A Value Manager's Take on Disruption: Advancements In Precision Medicine

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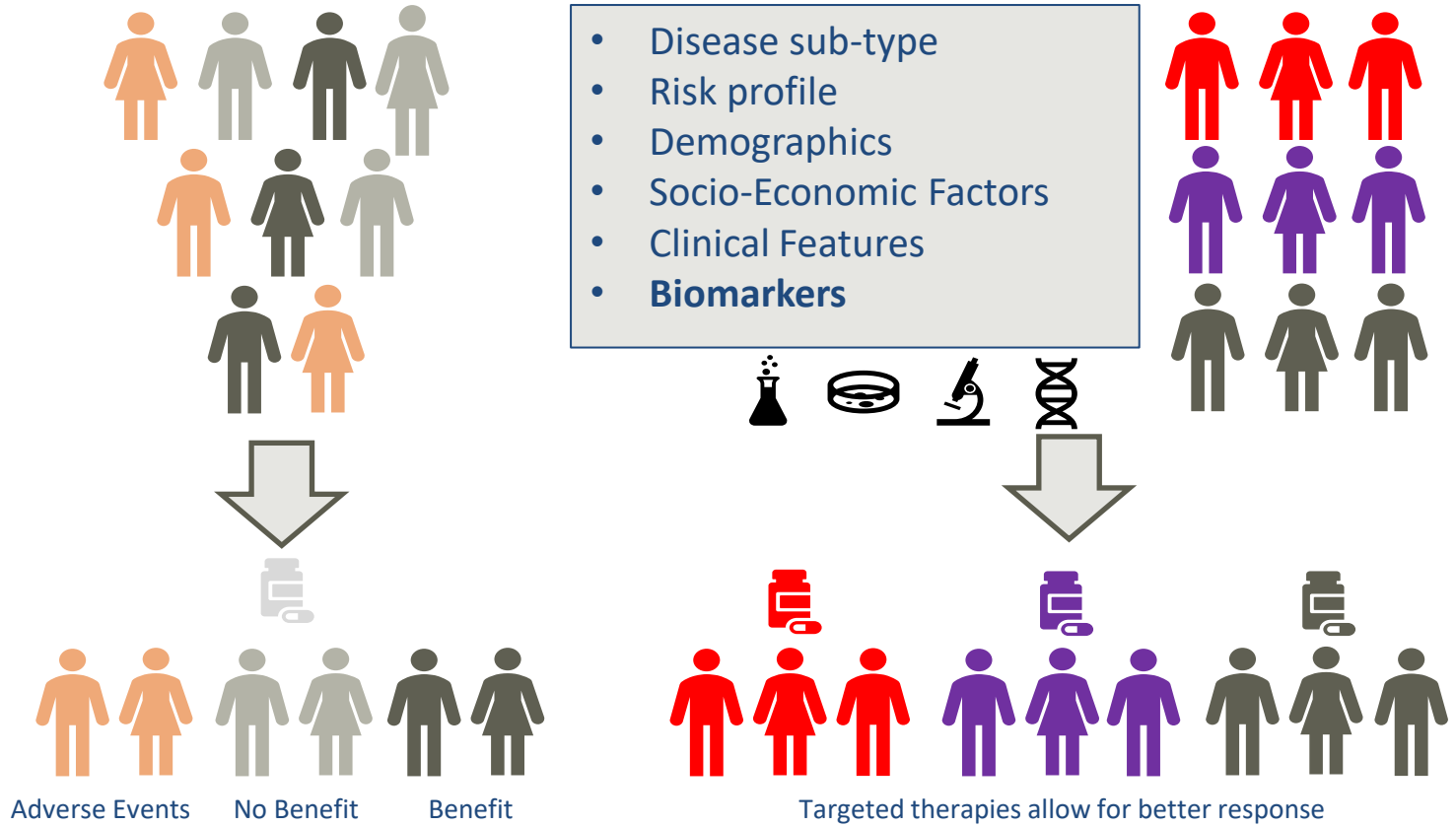
Causeway Capital Management LLC
11111 Santa Monica Blvd., 15th floor
Los Angeles, CA 90025
www.causewaycap.com

Agenda

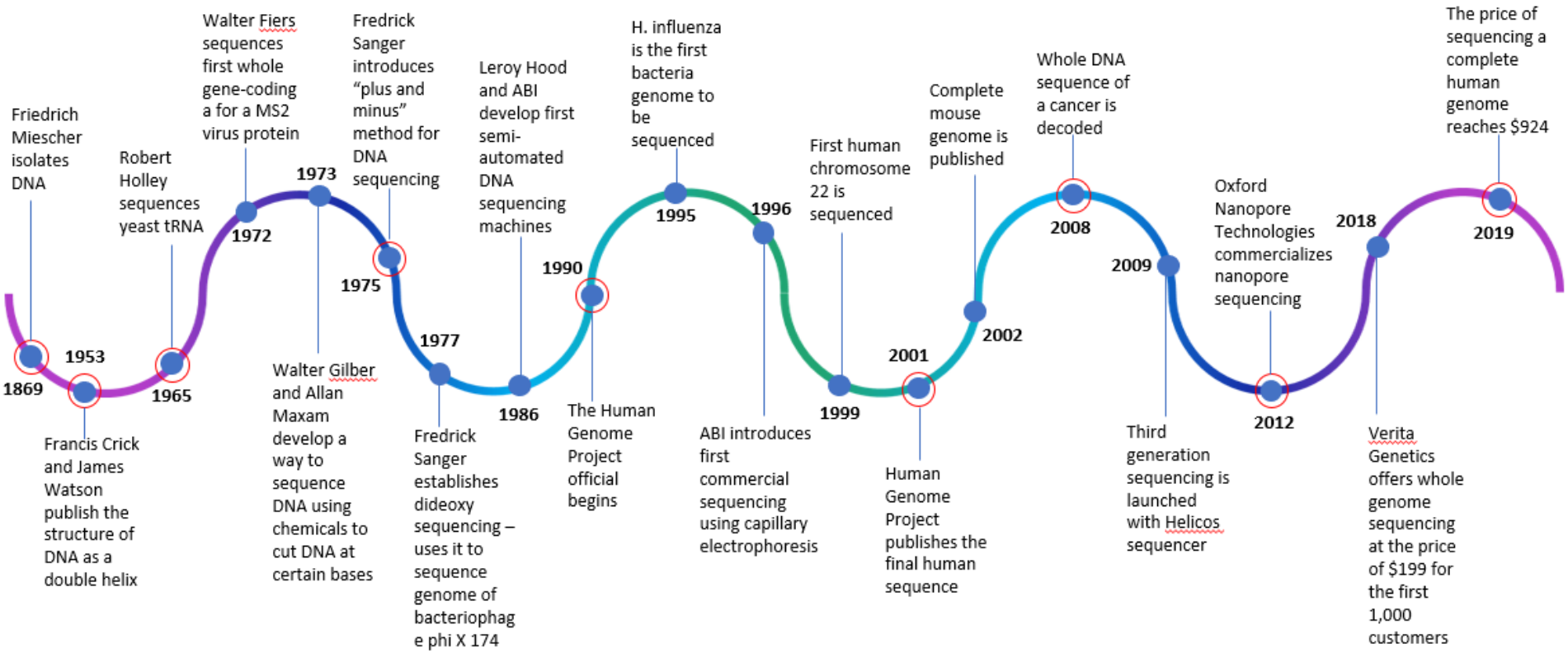
1. What Is Precision Medicine?
2. How To Invest
3. Gene Therapy – The Next Frontier
4. Appendix

What is Precision Medicine?

