one

- When treating cancer, drug repositioning refers to the use of FDA-approved drugs *in combinations* intended to address gene mutations in *novel* ways
- …as there is a greater likelihood that a novel multi-Rx treatment will yield a better outcome the first time vs. repeated attempts using ordinary Rxs
- Typically, but not always, combination Rx therapies involve the use of at least one drug as intended

Novel (Multi-Drug) Combination Cancer Therapies

Combination therapy is a treatment modality that combines two or more therapeutic agents to *enhance efficacy* (versus the single drug approach) in a targeted and *synergistic* or *additive* way

- Since 1965, combination therapies have been used to treat many diseases, e.g., *multi-drug HIV cocktail*
- FDA-approved combination drug treatments to treat cancer date back to the 1990's
- They've been so successful that manufacturers now research/market *pre-packaged combination therapies*
- A highly-publicized example is *OPDIVO + YERVOY*
- When used in combination, dosages are cut by ½ to ⅔

Genomic-Based Targeted Cancer Treatments

The premise behind genomic-based targeted therapies is based on the recognition that each patient's tumor is unique, and that traditional *one-size-fits-all* treatment is suboptimal in 2022

- Because we know today that the molecular profile of a tumor mutation is as important *as the organ of origin,* we can develop personalized drug treatments
- These *custom-designed, tumor-specific* therapies leverage a tumor's unique characteristics to treat it
- They do this by *destroying* targeted cells, *changing* proteins and otherwise *directing* the thwarting of the abnormal, uncontrolled over-growth of cells (cancer)

Advanced Clinical Decision Support Systems

Clinical decision support systems are computer-based health information technologies intended to improve healthcare delivery by *augmenting clinicians in their complex decision-making*

These platforms integrate and process

- patient-specific diagnostic and treatment data,
- targeted curated clinical knowledge, and
- intelligently filtered health information

to leverage knowledge, observations, analysis and data *not otherwise obtainable/interpretable by humans*

CDSS demonstrate effectiveness and create guidance, advice, recommendations and policy

Healthcare *Artificial Intelligence (AI)*

AI is the computer mimicking of the problem-solving and decision-making capabilities of humans

- AI use is expanding and *driving a paradigm shift* in how we approach / treat diseases like cancer
- Investment in Healthcare AI has *exploded*
- AI is fastly becoming the *basis* of CDSS systems
- Healthcare AI now enables us to translate complex data into *comprehensible, actionable insights*
- Healthcare AI helps us to *more accurately, quickly and effectively diagnose and treat cancer*

Healthcare AI *in Practice*

Imaging

AI can identify abnormalities and microscopic imaging changes better and faster than humans; ***CureMetrix*** improves disease detection and cancer survival by reducing false positives and unneeded follow-up care

Repetitive Administrative Tasks

AI is automating healthcare's most repetitive tasks, freeing up administrators to work on higher-level ones; ***Olive***'s AI platform automates everything from insurer eligibility checks to unpaid claims for medical offices

Patient Flow Optimization

The ***Qventus*** AI-based automated platform prioritizes patient illnesses and injury, tracks hospital waiting times and even charts the fastest ambulance routes; to quickly prioritize hospital activity to benefit all patients

Identifying Diagnosis Errors

Viz.AI helps to detect and identify the misdiagnosed illnesses and medical errors that result from over-worked medical workers and incomplete medical files and lead to an estimated 10% of US deaths

Robotic Surgery

Vicarious Surgical combines AI and virtual reality to enable surgeons to virtually shrink and explore the inside of a patient's body in detail, with precision, flexibility and control that exceeds human capability.

Data Mining

Valuable medical data, lost or unidentified in silos, is now available in minutes; ***Tempus*** uses AI to distill the world's largest collection of clinical and molecular data, to give MDs insight into personalized therapies

Is AI-Supported Comparative Effectiveness Research *the Solution* ?

- The standard for a drug to get FDA approval is *fairly low* and not all approved drugs justify the high price set by their maker
- This is especially so if the new drug is *no better* than existing ones
- *Misplaced incentives* and *conflicts of interest* in the Rx industry require payers to abandon obsolete drug assessment methods

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- Comparative effectiveness analysis looks at *evidence as to how well a drug works vs. others* by
  - looking at active-controlled trials, or
  - performing a rigorous, scientific meta-analysis to get a full, realistic view of a Rx's true effectiveness
- *All clinical trials / relevant drugs* are considered, evaluated, ranked, objectively and with no bias

CER asks: Does the data show a clinically significant difference on a clinically meaningful outcome?

Deep Dive: **CureMatch®**

AI-Supported Precision Oncology Pharmacy Management

Customized Cancer Therapies Matched to a Tumor's Unique Genomics

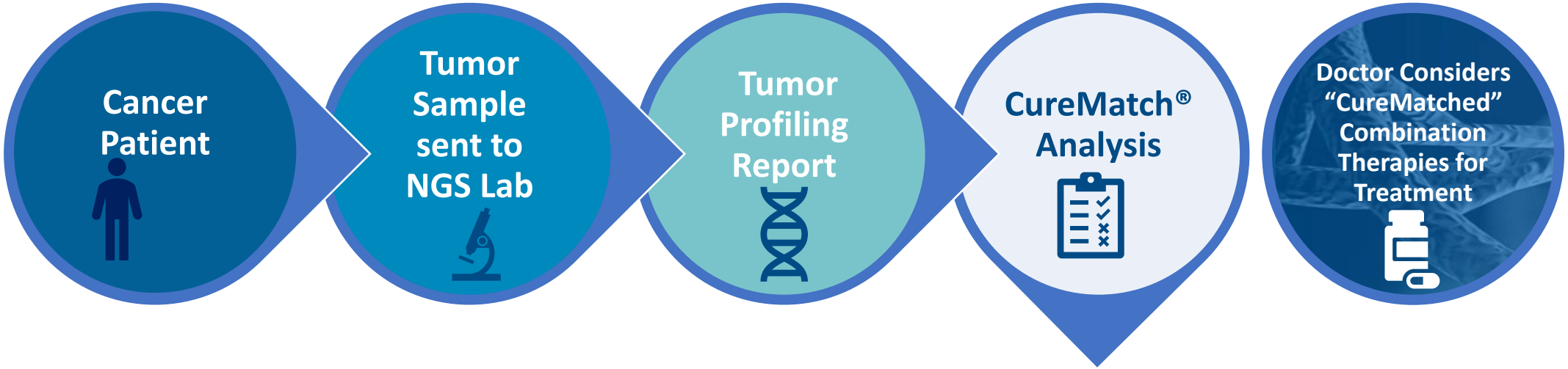
Understanding that cancer is complex, and that every cancer is different, CureMatch® leverages genomics, a curated knowledgebase, artificial intelligence and a supercomputer to unravel this complexity to find and match the right drugs to the unique molecular makeup of a patient's tumor

