

The Power of Convergence in the Fight Against Cancer

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Potential Conflict of Interest

Alnylam Pharmaceuticals— co-Founder,
Stockholder, Member of Board of Directors,
and Chair of Scientific Advisory Board

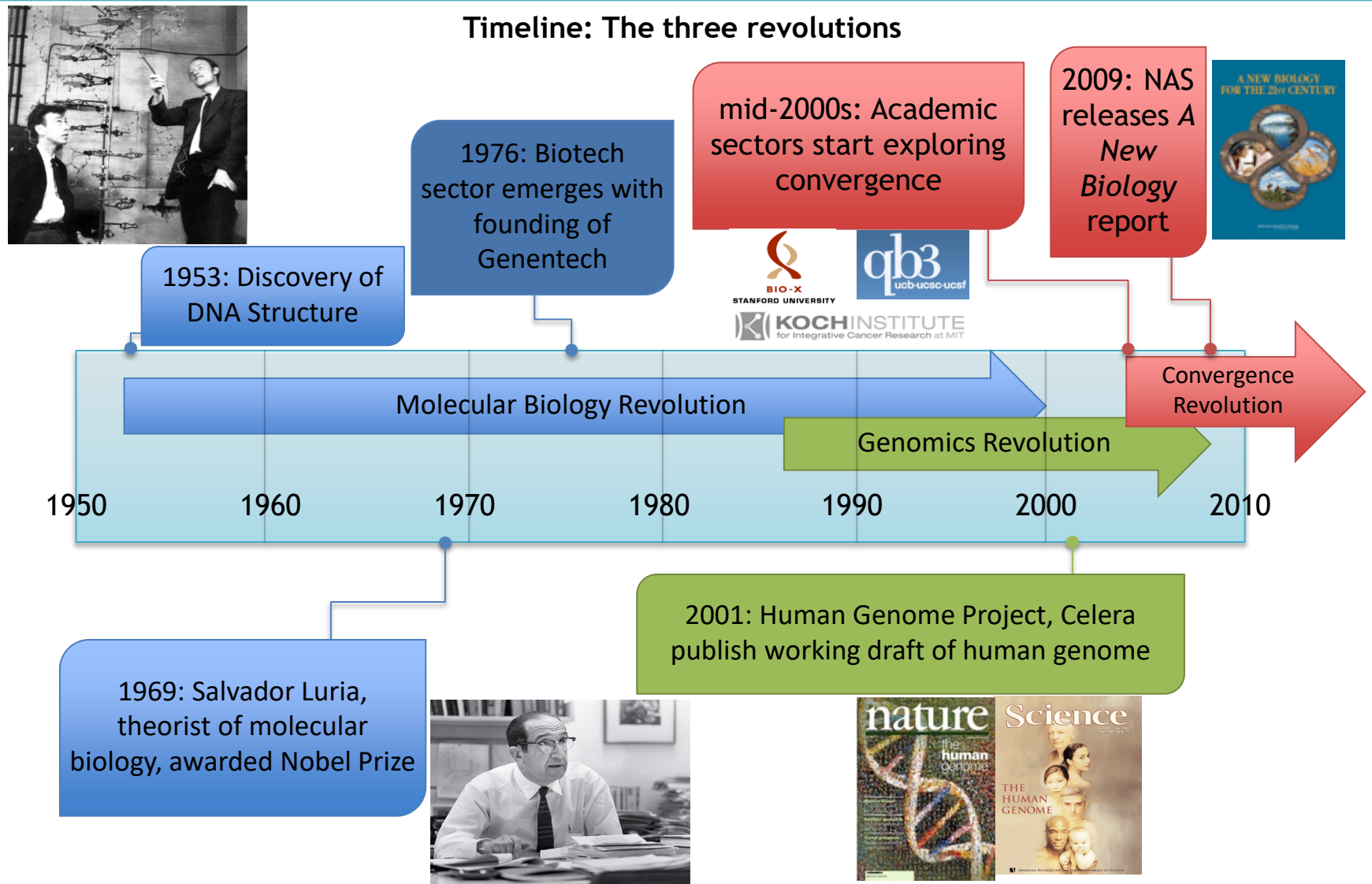
Dewpoint, Skyhawk— Advisor

Polaris, Longwood— Advisor and Investor

Danaher— Consultant

Convergence timeline

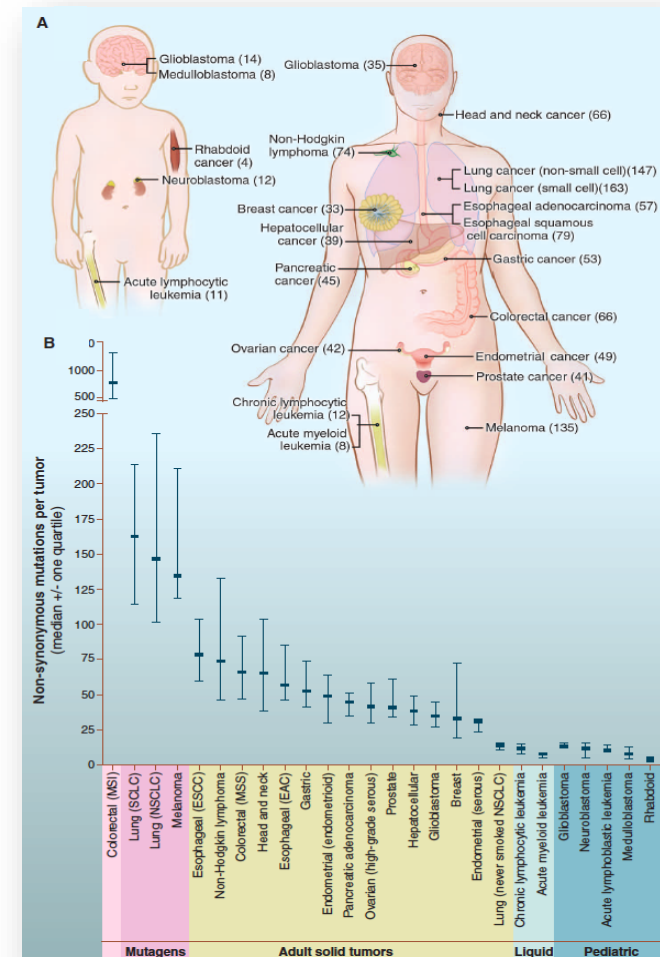
Timeline: The three revolutions



50 Years of MIT Cancer Research



Human genome 2003 - genetic diseases and cancer



COSMIC, Sanger-UK (2013)
Vogelstein and colleagues (*Science*, 2013)

Convergence - Precision treatment of cancer: AI transformation

- AlphaFold protein structure
- Docking drugs on protein
- Identification of new targets - pathways, network, structures

ALK story: progress and challenges

- Anaplastic lymphoma kinase ALK-positive cancer was discovered in 2007.
- ALK-positive cancer is the result of rearrangements of the EML4 and ALK genes creating a fusion oncogene called EML4-ALK
- 20 years ago, stage 4 ALK-positive non-small cell lung cancer had a 5-year survival rate of 2%, it is now about 50% when treated correctly.
- Patients with more advanced stages relapse sooner through resistance to targeted treatment.