- Precision medicine, sometimes known as personalized medicine or stratified medicine, is an innovative approach to tailoring disease prevention and treatment according to differences in people's genes, environments, and lifestyles.
- The goal of precision medicine is to target the right treatments to the right patients at the right time.
- A Key part of precision medicine is the use of predictive biomarkers, which identify patient subgroups most likely to benefit (or least likely to experience harm) from an intervention.



The DNA Revolution



Sources: GATC Biotech, genome.gov

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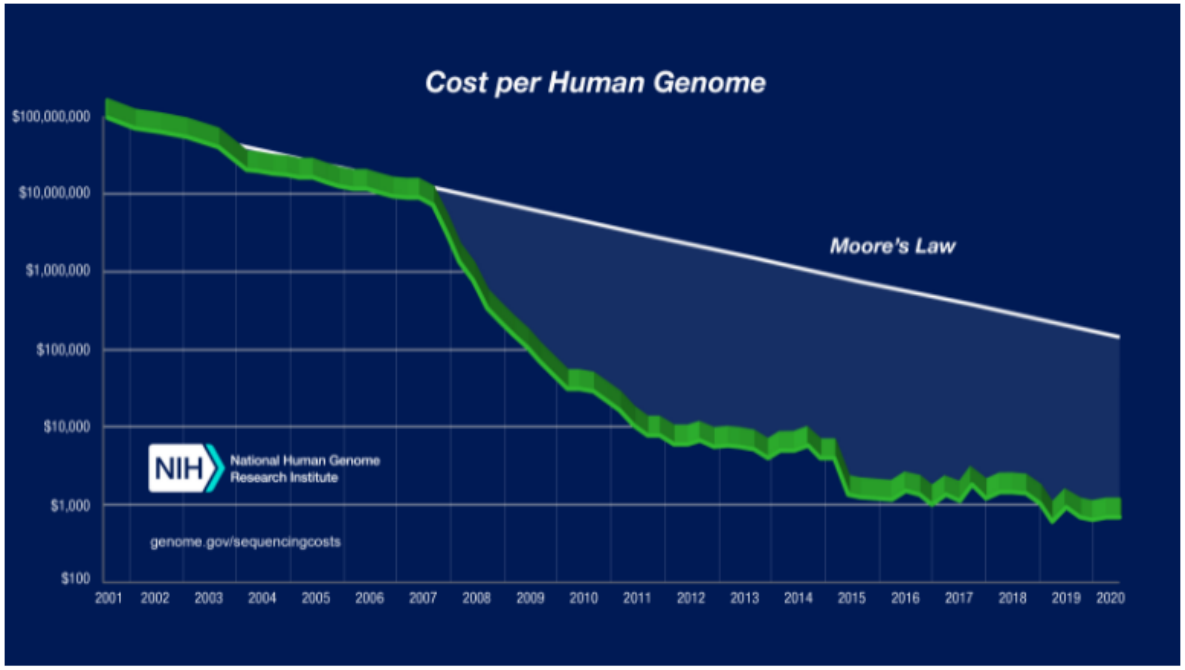
Innovation Drives Affordability In Sequencing

- Whole-genome sequence has been replaced by targeted sequencing. By reducing the amount of DNA that is sequenced, the amount of laboratory manipulation is significantly reduced.
- Data quality has improved significantly – scientists have moved from finished sequence (covering 90% of the genome at 99.99% accuracy) to draft sequence (covering 95% of the genome at 99.9% accuracy) with significant costs savings.
- Beginning in 2008, the cost data reflects the usage of next-generation sequencing platforms versus the Sanger-based chemistry and capillary based instruments (first generation).



Cost per genome data - 2020

Source: National Institutes of Health

Moore's Law describes a trend in the technology industry that involves the doubling of computing power ever two years. Technology improvements that outpace Moore's Law are generally regarded to be doing well.

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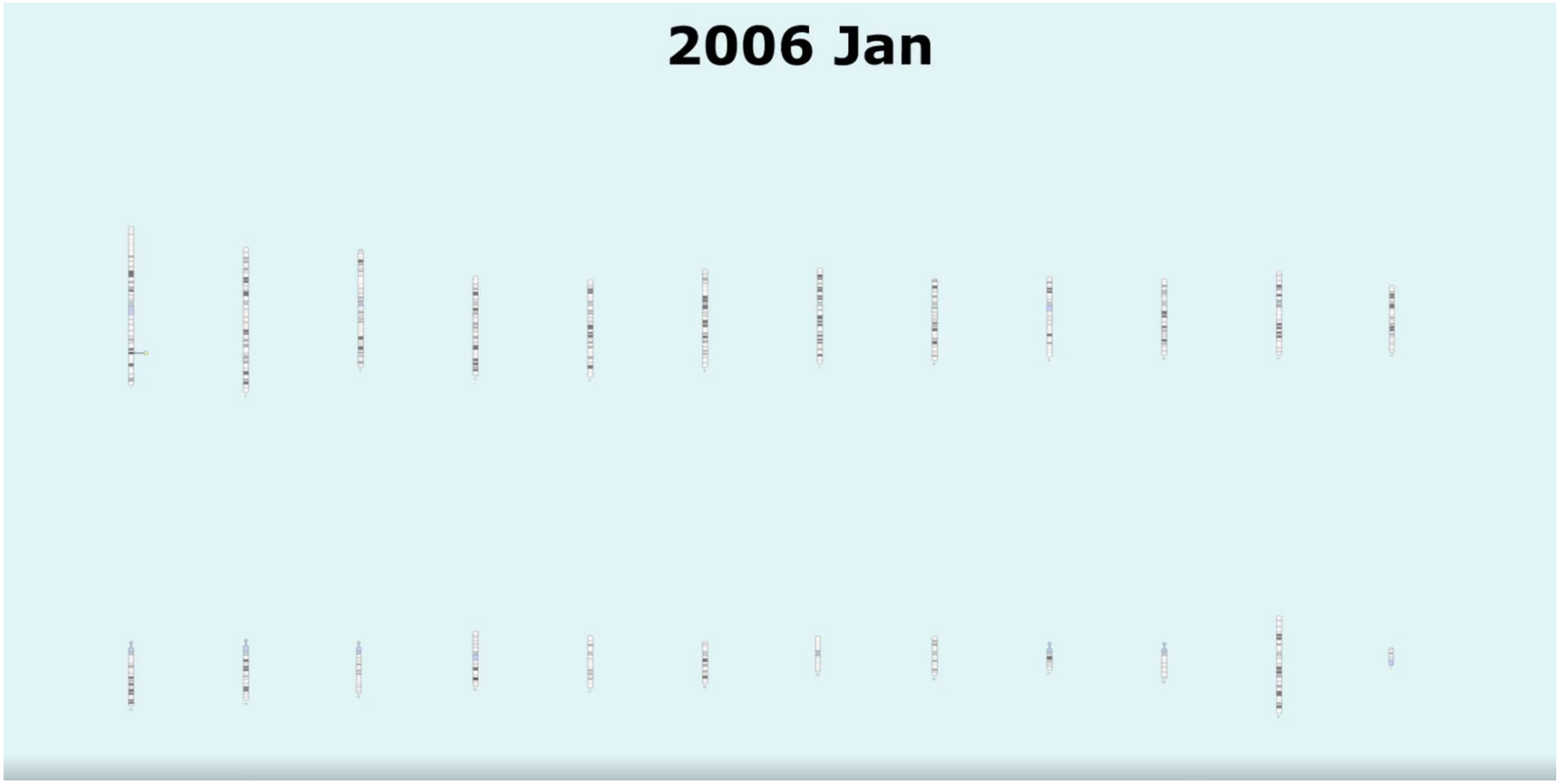
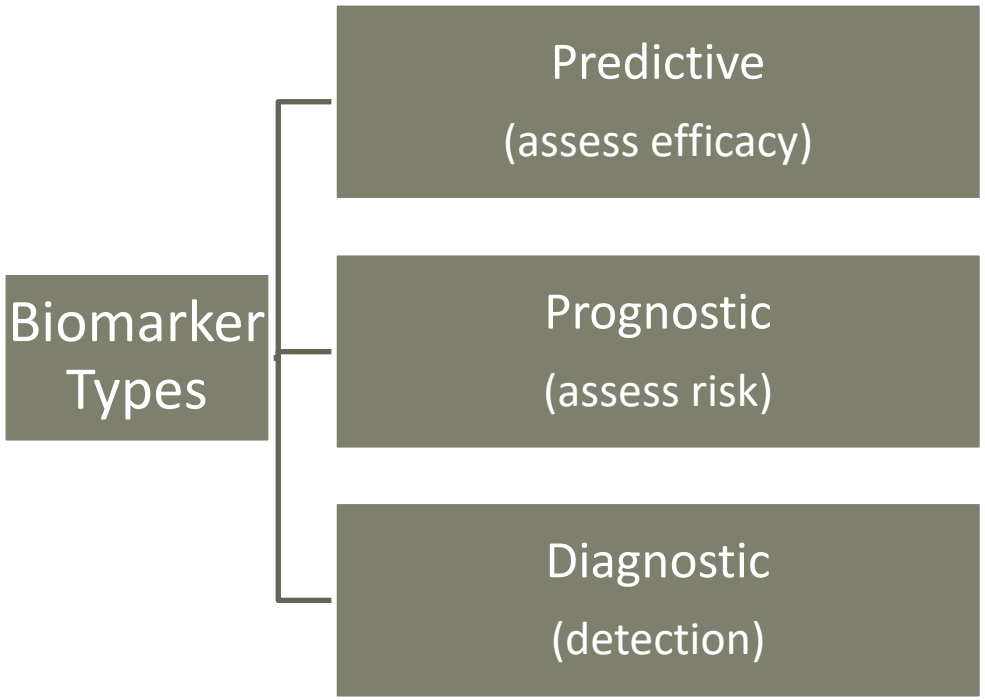
Availability Drives Disease Mapping