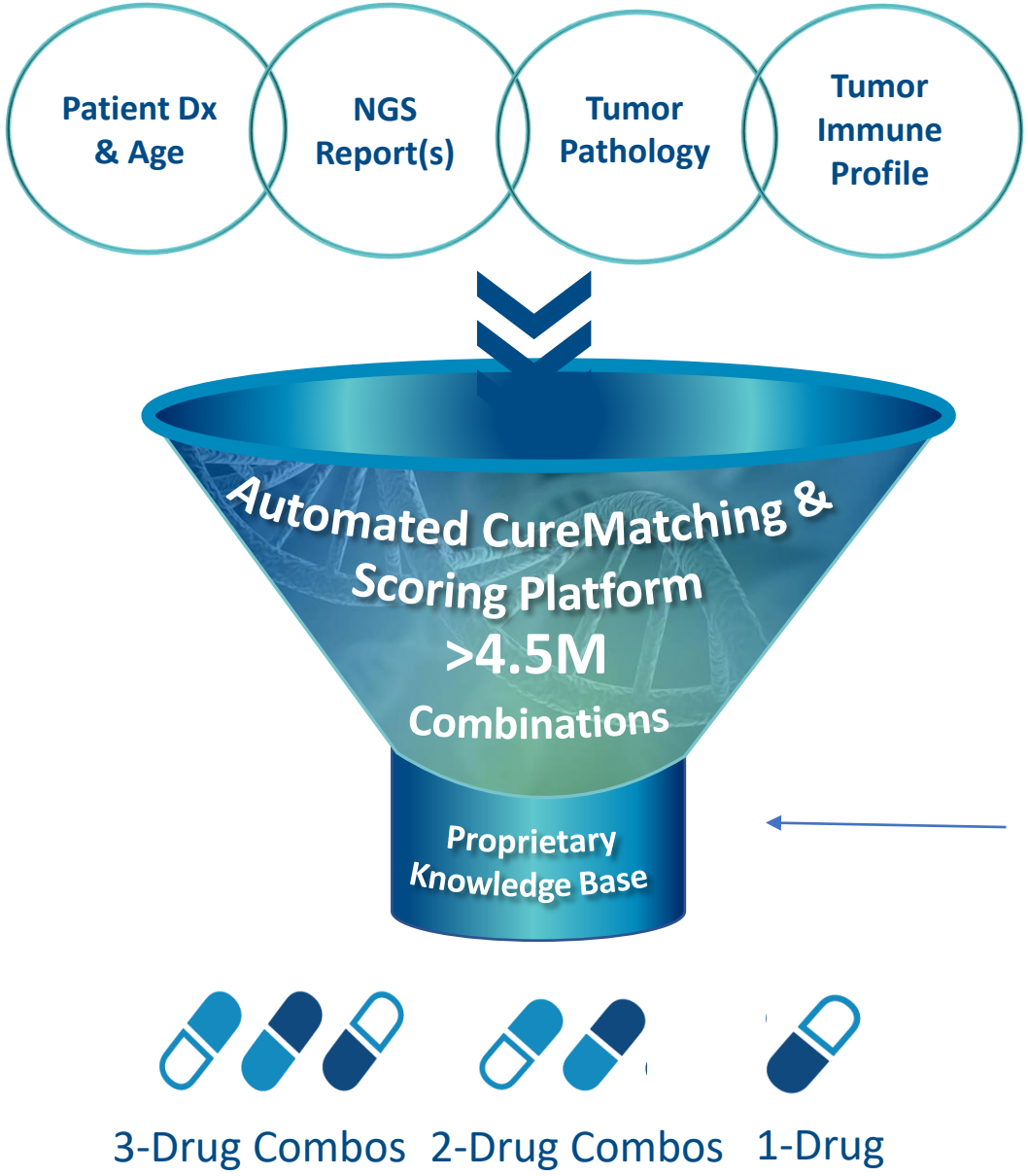
RPA Network Research Consortium
Healthcare-Focused Non-Profit Enterprise

What CureMatch® Does *from a Clinical Perspective*

- The 300+ cancer drugs approved by the FDA generate *4.5+ million* 1-, 2- and 3-drug combinations
- CureMatch's curated knowledgebase and AI-powered algorithm use a tumor's DNA profile to identify every actionable mutation and the Rxs best able to address them
- CureMatch® recommendations are based on a tumor's genomic profile and drug's that are most likely to produce higher progression-free and overall cancer survival rates
- Its clear, concise report scores and ranks 1-, 2- and 3-drug therapies that best target the cancer at a genomic level

How CureMatch® Works *in Practice*





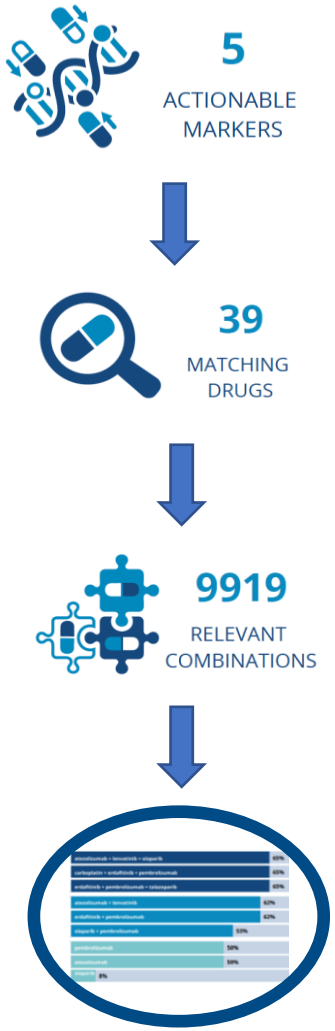
How CureMatch®
Leverages AI

Manually Curated Evidence:

- Clinical Genomics
- Pharmacology
  - Drug Mechanisms
  - Drug Labels
- Clinical Trials

AI Does *What Humans Are Unable To Do*

CureMatch®
Algorithm



Match to drugs capable of targeting the 5 markers (based on expertly curated knowledgebase content)

Put together all possible 2- and 3-drug combinations of the 39 drugs

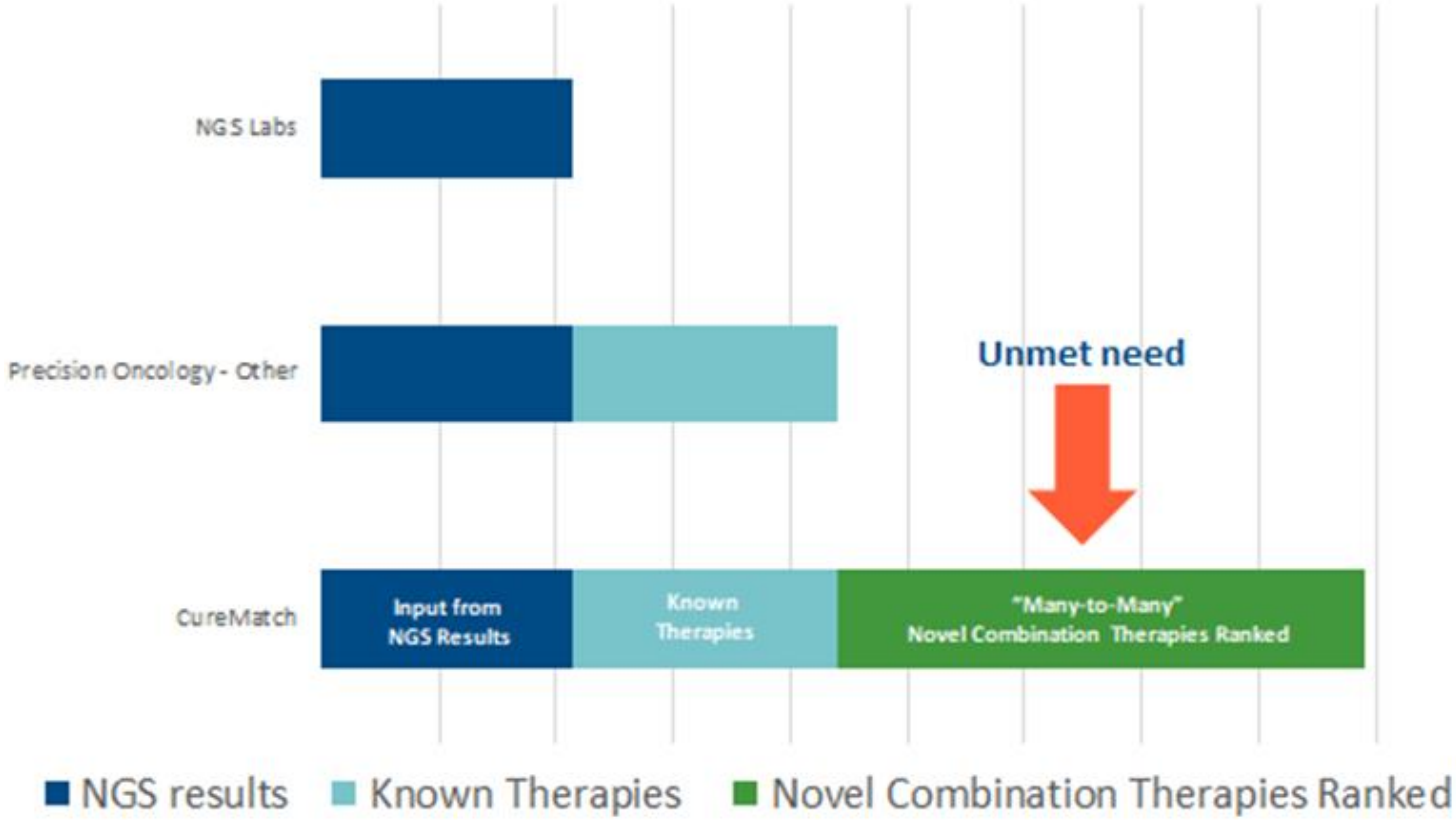
Filtered, Scored and Ranked

3
ON COMPENDIA DRUGS

Note: only 3 drugs are on compendia for this indication

Only the 9 Best-Matched
Treatment Options are Reported

Bridging the Gap *between NGS Labs and Clinicians*



Only CureMatch's patent-pending *proprietary technology* can match *"many-to-many"* mutation combinations with *novel drug combinations* for each patient's unique molecular tumor profile