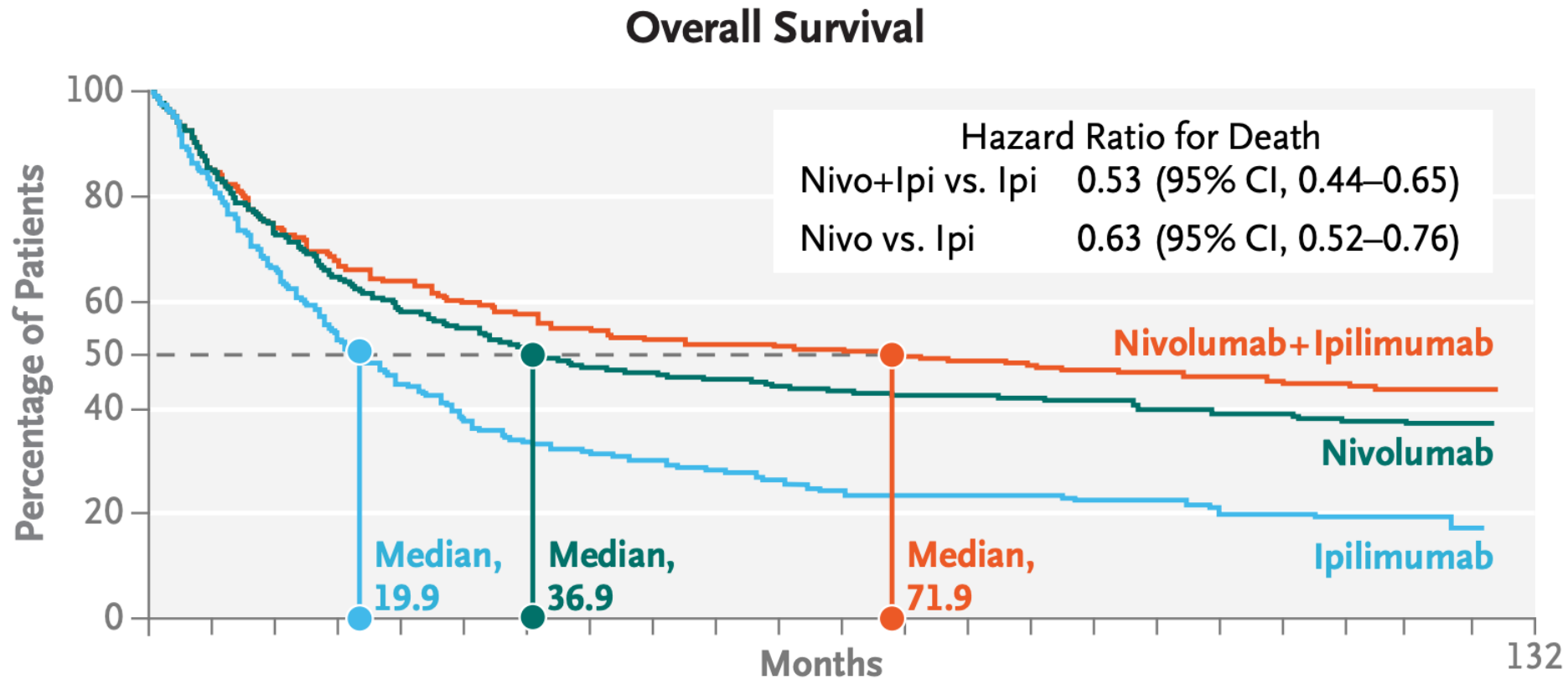
Cancer Gene Census- Sanger COSMIC

- 578 genes - document activity in cancer
- 936 - drugs listed relevant to 237 genes
- 2224 - treatment combinations
- 6244 - total clinical trials