Source: GWAS Catalog

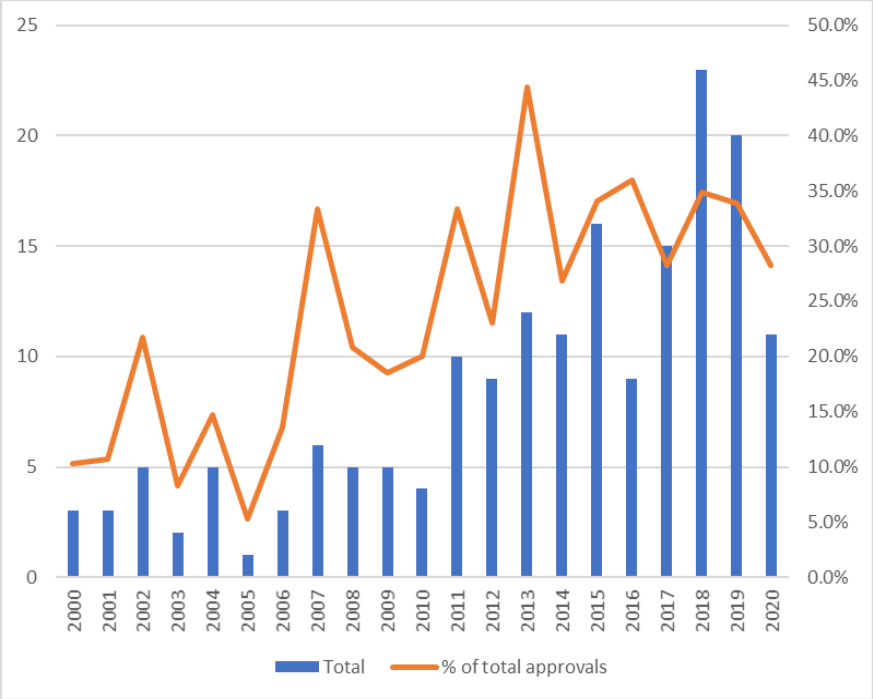
Biomarkers – The Essential Toolset

- Biomarkers play a crucial role in the development of precision medicine.
- Narrowly defined, biomarkers are measurable indicators of the presence or the amount of expression of a particular gene mutation.
- Predictive Biomarkers indicate the likely effect of a specific therapy on the patient (examples are HER2 positivity in breast cancer, KRAS mutations).
- Prognostic Biomarkers inform physicians about the risk of clinical outcomes (examples are PSA levels in prostate cancer, BRCA1 and BRCA2 gene mutation in breast cancer).
- Diagnostic biomarkers are used to diagnose a particular disease (examples are troponin and creatinine kinase in heart attacks, PSA in prostatitis).

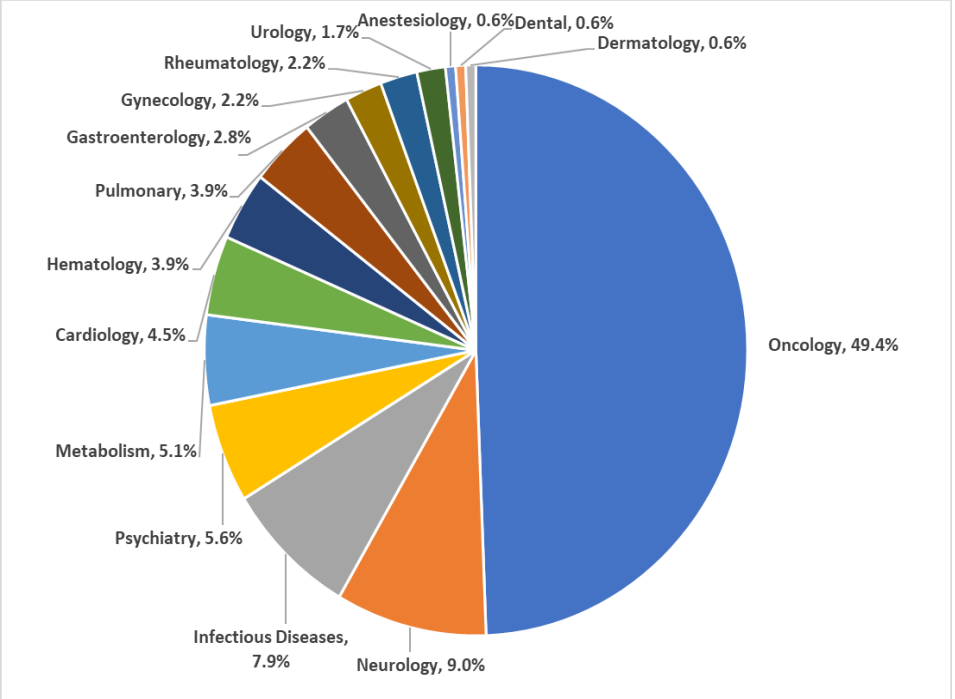


Drugs Using Biomarkers are Growing

DRUG APPROVALS LINKED TO BIOMARKERS ARE GROWING IN NUMBER AND SHARE



ONCOLOGY LEADS IN BIOMARKER APPROVALS BUT THE TECHNOLOGY IS WIDELY USED



Source: Kim, J.A.; Ceccarelli, R.; Lu, C.Y. Pharmacogenomic Biomarkers in US FDA-Approved Drug Labels (2000–2020). J. Pers. Med. 2021, 11, 179. https://doi.org/10.3390/jpm11030179