CureMatch® *Report*

***PreciMatch*™ Therapy Matching Score**

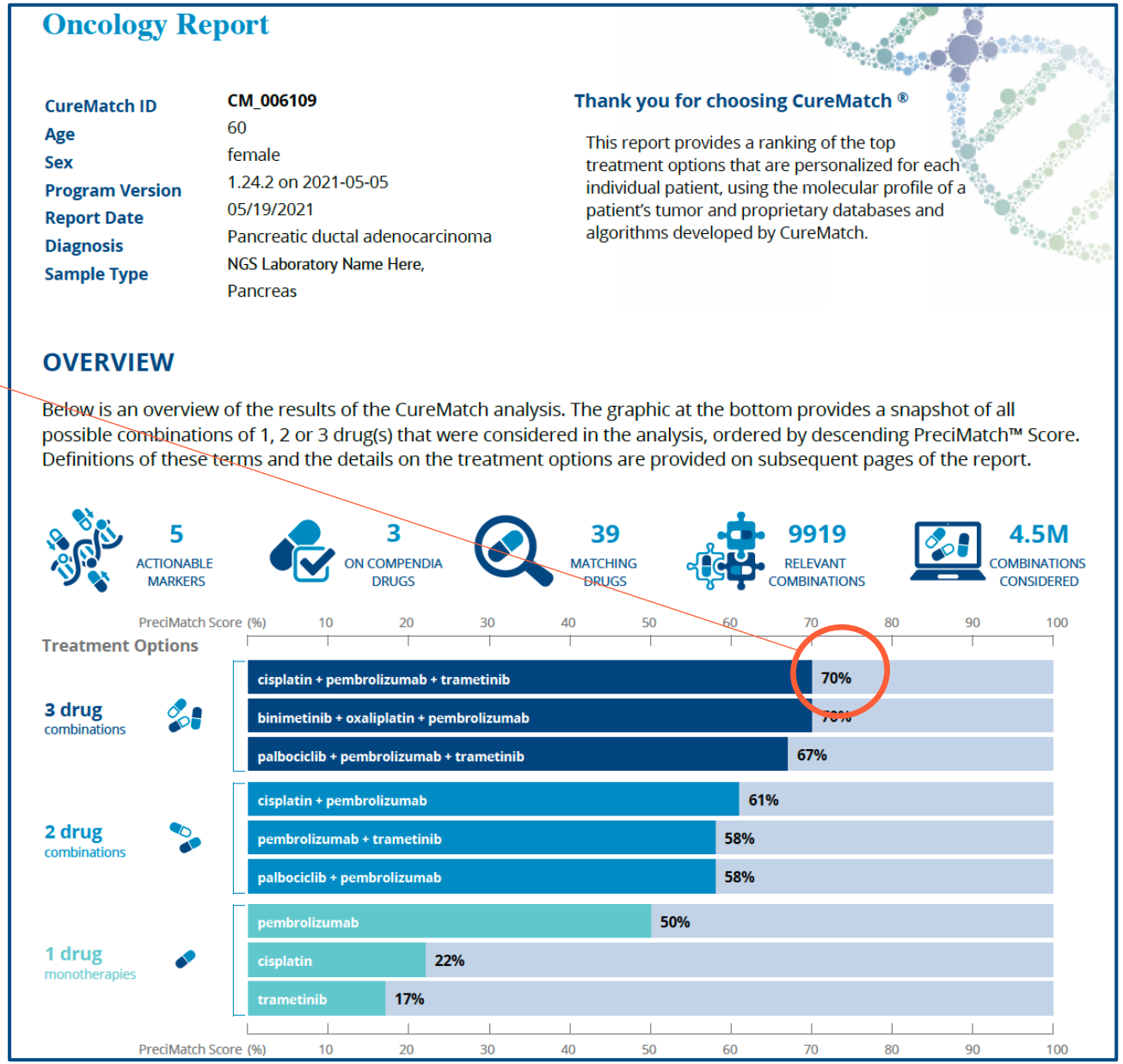
Represents the degree to which a given therapy option addresses a patient's specific molecular cancer profile

Physician's Choice Option

Physicians can input any drug or drug combination to be scored

- Included for scoring
  - Standard-of-care
  - Immunotherapy
  - Chemotherapy
  - Hormone Therapy
- Excluded for scoring:
  - Rxs due to past failure/other factors

CureMatch® analysis can account for any drug resistance, pharmacogenetics & toxicity



Oncology Report

CureMatch ID	CM_006109
Age	60
Sex	female
Program Version	1.24.2 on 2021-05-05
Report Date	05/19/2021
Diagnosis	Pancreatic ductal adenocarcinoma
Sample Type	NGS Laboratory Name Here, Pancreas

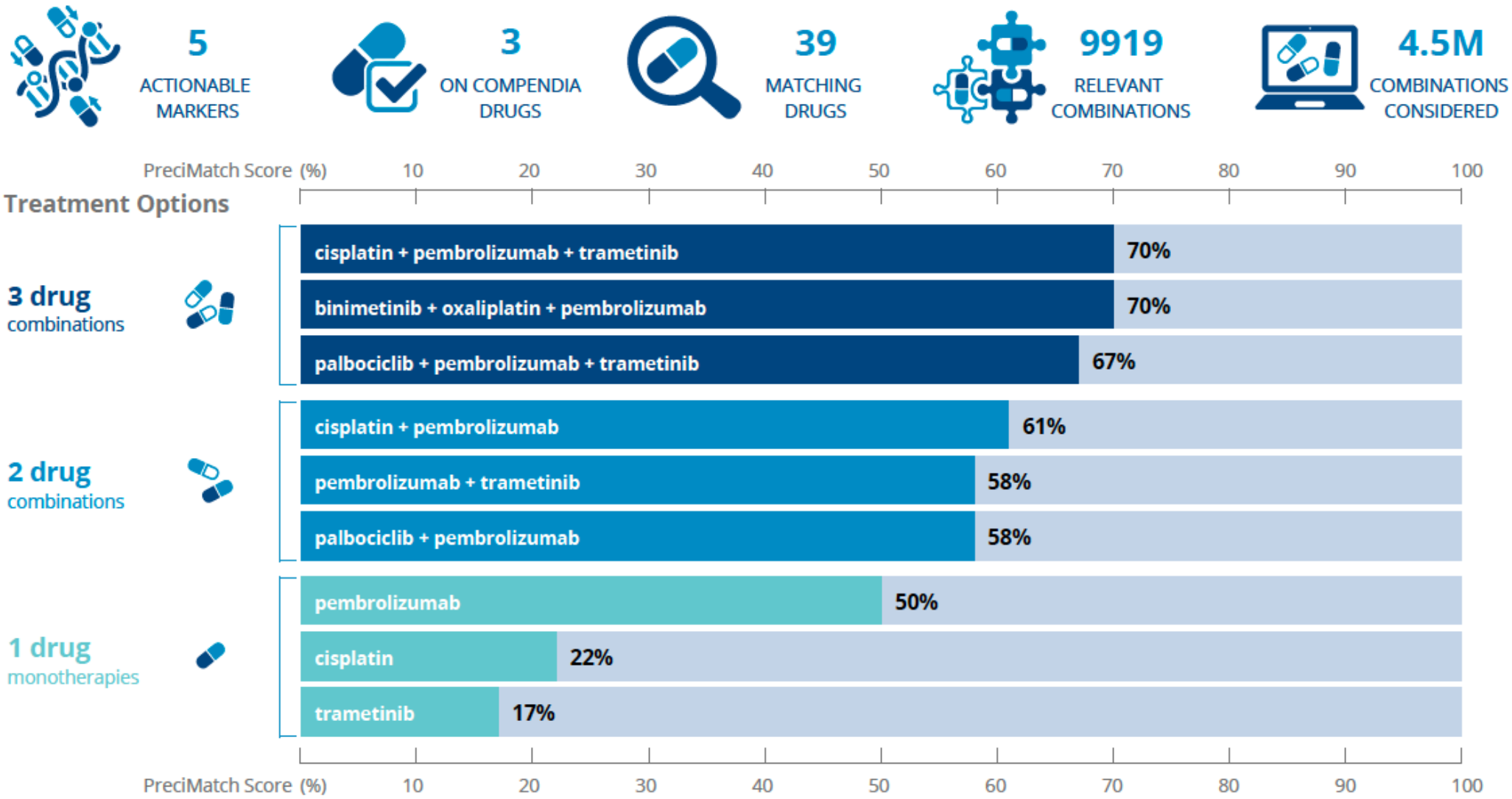
Thank you for choosing CureMatch ®

This report provides a ranking of the top treatment options that are personalized for each individual patient, using the molecular profile of a patient's tumor and proprietary databases and algorithms developed by CureMatch.