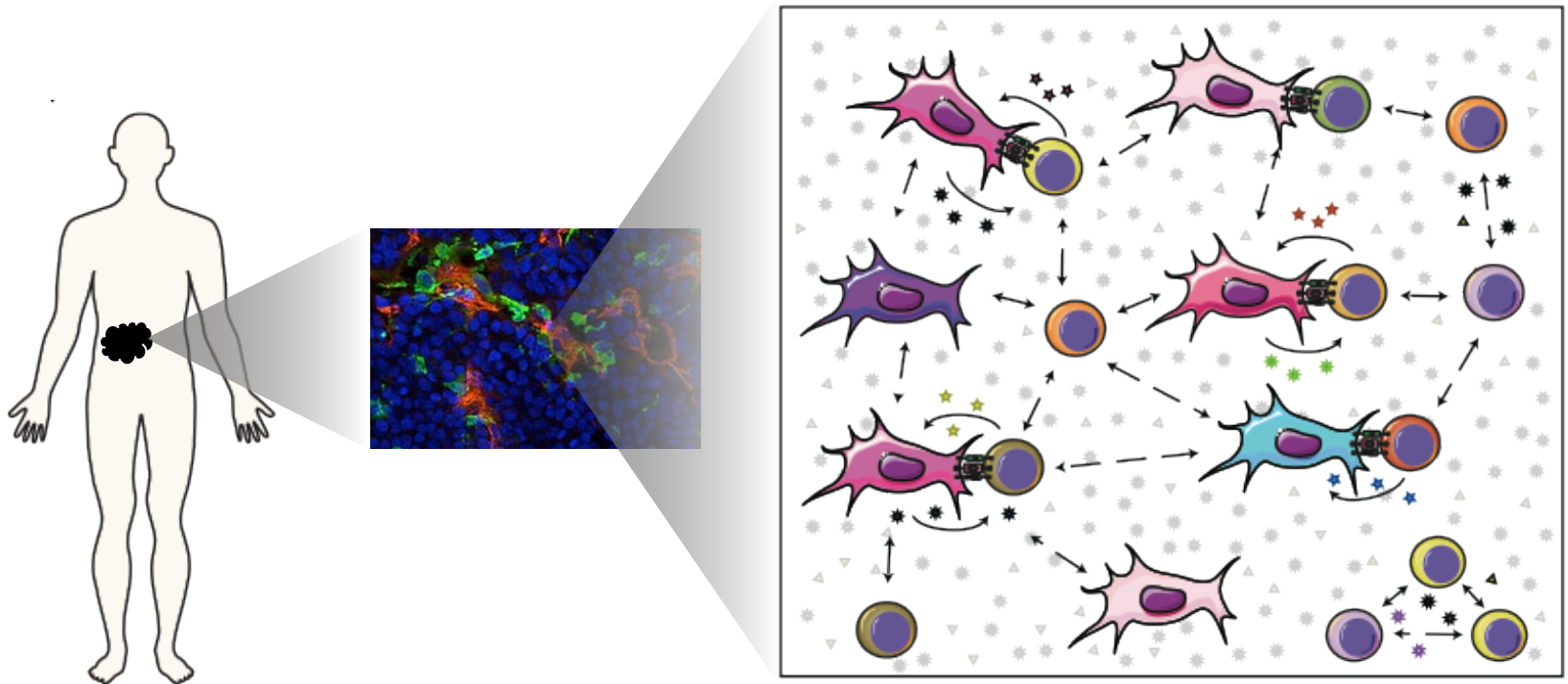
Convergence - Immunological treatment of cancer

- Identification of specific antigens and immune cell recognition
- Network of immune cells and matrix cells interaction
- Signals controlling immune cell response

Long-term survival of Melanoma patients treated with immunotherapy



Tumor: a complex cell circuit



If we know the circuit, we can manipulate it

Combination therapy and CAR-T cells

“adaptive-centric” therapy:

“innate-centric” therapy:

amph-vaccines

(Trp2, gp100, ...)

V

I

Extended half-life IL-2
(IL-2-albumin fusion)

A

anti-tumor antibody

(TA99)