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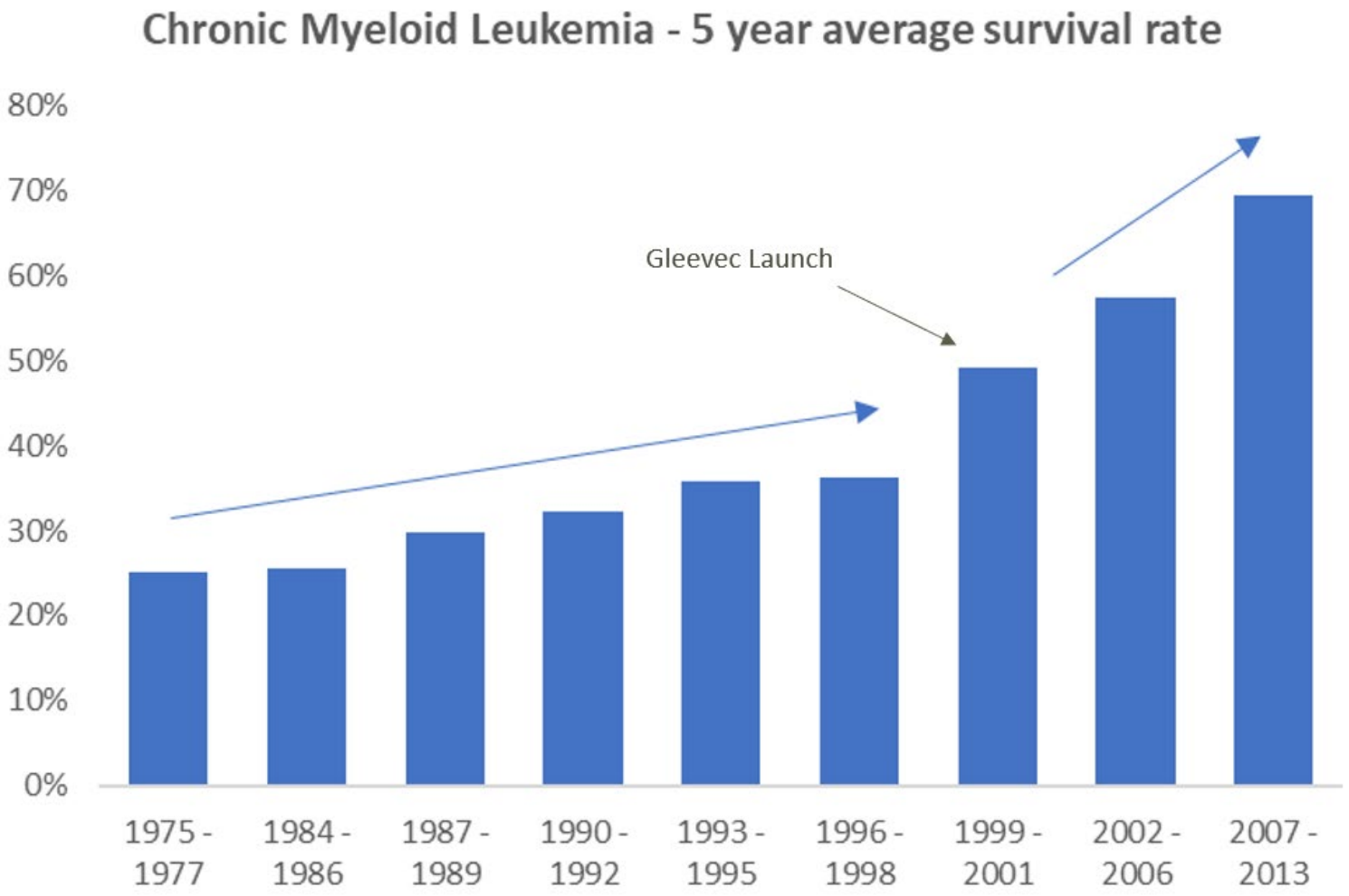
Case Study: Gleevec



Source: SEER Cancer Statistics Review, 1975-2014, National Cancer Institute

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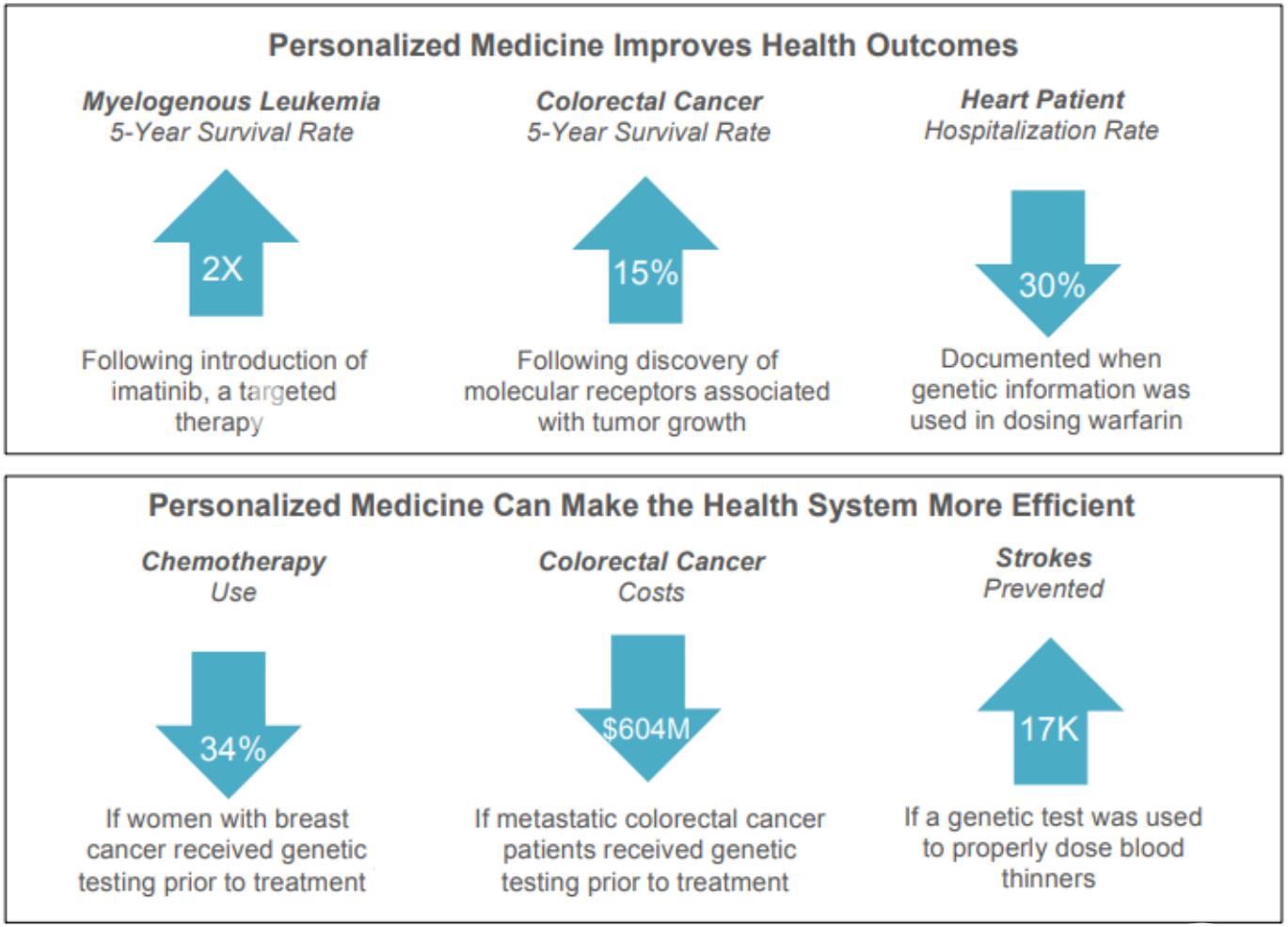
Health Outcomes And Savings Are Supportive