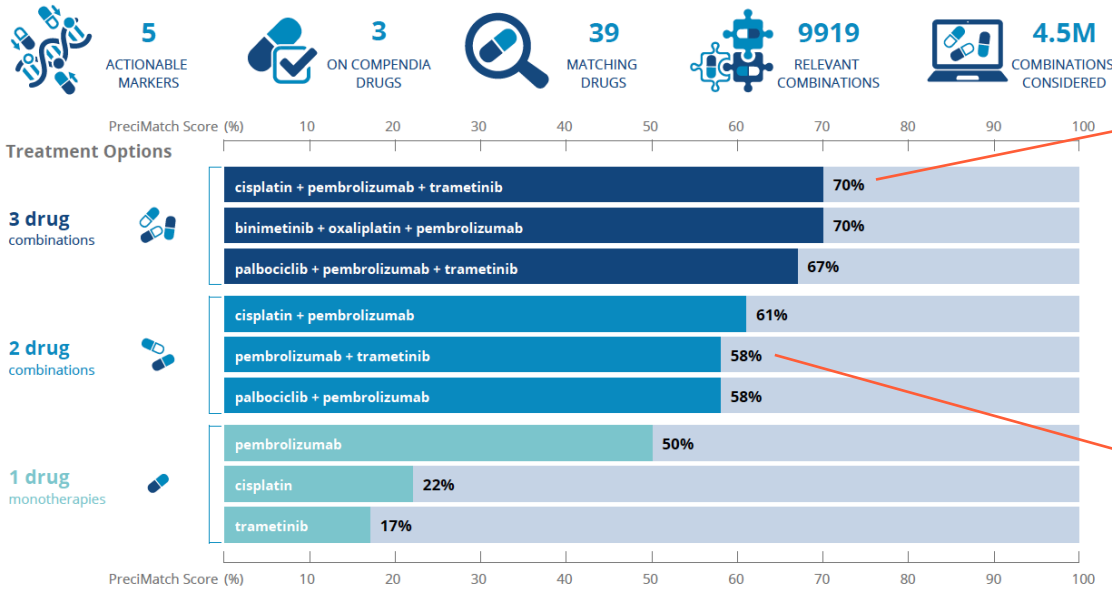
OVERVIEW

Below is an overview of the results of the CureMatch analysis. The graphic at the bottom provides a snapshot of all possible combinations of 1, 2 or 3 drug(s) that were considered in the analysis, ordered by descending PreciMatch™ Score. Definitions of these terms and the details on the treatment options are provided on subsequent pages of the report.

CureMatch® *Report*



Rationale / References
for Each Therapy Option



Targeting Description shows exactly how each drug in each option (mono- or combination therapy) addresses the cancer biomarkers

PreciMatch Score	DRUGS	TARGETING DESCRIPTION	INDICATIONS & RECOMMENDATIONS	
			FDA	OFF-LABEL
70%	**cisplatin**	via DNA Damage	✓	
	pembrolizumab	CD274 (PD-L1)	✓	
	trametinib	KRAS via MAP2K1, MAP2K2		✓

Contraindications
- cisplatin: hearing impairment, renal failure, renal impairment

Black-Box Warning
- cisplatin: Nephrotoxicity: cisplatin for injection can cause severe renal toxicity, including acute renal failure. Ensure adequate hydration. Consider dose reductions or alternative treatments in patients with renal impairment.
Peripheral Neuropathy: cisplatin for injection can cause dose related peripheral neuropathy.
Nausea and Vomiting: cisplatin for injection can cause severe nausea and vomiting. Premedicate with antiemetics.
Myelosuppression: cisplatin for injection can cause severe myelosuppression with fatalities due to infections. Monitor blood counts and interrupt therapy accordingly.

Drug-drug interactions
There may be drug-drug interactions that are not listed here. Administering drug combinations is at the discretion of the physician.

Examples of existing clinical trials using matched drugs
While clinical trials using some of these drugs alone or in combination with other drugs exist, no clinical trials testing this exact association of drugs can be found.

58%	**pembrolizumab**	CD274 (PD-L1)	✓	
	trametinib	KRAS via MAP2K1, MAP2K2		✓

Drug-drug interactions
There may be drug-drug interactions that are not listed here. Administering drug combinations is at the discretion of the physician.

Examples of existing clinical trials using matched drugs:
- NCT02130466: A Study of the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination With Trametinib and Dabrafenib in Participants With Advanced Melanoma (MK-3475-022/KEYNOTE-022) (Merck Sharp & Dohme Corp., Active, not recruiting)
- NCT03149029: Abbreviated MAPK Targeted Therapy Plus Pembrolizumab in Melanoma (Massachusetts General Hospital, Active, not recruiting)
- NCT03225664: Trametinib and Pembrolizumab in Treating Patients With Recurrent Non-small Cell Lung Cancer That Is Metastatic, Unresectable, or Locally Advanced (M.D. Anderson Cancer Center, Active, not recruiting)
- NCT03299088: Pembrolizumab and Trametinib in Treating Patients With Stage IV Non-Small Cell Lung Cancer and KRAS Gene Mutations (University of California, Davis; Active, not recruiting)

REFERENCES

[1] https://www.ncbi.nlm.nih.gov/gene/894
[2] https://omim.org/entry/123833
[3] https://ghr.nlm.nih.gov/gene/CCND2
[4] https://omim.org/entry/123837
[5] Nakayama K, Shamima Y, Ishikawa M, Katagiri A, Iida K, Miyazaki K. Nakayama N, "Gene amplification CCNE1 is related to poor survival and potential therapeutic target in ovarian cancer.," Cancer., vol. 116, no. 11, pp. 2621-34, Jun 2010.
[6] Weir BA, Au-Yeung G, Alsop K, Mitchell G, George J Etemadmoghadam D and Davis S, D'Andrea AD, Simpson K, Hahn WC, Bowtell DD. Australian Ovarian Cancer Study Group, "Synthetic lethality between CCNE1 amplification and loss of BRCA1.," Proc Natl Acad Sci U S A. , vol. 110, no. 48, pp. 19489-94, Nov 2013.
[7] https://www.ncbi.nlm.nih.gov/gene/2255

Scoring Physician Choice Options

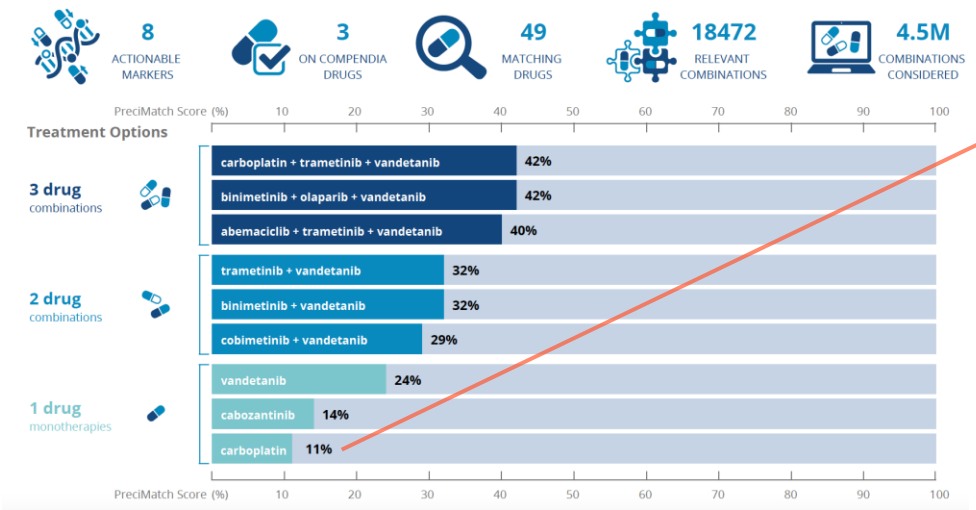
CureMatch ID	**CM_006143**
Age	88
Sex	female
Program Version	1.25.3 on 2021-09-22
Report Date	11/02/2021
Diagnosis	Squamous cell carcinoma
Sample Type	Guardant 360, Blood; FoundationOne, Lymph node

Thank you for choosing CureMatch ®

This report provides a ranking of the top treatment options that are personalized for each individual patient, using the molecular profile of a patient's tumor and proprietary databases and algorithms developed by CureMatch.

OVERVIEW

Below is an overview of the results of the CureMatch analysis. The graphic at the bottom provides a snapshot of all possible combinations of 1, 2 or 3 drug(s) that were considered in the analysis, ordered by descending PreciMatch™ Score. Definitions of these terms and the details on the treatment options are provided on subsequent pages of the report.