recruit innate
immune effectors

**B16F10
melanoma**

T-cells

NK cells

neutrophils

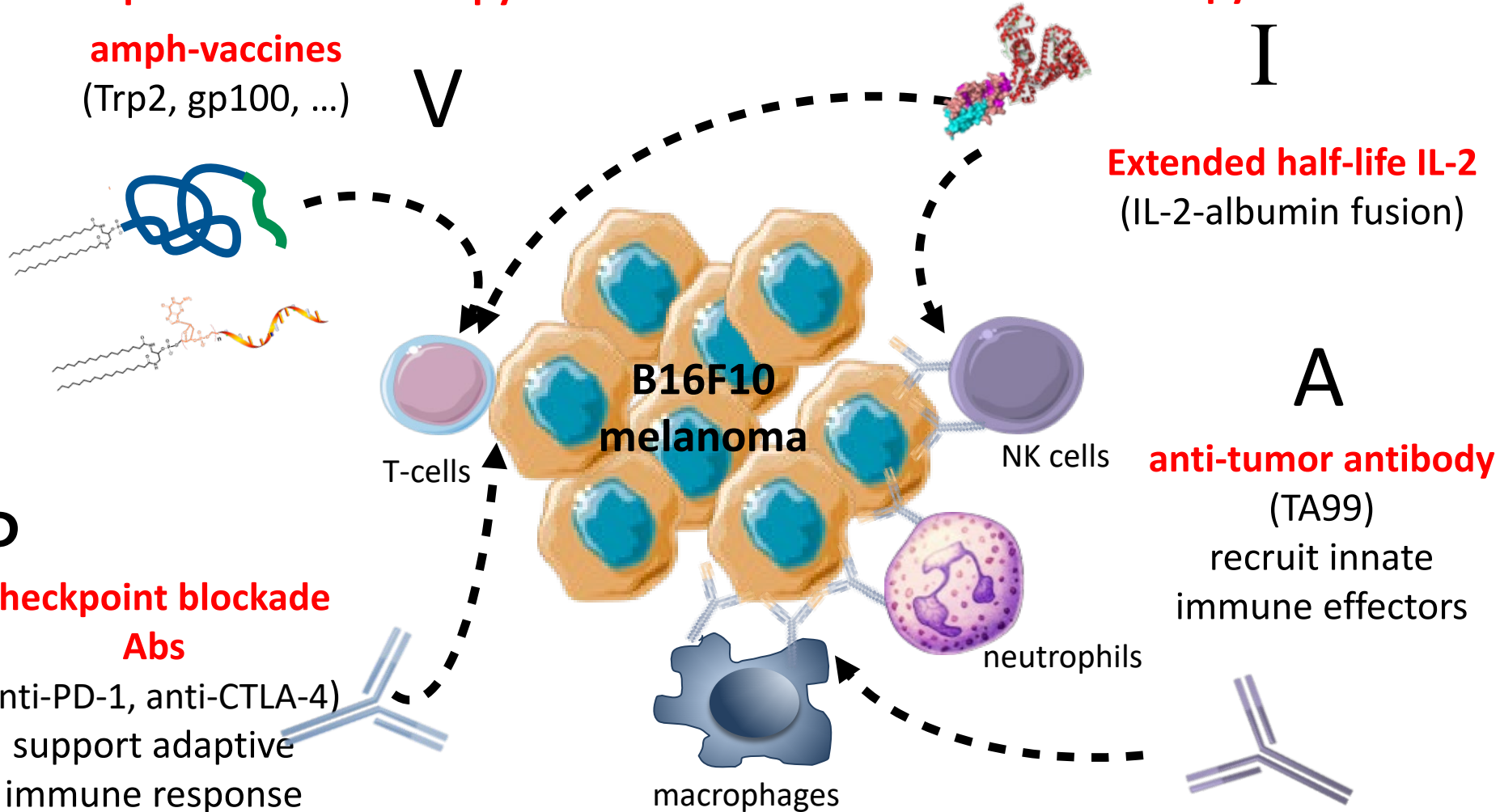
macrophages

P

Checkpoint blockade

Abs

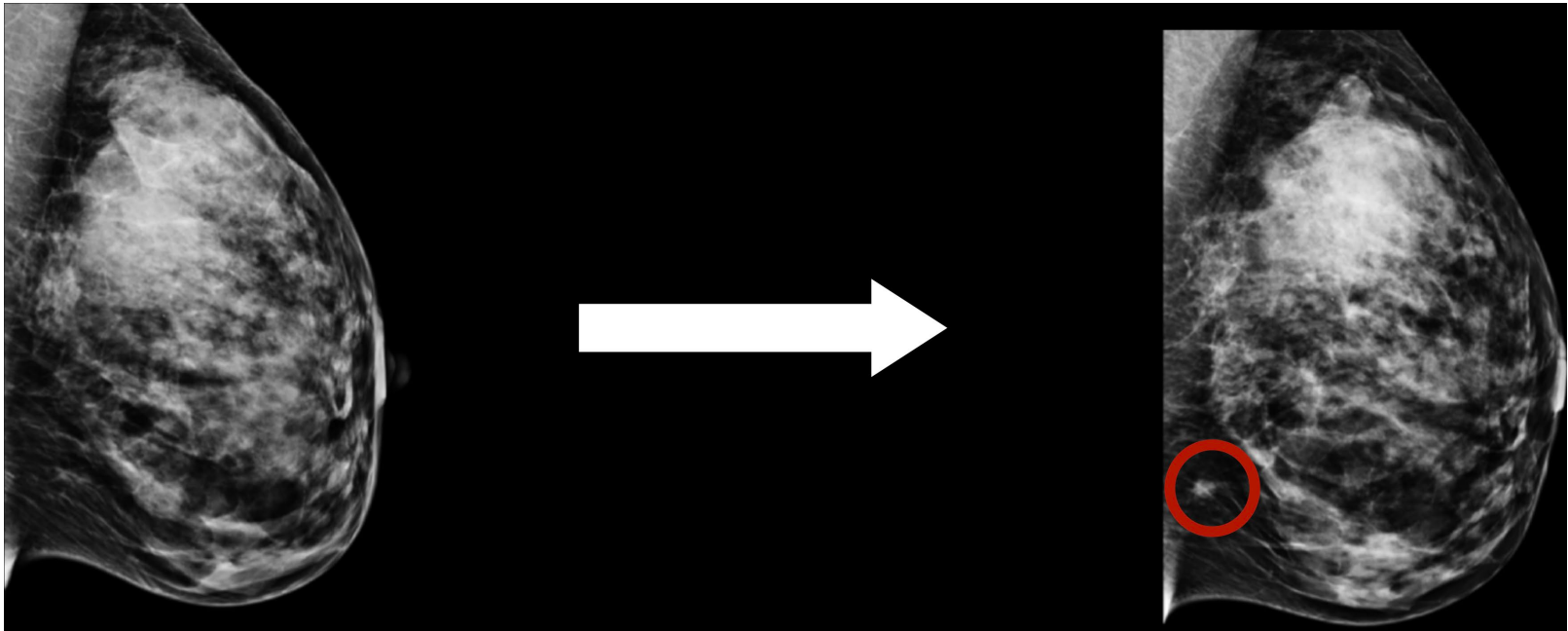
(anti-PD-1, anti-CTLA-4)
support adaptive
immune response



Convergence - Interception of cancer

- Prediction of future cancer risk
- Accurate and effective early detection of cancer
- Design education and evaluation supporting implementation including access

Prediction future cancer risk



3-year progression
Regina Barzilay

Validation in diverse population

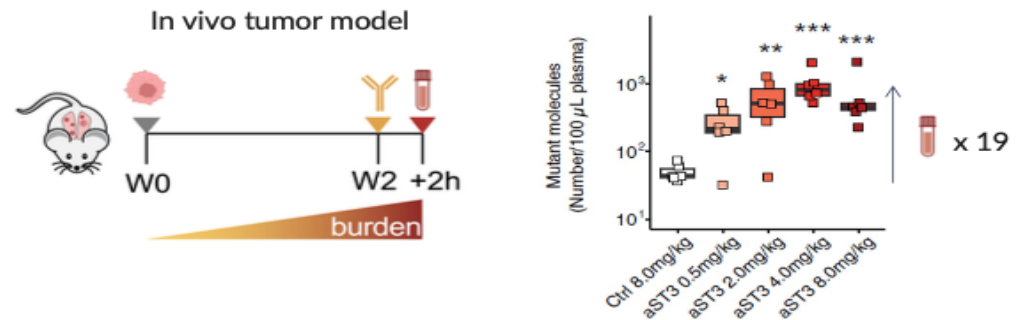


Detection of tumor DNA in model 20x

AM-01 blocks nuclease degradation & cellular uptake of ctDNA



AM-01 (aST3) significantly increases ctDNA recovery



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RESEARCH ARTICLE | LIQUID BIOPSY

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Priming agents transiently reduce the clearance of cell-free DNA to improve liquid biopsies

CARMEN MARTIN-ALONSO, SHERVIN TABRIZI, KAN XIONG, TIMOTHY BLEWETT, SAINETRA SRIDHAR, ANDJELA CRNJAC, SAHIL PATEL, ZHENYI AN, AHMET BEKDEMIR, AND VIKTOR A. ADALSTEINSSON +11 authors Authors info & Affiliations