Source: Personalized Medicine Coalition

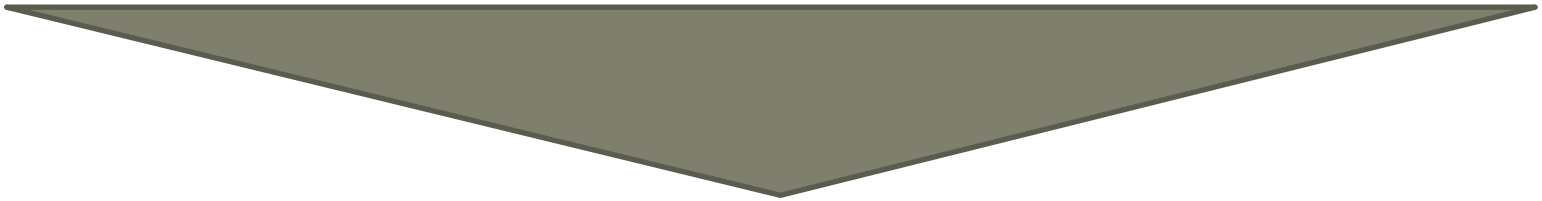
Companies With Pharmaceutical and Diagnostics Expertise Are Uniquely Positioned

Pharmaceuticals

- Leading oncology company globally
- Innovation leadership with focus on biomarkers for development
- Multiple platforms to leverage immunotherapy approach to cancer
- Long history of focus on precision medicine and targeted therapies

Diagnostics

- Large in-vitro diagnostic company globally
- Leader in Diagnostic R&D spending
- Large installed base of diagnostics and broad menu of assays on one integrated platform
- Pharma partner of choice across the development process in oncology



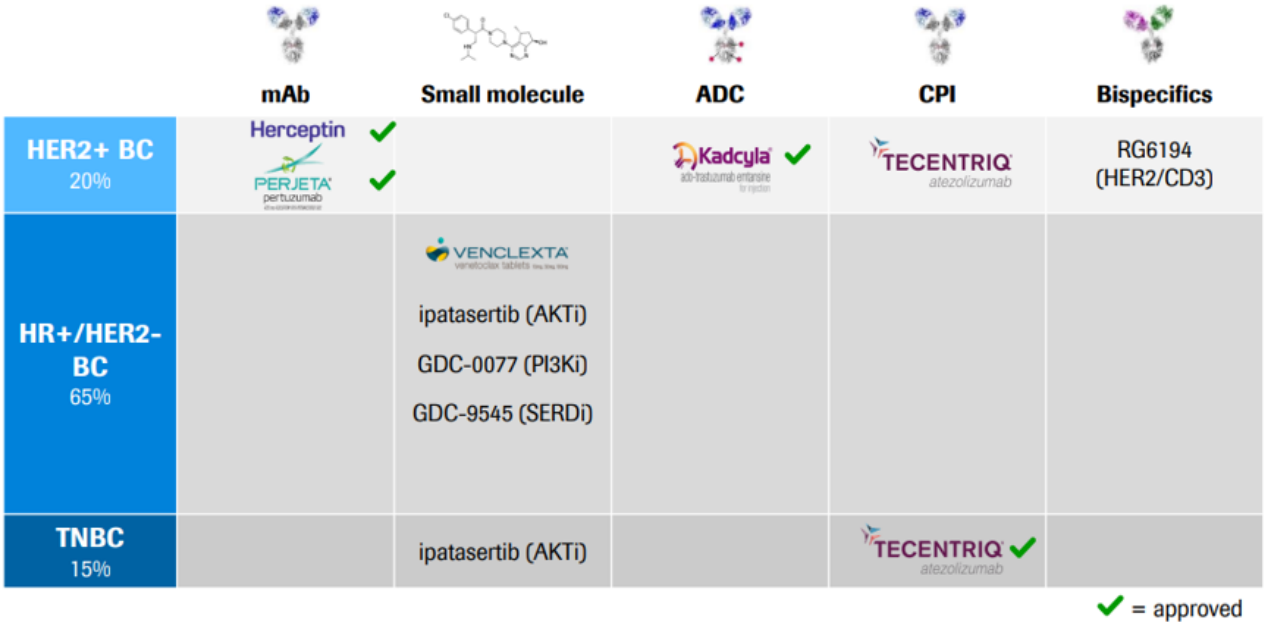
Blending pharmaceutical and diagnostics assets creates a privileged position to develop precision medicine and healthcare

Breast Cancer Portfolio Example

- Through biomarker development, the entire breast cancer market can be addressed.
- The company has occupied a dominant position in HER2+ BC since the advent of Herceptin.
- Pipeline is now addressing the HR+/HER2- BC patient population.
- Triple negative breast cancer remains the most difficult to address form, but solutions using alternative biomarkers are under development.

Largest breast cancer portfolio

Expanding beyond HER2+ breast cancer



mAB=monoclonal antibody; ADC=antibody drug conjugate; CPI=checkpoint inhibitor; TNBC=triple negative breast cancer; Venclexta in collaboration with Abbvie

Source: Company report

Triple Negative Breast Cancer ("TNBC") – What is It?

Think of a cancer cell as a house. To get inside to destroy the cancer, we must bypass three locks on the front door: estrogen, progesterone, and HER2.

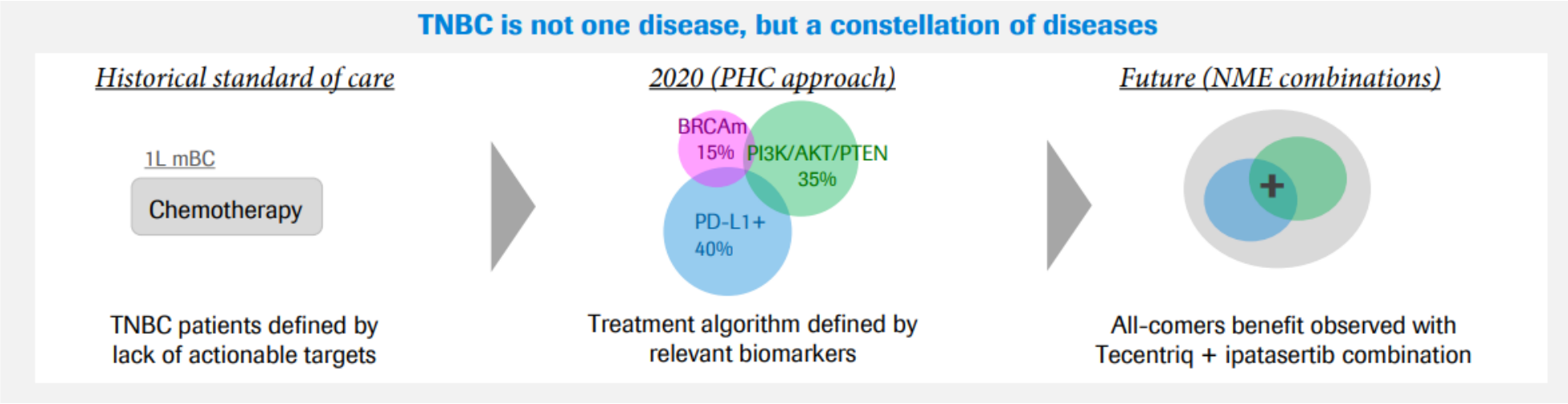
If your cancer tests positive for these three locks, which are known as *receptors,* then doctors have a few keys they can use to get inside the cell to destroy it.

If you have triple-negative breast cancer, those locks aren't there. So the keys doctors usually use won't work. But chemotherapy is still an effective option.

Source: CDC.gov

Pursuing Precision Medicine in TNBC

- One approach to TNBC is to look for alternative biomarkers (BRCAm, PD-L1+, PI3K) active in other type of cancers.
- The PD-L1 inhibitor Tecentriq has been approved in the use in TNBC.
- Combination therapies may be developed to address the remaining gene expression in TNBC.