PreciMatch Score	DRUGS	TARGETING DESCRIPTION	INDICATIONS & RECOMMENDATIONS	
			FDA	OFF-LABEL
Although PreciMatch has not been able to score the requested combination of drugs, the following partial matches were scored				
11%	**carboplatin**	BARD1 via DNA damage	✓	

Contraindications
- carboplatin: bleeding

Black-Box Warning
- carboplatin: Carboplatin injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.
Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug related side effect.
Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin injection administration, Epinephrine, corticosteroids, and antihistimines have been employed to alleviate symptoms.

Drug-drug interactions
There may be drug-drug interactions that are not listed here. Administering drug combinations is at the discretion of the physician.

Examples of existing clinical trials using matched drugs
While clinical trials using some of these drugs alone or in combination with other drugs exist, no clinical trials testing this exact association of drugs can be found.

When available, *clinically alternative drugs* are identified

68%	**pembrolizumab**	TMB	✓	
	trametinib	KRAS via MAP2K1, MAP2K2 NF1 via MAP2K1, MAP2K2		✓

Examples of alternative drug(s) forpembrolizumab
dostarlimab-gxly[1], atezolizumab, avelumab, cemiplimab-rwlc, durvalumab, nivolumab

Examples of alternative drug(s) for trametinib
binimetinib

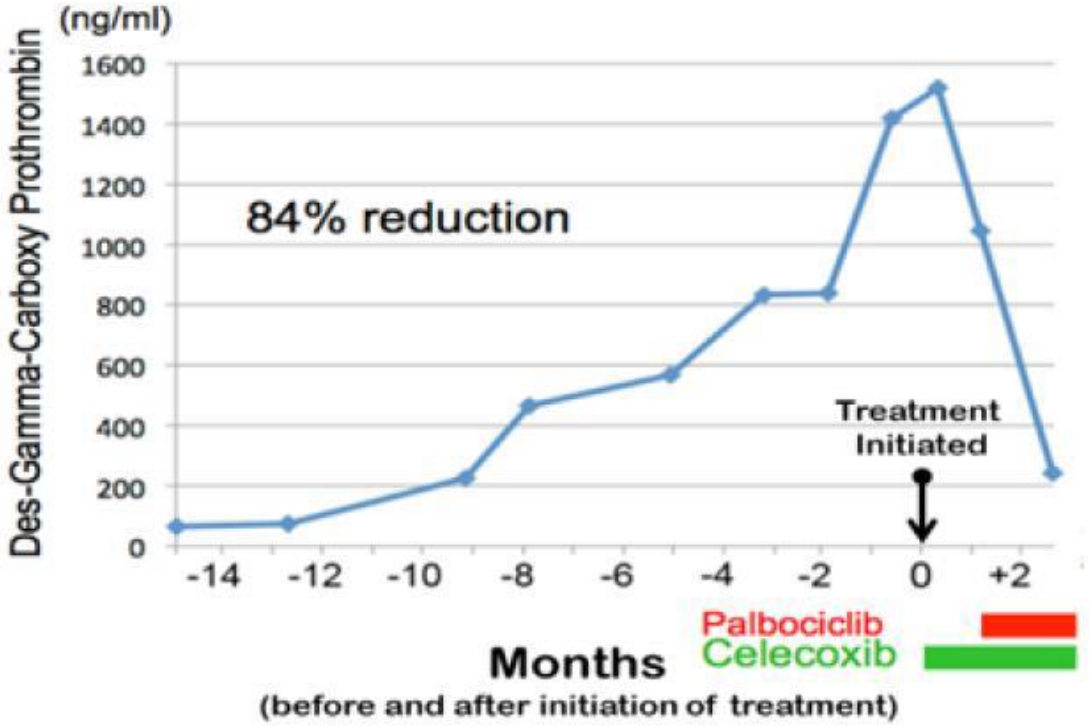
Examples of drug-drug interactions
There may be drug-drug interactions that are not listed here. Administering drug combinations is at the discretion of the physician.

Examples of existing clinical trials using matched drugs:
- NCT03149029: Abbreviated MAPK Targeted Therapy Plus Pembrolizumab in Melanoma (Massachusetts General Hospital, Active, not recruiting)
- NCT03299088: Pembrolizumab and Trametinib in Treating Patients With Stage IV Non-Small Cell Lung Cancer and KRAS Gene Mutations (University of California, Davis, Active, not recruiting)
- NCT02130466: A Study of the Safety and Efficacy of Pembrolizumab (MK-3475) in Combination With Trametinib and Dabrafenib in Participants With Advanced Melanoma (MK-3475-022/KEYNOTE-022) (Merck Sharp & Dohme LLC, Completed)
- NCT03225664: Trametinib and Pembrolizumab in Treating Patients With Recurrent Non-small Cell Lung Cancer That Is Metastatic, Unresectable, or Locally Advanced (M.D. Anderson Cancer Center, Active, not recruiting)

Physician's Selection

Physicians can have us score any drugs or drug combinations that they are considering for the patient

Case Study *Metastatic Liver Cancer – Patient 1*



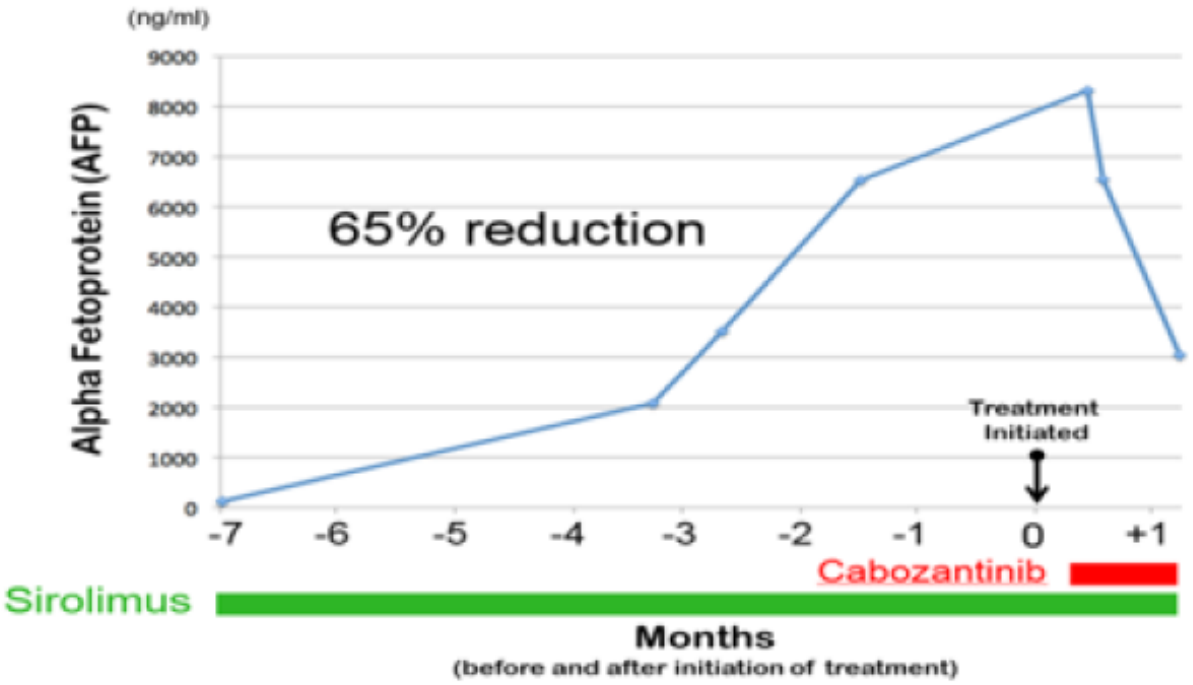
A 62-year-old man diagnosed with liver cancer was initially treated with chemo-embolization yet it metastasized / spread.

Despite subsequent therapy with sorafenib, disease progression continued until a personalized medicine approach was taken.

A liquid biopsy was taken, an NGS test performed, and mutations were revealed. The patient was then CureMatched®.

The highest ranked option was a 2-drug personalized combination therapy using palbociclib and celecoxib, with each targeting specific mutations. The oncologist selected this option, and the patient's condition stabilized as a result of the personalized approach.

Case Study *Metastatic Liver Cancer – Patient 2*



A 64-year-old woman diagnosed with liver cancer, was treated with chemo-embolization while awaiting a transplant.