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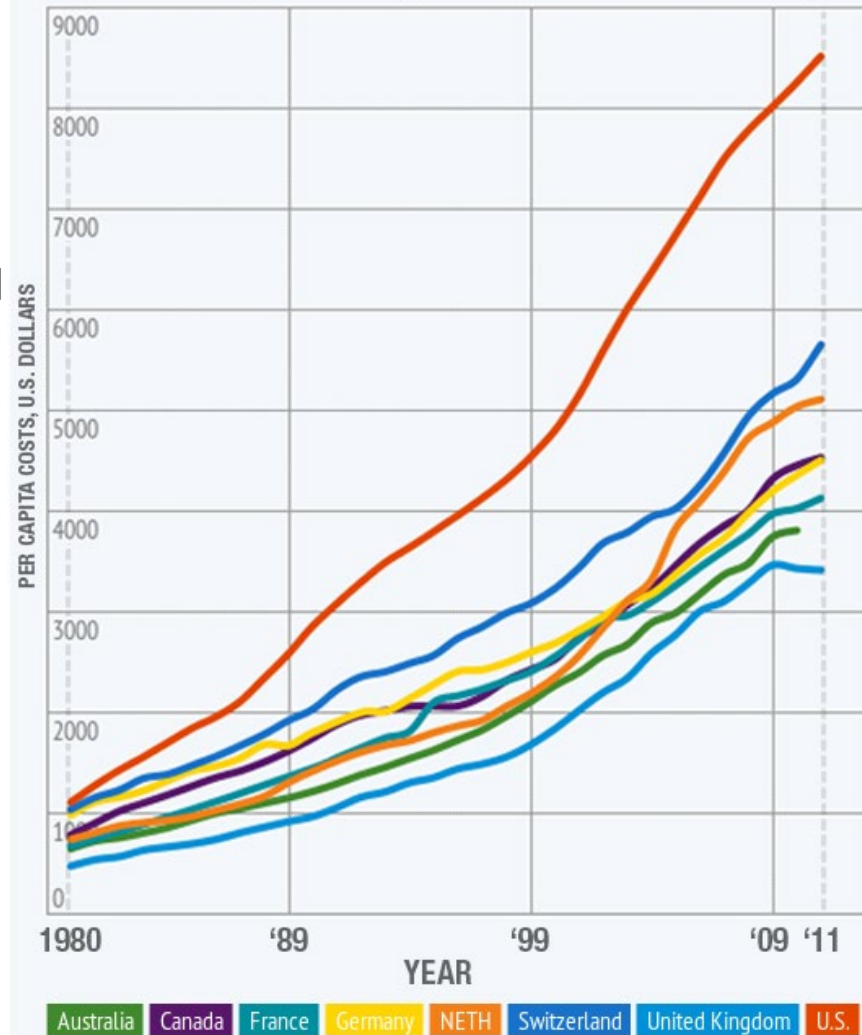
Sangeeta N. Bhatia

Health care costs in the United States

The cost of healthcare will restrict introduction of new innovations unless the system becomes more cost efficient. This will require incorporation of new technology, science and systems from bench to patient to payment.

HEALTH CARE COSTS: WE'RE NUMBER ONE!

Not only does the U.S. have the highest per-capita health costs in the world, but they've been going up faster than in other rich countries for the past three decades - yet we haven't gotten more or better care for our money.