"PHC" refers to precision healthcare. "NME" refers to new molecular entity, a drug with an active ingredient that has not been approved by the FDA.

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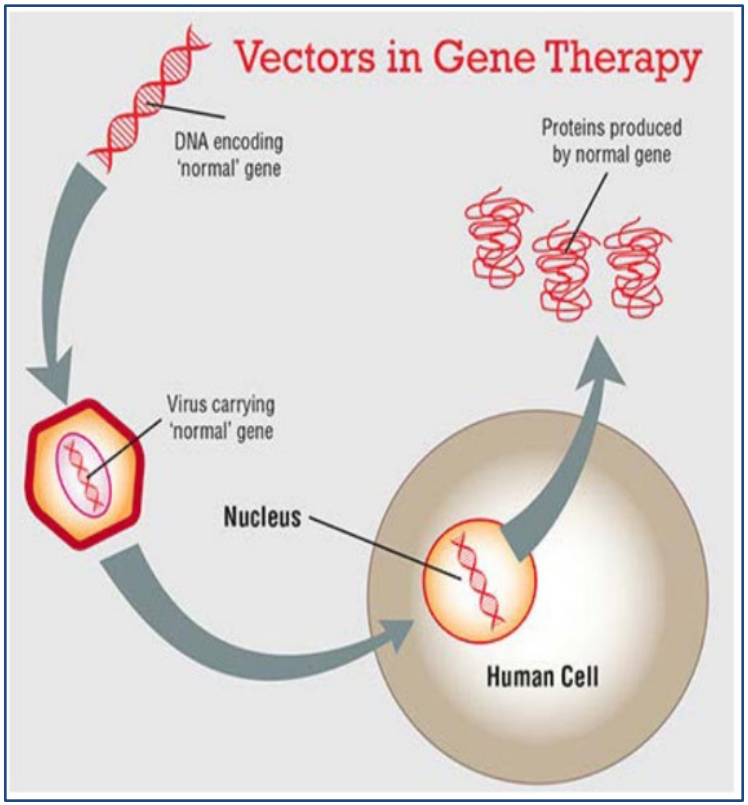
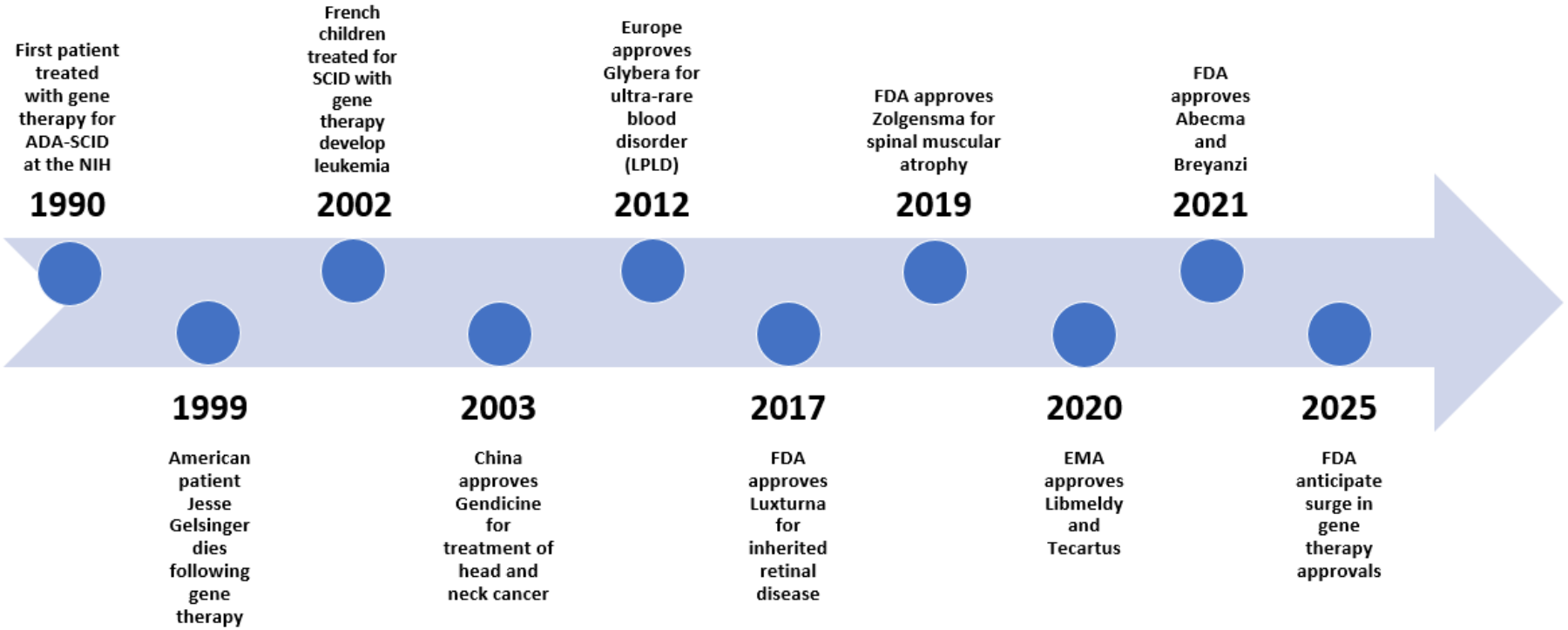
Gene Therapy – The Next Big Thing?

- The AMA defines gene therapy as “a novel approach to treat, cure, or ultimately prevent disease by changing the expression of a person’s genes”.
- The goal of gene therapy is the restoration of normal biological function by repairing (or substituting) the underlying defective gene.
- Gene therapy can be persistent (single administration) or transient (multiple administration) depending on the vector used.
- Gene therapy works best with diseases that are cause by a single defective gene, rather than multiple gene defects.



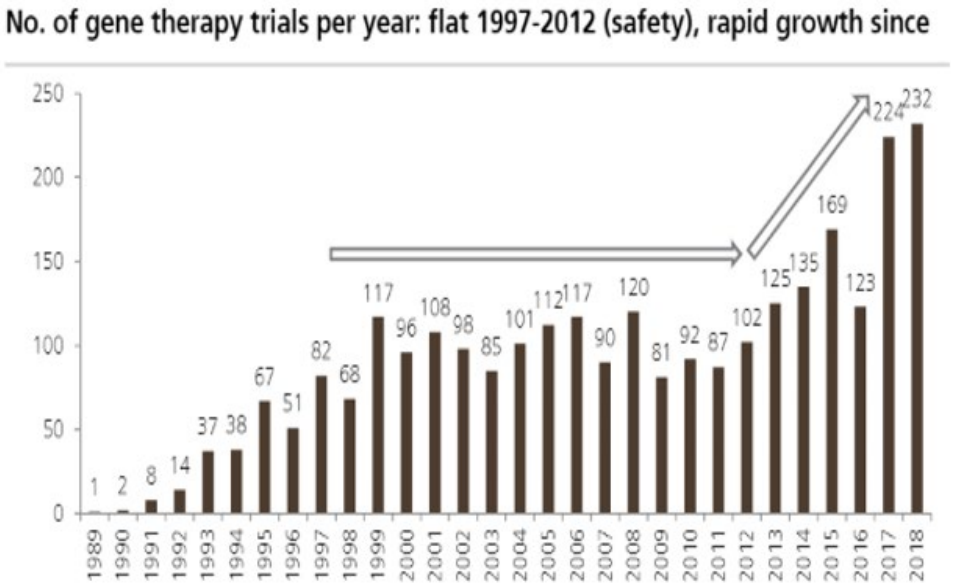
Source: https://www.retina-specialist.com/article/gene-therapy-the-new-frontier-for-inherited-retinal-disease

Gene Therapy – a Timeline



Reacceleration of Gene Therapy

- Advancements in genomics led to a growing number of clinical trials for gene therapies in the 1990s.
- Safety concerns around the vector to deliver the therapy halted progress.
- In 2012 trials started growing again thanks to the adoption of safer vectors (AAV).
- While there are still questions to be answered around the safety of the AAV vectors, we have seen an acceleration for gene therapy related approvals.