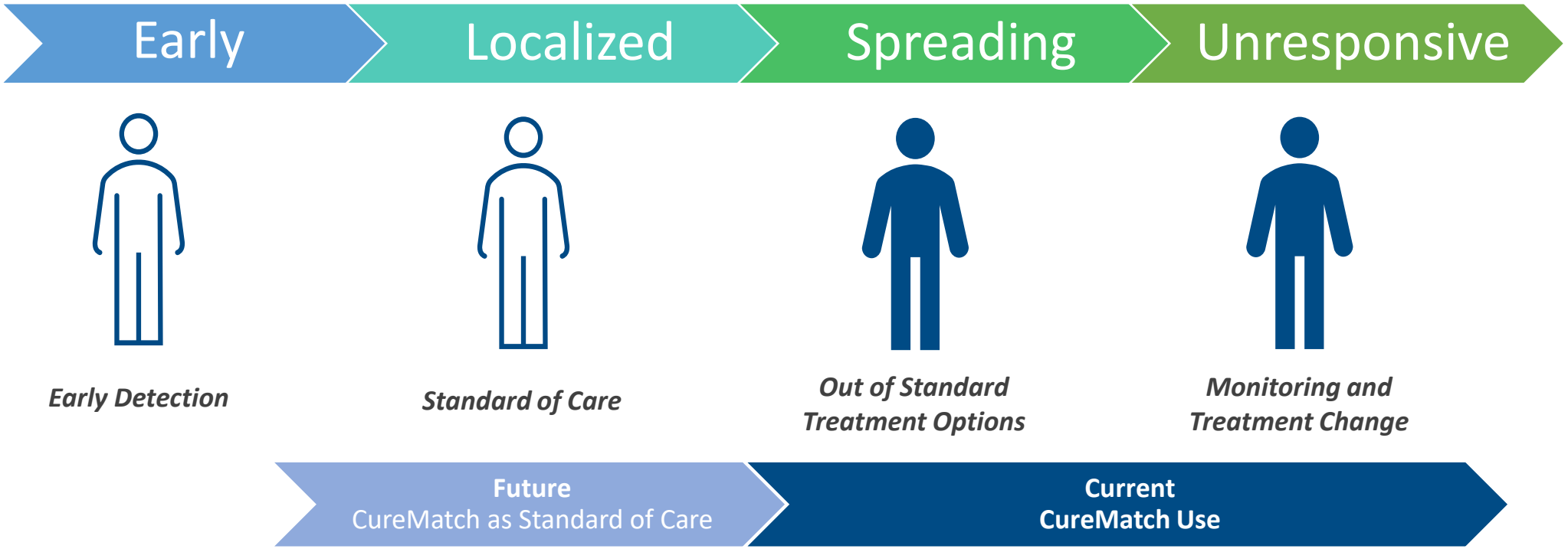
A year after the transplant, she received a gastrointestinal cancer diagnosis, then adopted a precision medicine approach.

Both solid and liquid biopsies were taken, NGS performed, and mutations revealed. This data was integrated and put into the CureMatch® platform.

The highest ranked option was a personalized 2-drug combination using cabozantinib and sirolimus, each targeting specific mutations. Within a month, a lack of tumor growth appeared.

As a result of this personalized combination therapy, the patient's condition stabilized.

Therapy Matching *in the Cancer Care Continuum*



Clinical Utility for CureMatch® Cancer Therapy Matching Solution

Clinical *Evidence*

Numerous peer-reviewed studies, published in leading scientific journals, show that with CureMatch® a clinician is 350% more likely to select a more effective therapy option, the first time.

Genome Medicine

Molecular profiling of advanced malignancies guides first-line N-of-1 treatments in the I-PREDICT treatment-naïve study
Sicklick....Kurzrock, Genome Medicine 2021

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Significance of scores generated by a cancer therapy matching engine for patient outcomes.
Perlina, ASCO, 2021

nature medicine

Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study
Sicklick, Nature Medicine 2019

nature COMMUNICATIONS

Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy patients
Kato, Nature, 2020

cancers

The Crossroads of Precision Medicine and Therapeutic Decision Making
Boichard…..Kurzrock, Cancers, 2020

ESMO Open
Cancer Horizons

Comparison of Three Commercial Decision Support Platforms for Matching of Next-Generation Sequencing Results with Therapies in Patients with Cancer
Perakis, ESMO Open, 2020

Molecular Cancer Therapeutics

Precision Oncology: The UC San Diego Moores Cancer Center PREDICT Experience
Schwaerderle…Kurzrock, Molecular Cancer Therapeutics, 2016

RC Research Consortium

Adding Rx Price Data *Greatly Enhances Payer Utility*

Comparative Predictive Effectiveness Results					Treatment Value Analysis			
	Score	Recommended Treatment Options			Full Rx	Lower Dose	Value Index	
		Drug 1	Drug 2	Drug 3	1-Mo Cost	3-Mo. Cost	$/CM Point	
3-Drugs	**83%**	*Cisplatin*	*Palbociclib*	*Bevacizumab*	$ 27,689	$ 33,227	$ 400	**Best Value**
	83%	Carboplatin	*Palbociclib*	*Bevacizumab*	$ 27,950	$ 33,540	$ 404	
	78%	*Olaparib*	*Palbociclib*	*Sorafenib*	$ 44,480	$ 53,376	$ 684	
2-Drugs	58%	Carboplatin	*Bevacizumab*	Combination	$ 13,697	$ 24,654	$ 425	
	58%	*Olaparib*	*Bevacizumab*	of 3 Approved Drugs	$ 21,002	$ 37,804	$ 652	
	53%	Cisplatin	*Sorafenib*		$ 22,660	$ 40,778	$ 769	
1-Drug	33%	Carboplatin			$ 284	$ 853	$ 26	
	33%	Olaparib			$ 7,590	$ 22,769	$ 690	
	15%	*Sorafenib*			$ 22,637	$ 67,911	$ 4,527	

Each of these Approved On-Label Medications, are Popular, *Comparatively Low-Value,* Options

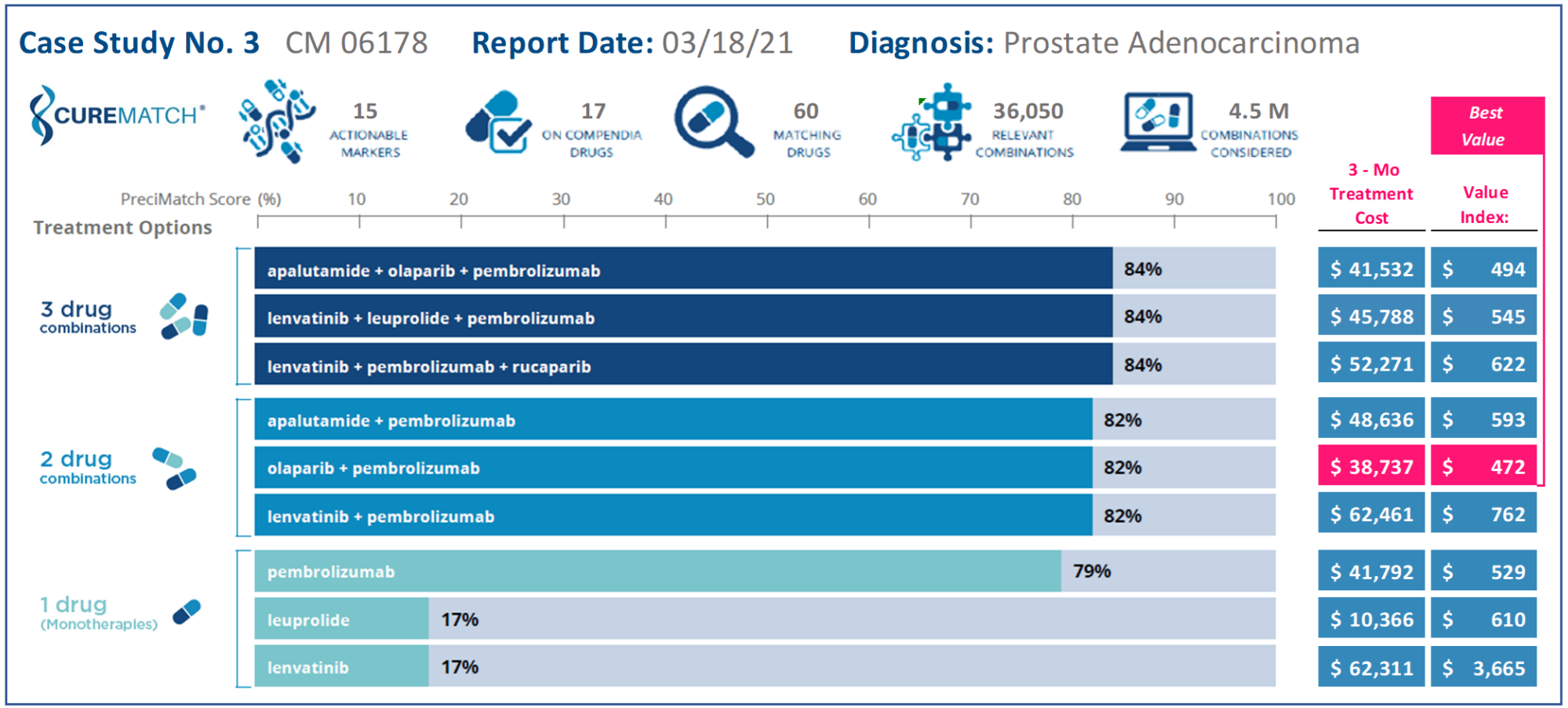
Approved drugs, used in an off-label combination for this indication, are in *italics*