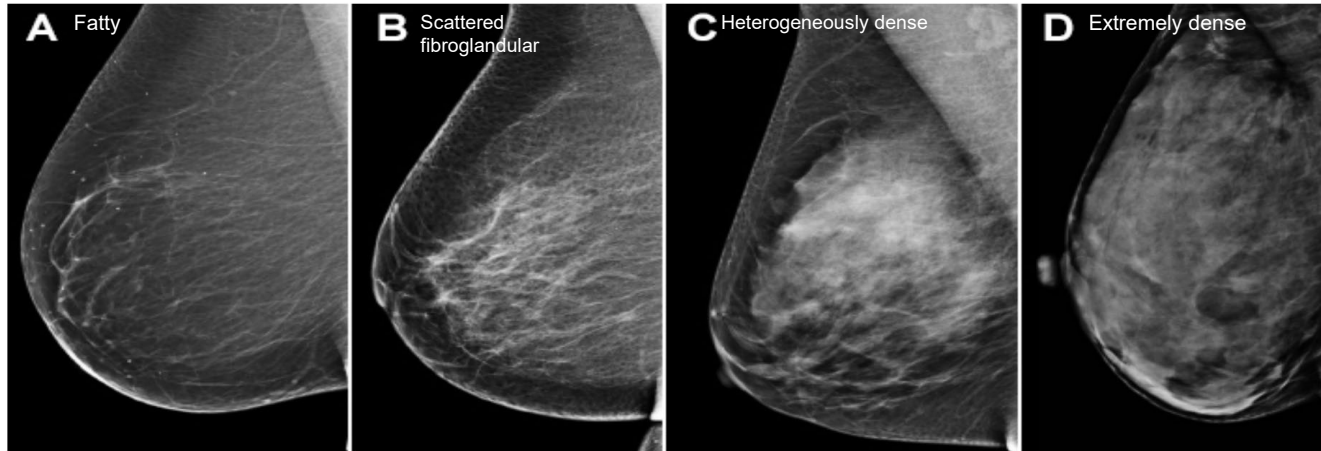


Source: The Commonwealth Fund

Interception of Cancer

1. Value-based evaluation of innovations in healthcare - patient benefit including well-being, productivity and cost.
2. Access to healthcare delivery - diagnosis, consulting and support by informed staff
3. Staff by team of primary care physicians, physician assistants, and nurse practitioners
4. Teams supported by IT - communicated and discussed with healthcare providers

Improving early detection of breast cancer



New federal law requires mammography providers to send breast density notifications

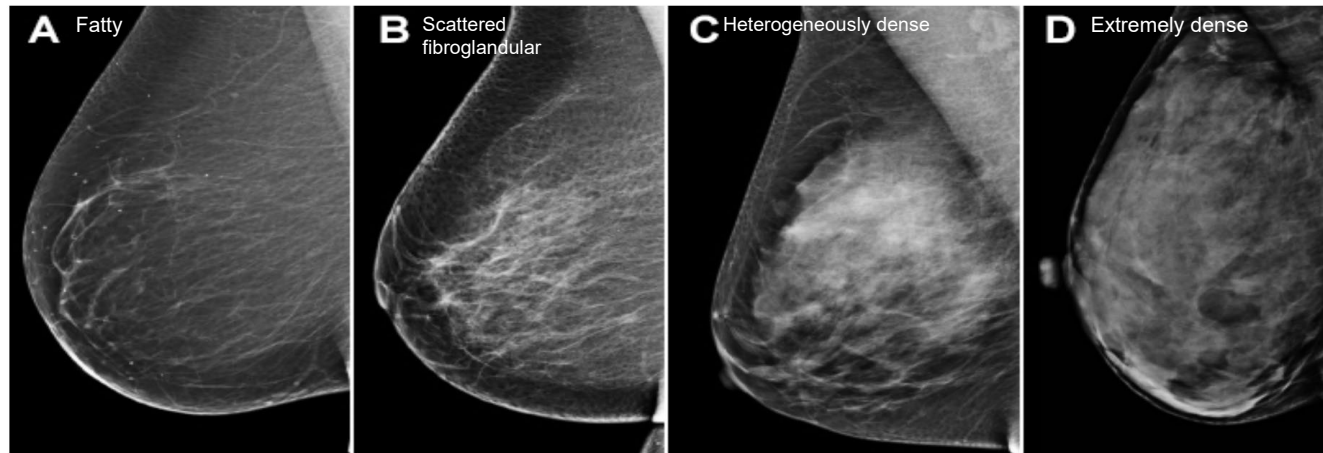
Michael Walter | February 19, 2019 | *Policy*



When President Donald Trump signed a federal funding bill into law on Feb. 15, it included text that said that all mammography providers must include updated information about breast density in reports sent to both patients and their physicians.

Regina Barzilay (KI)

Improving early detection of breast cancer



Forty percent of women are classified as “dense” breast for future monitoring while increase risk for this large group is probably not statistically enhanced.

Regina Barzilay (KI)

Thank you for the
opportunity to present
this lecture.

- Phil Sharp