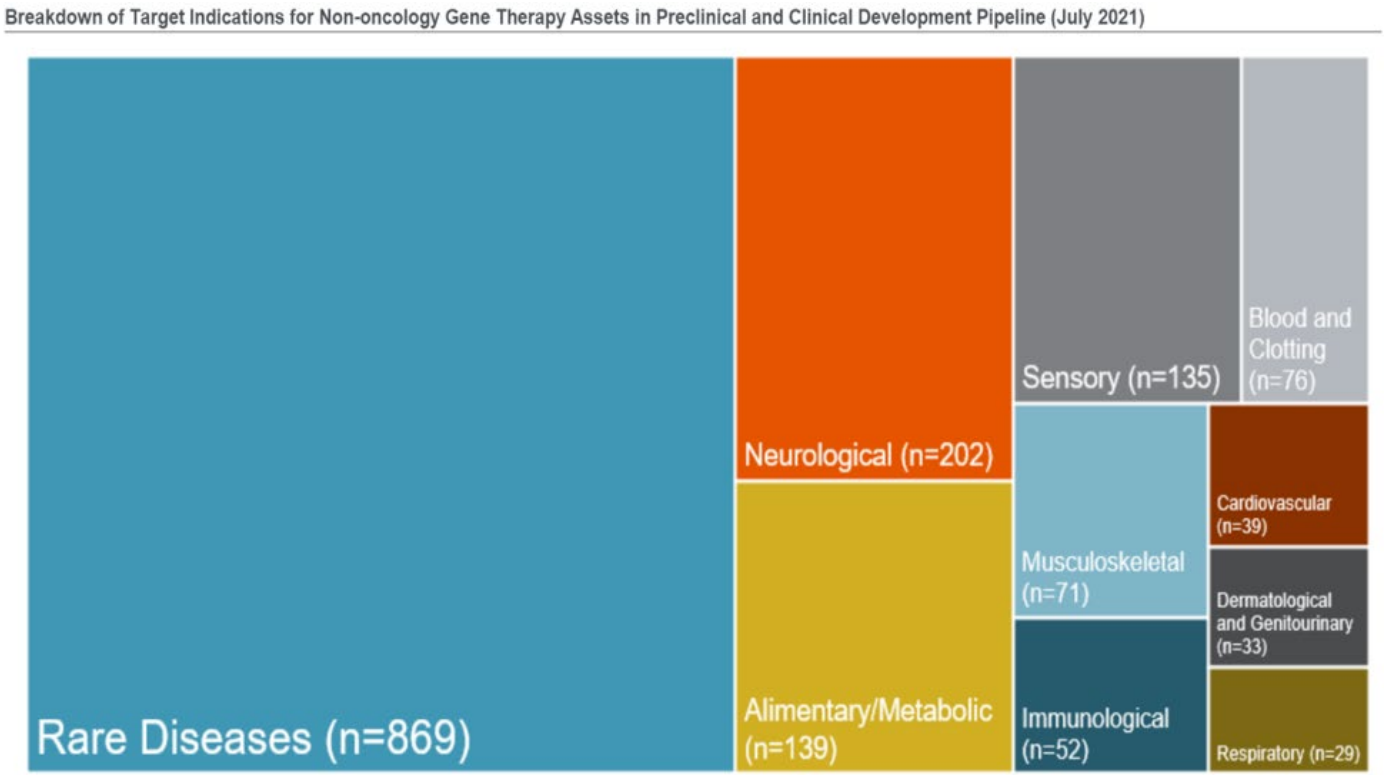


Product	Manufacturer	Target	FDA approval	EMA authorization
Abecma	Celgene	mulltiple myeloma	3/25/2021	No
Breyanzi	Juno Therapeutics	B-cell lymphoma	5/2/2021	No
Glybera	Chiesi Farmaceutici	lipoproteinn lipase deficiency	No	Withdrawn
Imlygic	Amgen	melanoma	10/27/2015	12/16/2015
Kymriah	Novartis	B-cell lymphoma	5/1/2018	6/29/2018
Libmeldy	Orchard Therapeutics	metachromatic leukodysrophy	No	44182
Luxturna	Spark Tehrapeutics	Leber congenital amaurosis	12/18/2017	11/22/2018
Provenge	Dendreon	prostate cancer	4/29/2010	Withdrawn
Ryplazim	Prometic Biotherapeutics	hypoplasminogenemia	6/4/2021	No
Strimvelis	Orchard Therapeutics	ADA-SCID	No	5/26/2016
Tecartus	Kite Pharma	mantel cell lymphoma	7/24/2020	12/14/2020
Yescarta	Kite Pharma	B-cell lymphoma	10/18/2017	8/23/2018
Zolgensma	Novartis	SMA Type I	5/24/2019	3/26/2022

Sources: Gene Medicine, UBS, FDA.gov

Focus on Rare Diseases

- Unsurprisingly, most trials under way are focused on rare and ultra-rare diseases.
- These diseases have often monogenetic identifiable causes.
- High price is easier to justify in a rare disease context.
- Outside of rare diseases, neurological disorders are a focus.

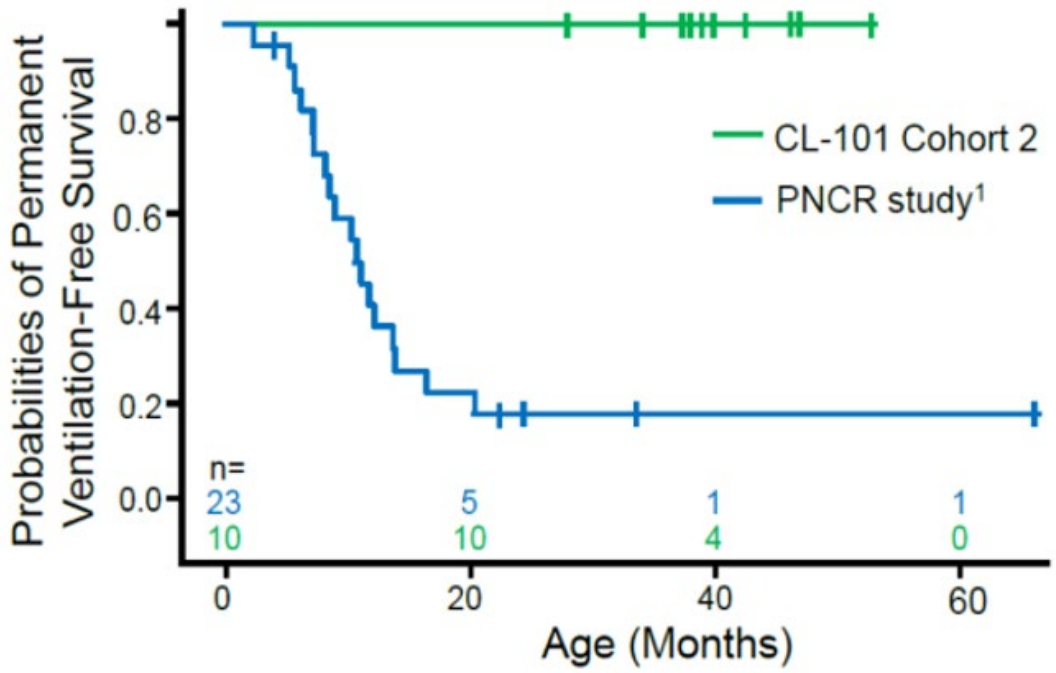


Sources: American Society of Gene + Cell Therapy, Piper Sandler

Zolgensma Example

- About 1,000 babies are born every year in the US and EU with Spinal Muscular Atrophy ("SMA").
- SMA has a monogenetic identifiable cause (SMN1 mutation/deletion).
- The only drug in the market (Spinraza) works by upregulating production from SMN2, leaving the most in-need patients with the worst outcomes.
- Zolgensma was approved under priority review in the US.