Value *= Best Therapeutic Match, for the Right Price, Based on Genomic Indication*

Value Index ($/CM Point) = (3-month-adjusted dose) divided by the CureMatch® score (%). In the example, the full cost of one month of cisplatin plus palbociclib plus bevacizumab is $27,689. After adjusting the dose and the 3-month interval, the cost is $33,227 for 3 months of therapy. As the matching score is 83% for this option, the cost per CM score percentage point (Value Index ($/CM)) is 400, a better value than the next best scoring option at 404.

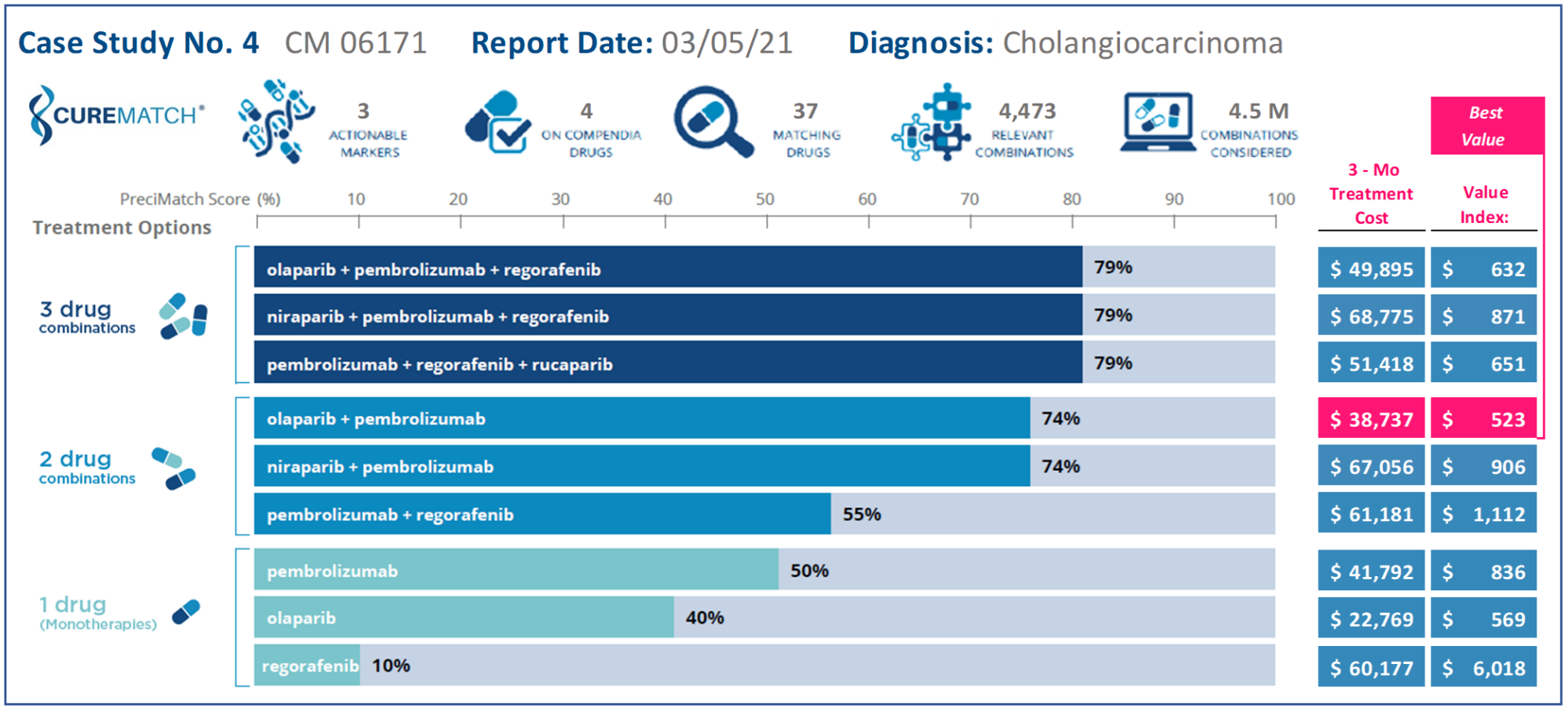
RC Research Consortium

Case Study *No. 3*



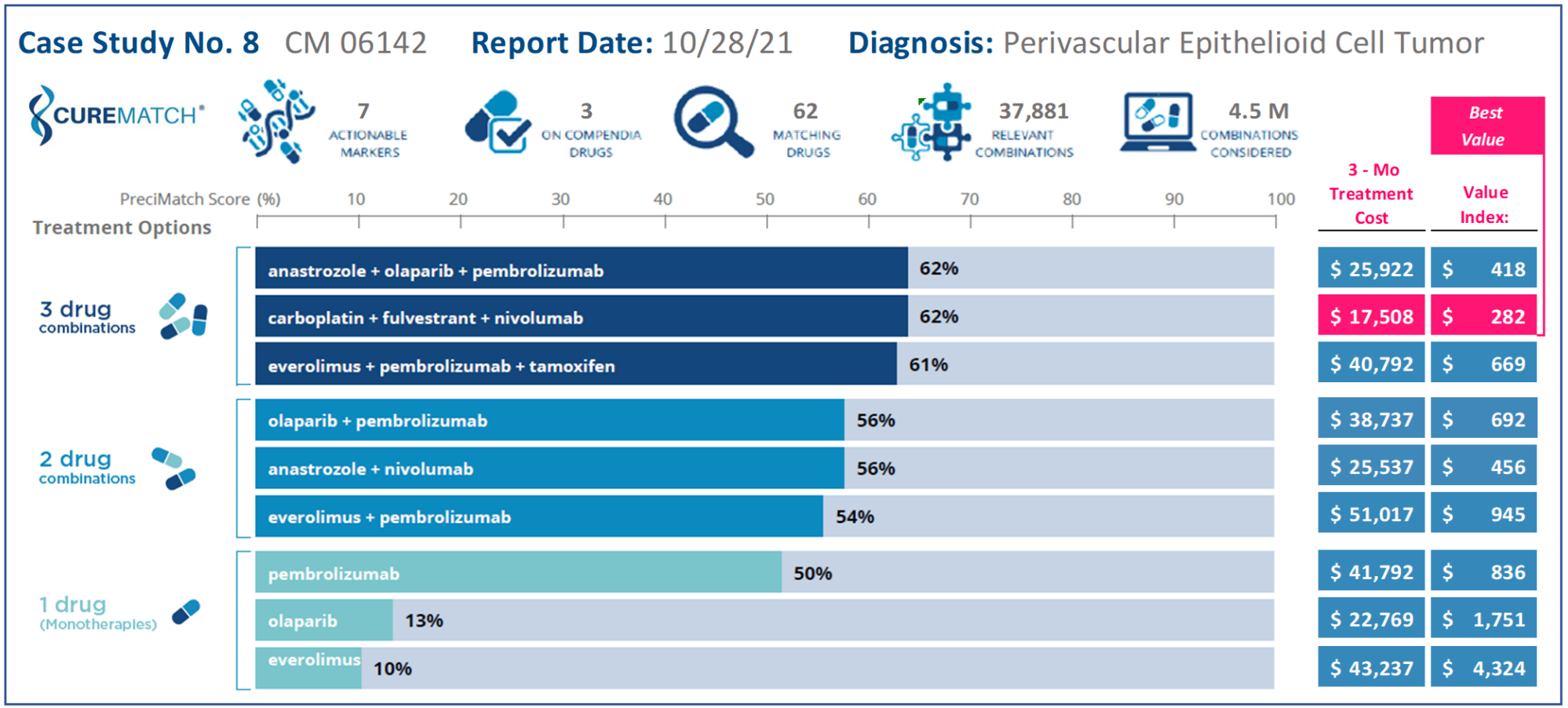
The 6 top-ranked therapies scored 82 – 84%; the *best value* being the *least costly*. Note the huge difference in the cost between the 2 low-clinical -value (17%) options.