Ventilation-free survival of Zolgensma patients in phase I study (green) vs. natural history study (blue)



Sources: Company presentation

Conclusion

- Precision medicine, an innovative approach to tailoring disease prevention and treatment for each individual, has already led to improved outcomes for patients. As the field advances, the practice can further improve quality of life for patients afflicted by a variety of diseases while also reducing healthcare costs.
- Companies that combine industry-leading pharmaceutical and diagnostics capabilities are uniquely positioned to develop precision healthcare.
- Gene therapy trials have accelerated and provide potential for breakthrough treatments for rare diseases and neurological disorders.

Appendix

Real World Applications Suggest Savings

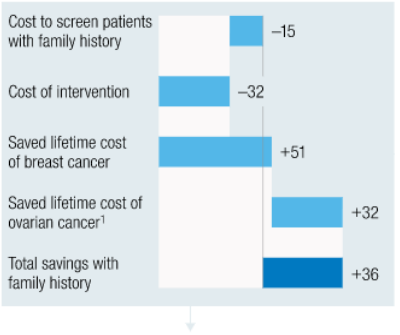
QUALITY AND DISEASE BURDEN ARE KEY CONSIDERATIONS AS NOT ALL BIOMARKERS SAVE MONEY

	Companion diagnostics			Procedure-focused diagnostics	Genetic-risk markers		
	Her2[2]	BCR-ABL[3]	Warfarin	AlloMap	BRCA1	BRCA1-F[4]	KIF6 (statin)
Savings from changed decision, $ thousand	40	80	2	4	25	25	–3.5
×							
Probability that diagnostic changes treatment decision, %	70	5	35	75	2	20	50
=							
Savings per test, $ thousand	28	4	0.7	3.1	0.5	5	<0
Cost of test, $ thousand	0.1	1	0.3	3	2–3	2–3	N/A
Cost savings for payers[1]	Yes	Yes	Yes	Yes	No	Yes	No

[1]Estimated savings per test is product of savings from single changed treatment decision and probability that any given patient will have a positive test (such that treatment decision is changed).
[2]Human epidermal growth factor receptor 2.
[3]Breakpoint cluster region–abelson tyrosine kinase.
[4]BRCA screening in an individual with a family history of breast cancer.

STABLE HEALTHCARE SYSTEMS BENEFIT MORE AND HIGH CHURN IS A CHALLENGE

Lifetime cost savings for 10 patients with family history of breast cancer screened for BRCA1



Cost savings may not accrue to payers, because of high patient churn

Plan types	Lifetime care • United Kingdom • Europe	Longest-term US plans • Medicare • Kaiser • Long-term employer	ASO[1] plans/ consolidated market • Most Blue Cross and Blue Shield plans • Mid-term employers	Typical non-ASO plans • HMO[2]
Average number of years patient with plan	N/A	10	5	3
Savings/loss per 10 patients, $ thousand	36	10	–6	–20

BRCA1 only cost effective for plans that capture most of the lifetime value

Methodology: Based on estimate of lifetime cost savings for 10 patients with family history of breast cancer who are screened for BRCA1 variants associated with high risk of breast cancer. Assumes total cost of screening 10 patients is ~$15,000, 20% of cases were positive, and in those, the two patients each received intervention consisting of mastectomy and salpingoophorectomy at total cost of ~$16,000. Savings are based on estimates of lifetime costs of breast cancer and ovarian cancer drawn up by various agencies—eg, California Breast Cancer Research Program. Figures were then applied to payers with different rates of member turnover to calculate savings. Approximate turnover rates are based on expert interviews as well as analysis of internal data from commercial payers.

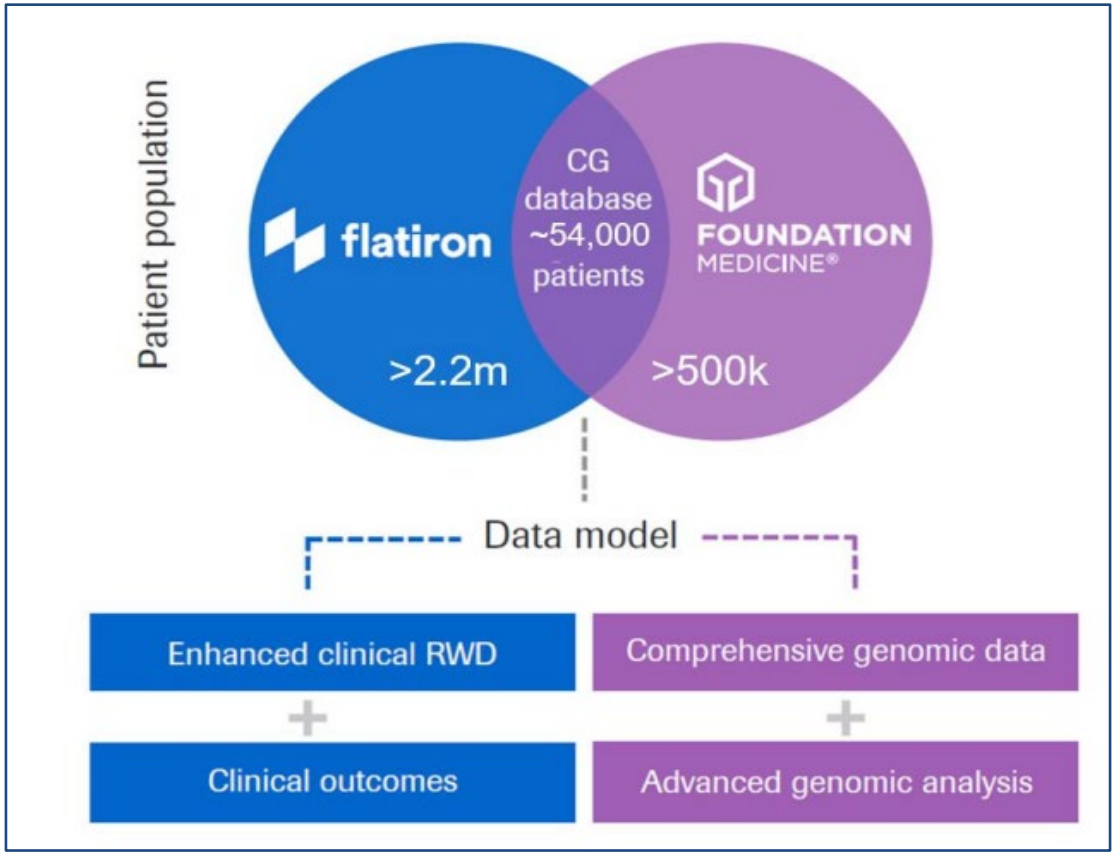
[1]Administrative services only.
[2]Health maintenance organization.

Source: McKinsey

Partnerships Opening New Avenues

Clinico-Genomic Databases

- Enhance understanding of genomics of rapidly progressive diseases.
- Provide history cohorts for gene defined populations.
- Improve prognostic classifiers (helps to target the right population).
- Example: CGBD analysis suggested higher incidence of brain metastases in patients with a certain mutation; informed the decision to pursue a brain-penetrant molecule.



Source: Company presentation

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