Case Study *No. 4*



The *best value* is a 2-drug combination, with a comparatively high score of 74%, creating a significant financial savings opportunity vs. the top-scoring 3-drug options.

Case Study *No. 8*



The best scoring option, a 3-drug *off-label* combination, represents the *best value,* with a score of 62%, while creating a significant financial savings opportunity vs. *all* of the scored options. Each of the 2 low-clinical-value options are far more costly.

Summary of ***Research Consortium*** **Study Findings**

Now available on

ResearchGate

medRxiv

Europe PubMed Central

ORIGINAL RESEARCH

Gaining Control of Combination Cancer Treatment Risk by Incorporating Cost and Value Data into the Drug Selection Process *at the Point–of–Care*

A Science - Based Method to Drive Value for Patients, Physicians, Health Systems and Payers

medRxiv 2022.02.13.22270914 Europe PMC PPR454868 DOI.org/10.1101/2022.02.13.22270914

TPA Network Research Consortium

Richard L. Nicholas

Abstract

The use of combination therapies*, as well as FDA-approved drugs for off-label indications, to treat advanced cancer, is widespread. While much is known about their clinical effectiveness, there exists no examination of the relative cost of novel multidrug combinations vs. traditional available therapy options, or study as to how knowledge about comparative therapy costs at the point-of-care can be leveraged by doctors, health systems, and payers. We found that:

1) combination multidrug cancer regimens may be *less costly* than monotherapies or other standard options;
2) novel, multidrug combinations are often *better financial values* than monotherapies or other standard options;
3) having treatment cost and value data, at the point of care, enables the prompt selection of more cost-effective medications and the avoidance of expensive low-value therapies that are financially wasteful.

We conclude that the effectiveness of value-based purchasing initiatives may be amplified if physicians and payers use comparative treatment cost/value data to enhance their cancer drug-selection decision making.

* Including combinations of immunotherapies, chemotherapies, targeted drugs with distinct mechanisms of action, etc.

What Can CureMatch® Do
for Payers ?

Drive Better Outcomes / Patient Satisfaction

- Select the best Rxs, at the earliest possible time
- Drive better responses with matched treatments
- Reduce patient financial toxicity
- Reverse drug decisions based on sunk costs

Eliminate Waste / Reduce Cost

- Avoid high-cost, low-clinical-value Rxs
- Extend the value-based construct to include oncology specialty pharmacy
- Reduce drug spend on wasteful Rxs

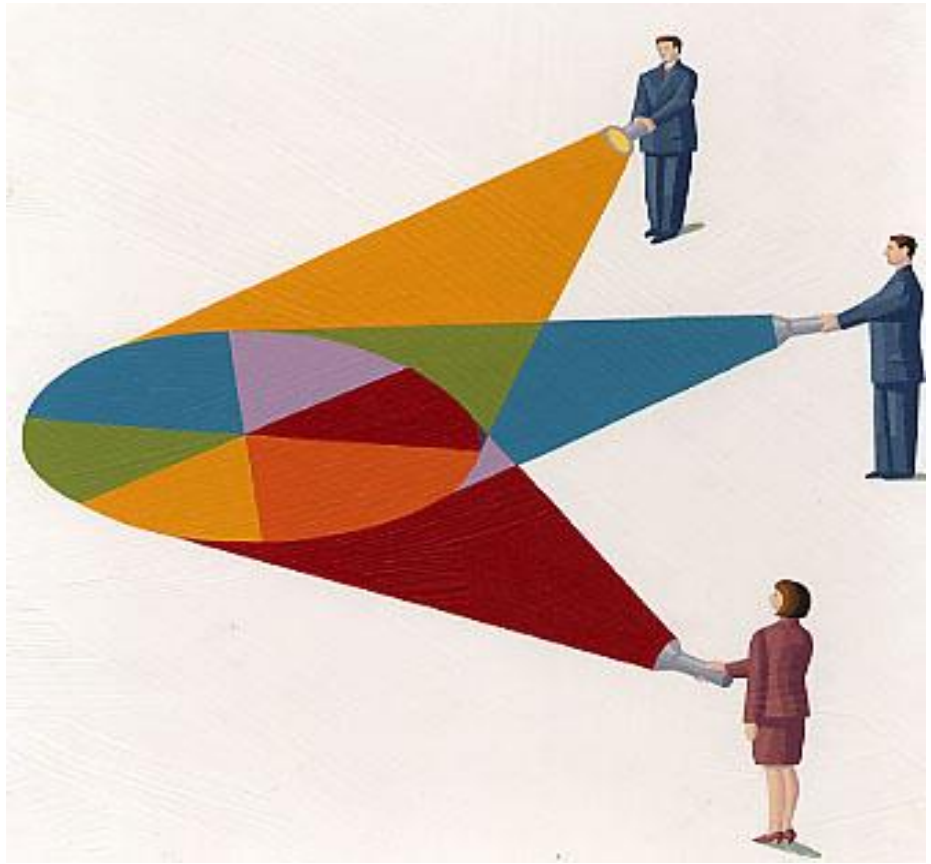
Promote Better Provider Relations

- Simplifies cancer Rx prior authorization to consistent, science-based process
- Supports novel multi-drug treatment

Mitigate Payer Liability / Risk

- Lessen adverse drug event risk
- Identify problematic drugs and outlier providers
- Buttress coverage / PA decisions with science

Healthcare AI *Use Cases*



- Commercial Payers and MCOs
- Union Health & Welfare Plans
- Employer ERISA Plan Sponsors
- Employer Stop Loss Reinsurers
- Third Party Administrators
- UR / Medical Care Managers
- Pharmacy Benefit Managers
- At - Risk Medical Providers
- Integrated Healthcare Networks
- Cancer Insurance Companies
- Benefit Brokers and Consultants

CureMatch® *Implementation Options*

CureMatch® can be deployed by payers in a variety of ways to enable them to be as passive or aggressive as they wish with respect to optimizing care and patient satisfaction and driving value

	A. *Informational*	B. *Judicious*	C. *Aggressive*	D. *Intense*
Patient Focus	• Current and/or Newly Diagnosed	• Current and/or Newly Diagnosed	• Both Current and Newly Diagnosed	• Both Current and Newly Diagnosed
Cancers	• Stages 2, 3 & 4	• Stages 3 & 4	• Stages 3 & 4	• All
CM-MD Consult	• Invitation	• Invitation	• Required	• Required
NGS Testing	• Optional / Free	• Optional / Free	• Required / Free	• Required / Free
CureMatching	• Optional / Free	• Optional / Free	• Incentivized / Free	• Required / Free
Impact on Rx Selection Parameters	• Physician free to follow or disregard CM Report findings	• Incentivized to follow CM Rx recommendations	• Penalized for not following CM Rx recommendations	• Required to follow CM Rx recommendations for plan coverage
Impact on Rx Coverage	• No Impact: MD free to prescribe any Rx	• Prohibitions on certain Rx's	• Prohibitions on certain Rx's	• Medical Necessity redefined by CM

The Need for, and Value of, *Translational Research*

On average, it takes *17 years* for a new medical technology to get into widespread clinical use as the research to prove *medical efficacy* differs from that to assess *ROI, cost-effectiveness, value*

- Technology that will constitute the norm and common-place in the lives of those who will live in the future, already exist today, *for some*. Change, in the interim, will simply be the adoption of these niche innovations by all.

EINPRESSWIRE

New Study Validates Payer/Physician Use of AI to Cut Wasteful Spending on High-Cost, Low-Value Cancer Drugs

- Translational research reduces the time it takes to get a new medical technology or healthcare innovation from the workbench into widespread real-world clinical use.

Key *Takeaways*

- New AI-supported precision medicine technology is proving to be *a critical tool to improving health outcomes and patient satisfaction* … while *reducing waste and cost, and driving value*
- Coupled with tumor-specific genomic data, Healthcare AI helps
  - doctors *choose the best course of treatment* for cancer patients, and
  - payers to *extend value-based purchasing to cancer*
- Many AI-supported healthcare technologies represent *high-value innovation opportunities* for payers, not just based on their obvious *clinical utility*, but for their ability to help *contain cost*
- Translational research and comparative effectiveness analysis, conducted in in real world settings, helps accelerate the adoption of emerging technologies/innovations by all stakeholders.

Thank You,

for Your Attention

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