Genomics in the Cancer Clinic

Richard C. Frank, MD

Director of Cancer Research

Nuvance Health

(Danbury, Norwalk, New-Milford Hospitals)

January 23, 2020

Genetics vs. Genomics-1

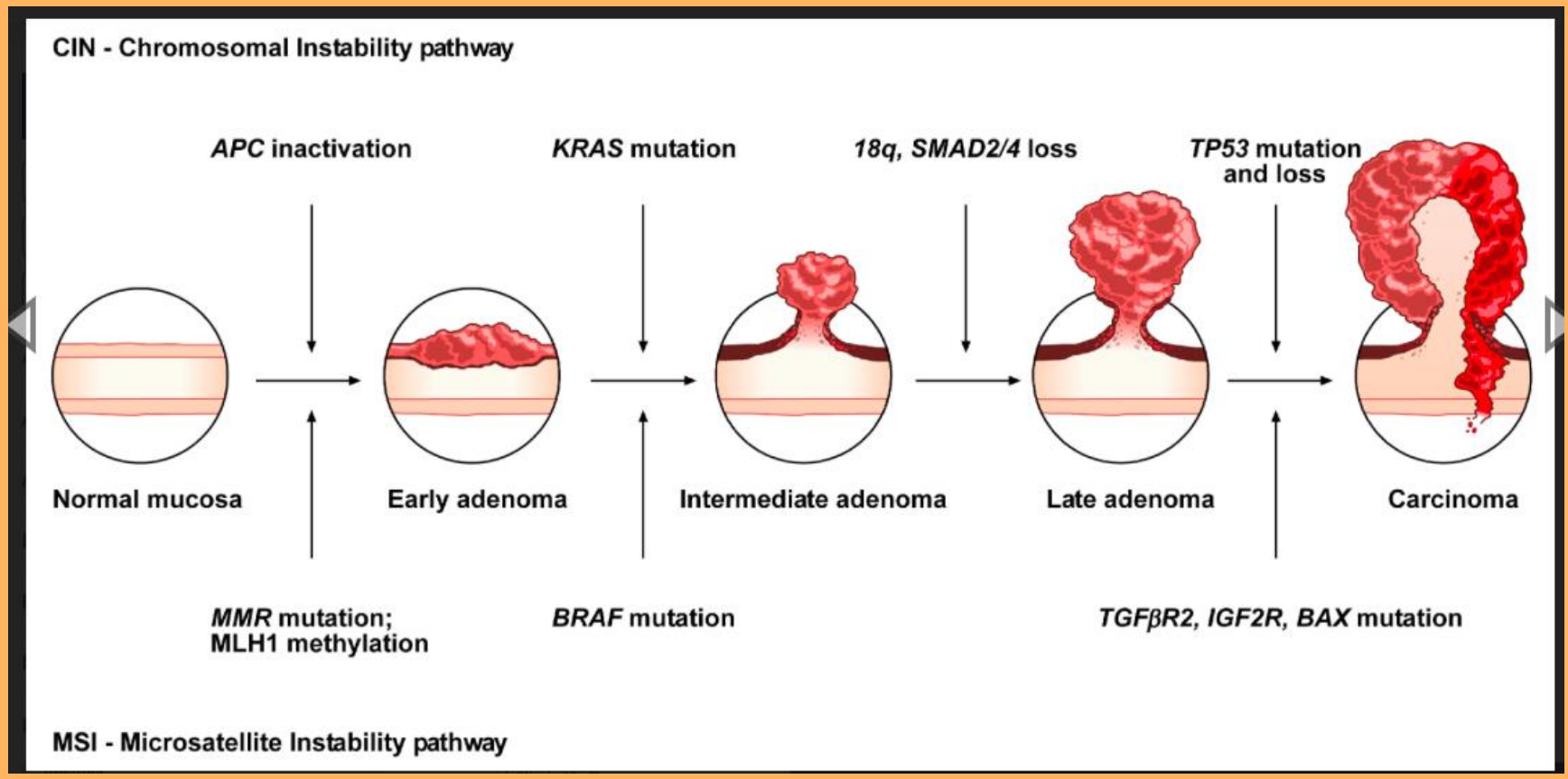
- **Oncologists utilize both GENETIC AND GENOMIC information to treat patients**
- **GENETICS: The DNA a person is born with (HEREDITY)**
- **Inherited DNA mutations predispose to cancer (BRCA1/2)**
- **Detected from the blood or saliva**
- **May or may not be known before a cancer diagnosis**
- **Oncologists follow national guidelines on testing e.g. NCCN (National Comprehensive Cancer Network)**
- **Results may affect how the cancer is treated**

Genetics vs. Genomics-2

- **GENOMICS: The DNA profile of a cancer:**
- **"How does the cancer DNA differ from normal?"**
- **Mutations acquired as a normal cell becomes a cancer cell**
- **Present only in the cancer, not the germline DNA**
- **Detected from a tumor biopsy > bloodstream**
- **Have important implications for the treatment of cancer**
- **Oncologists order "genomic profiling" from companies or their institution**

CANCER DEVELOPS BY ACCUMULATING

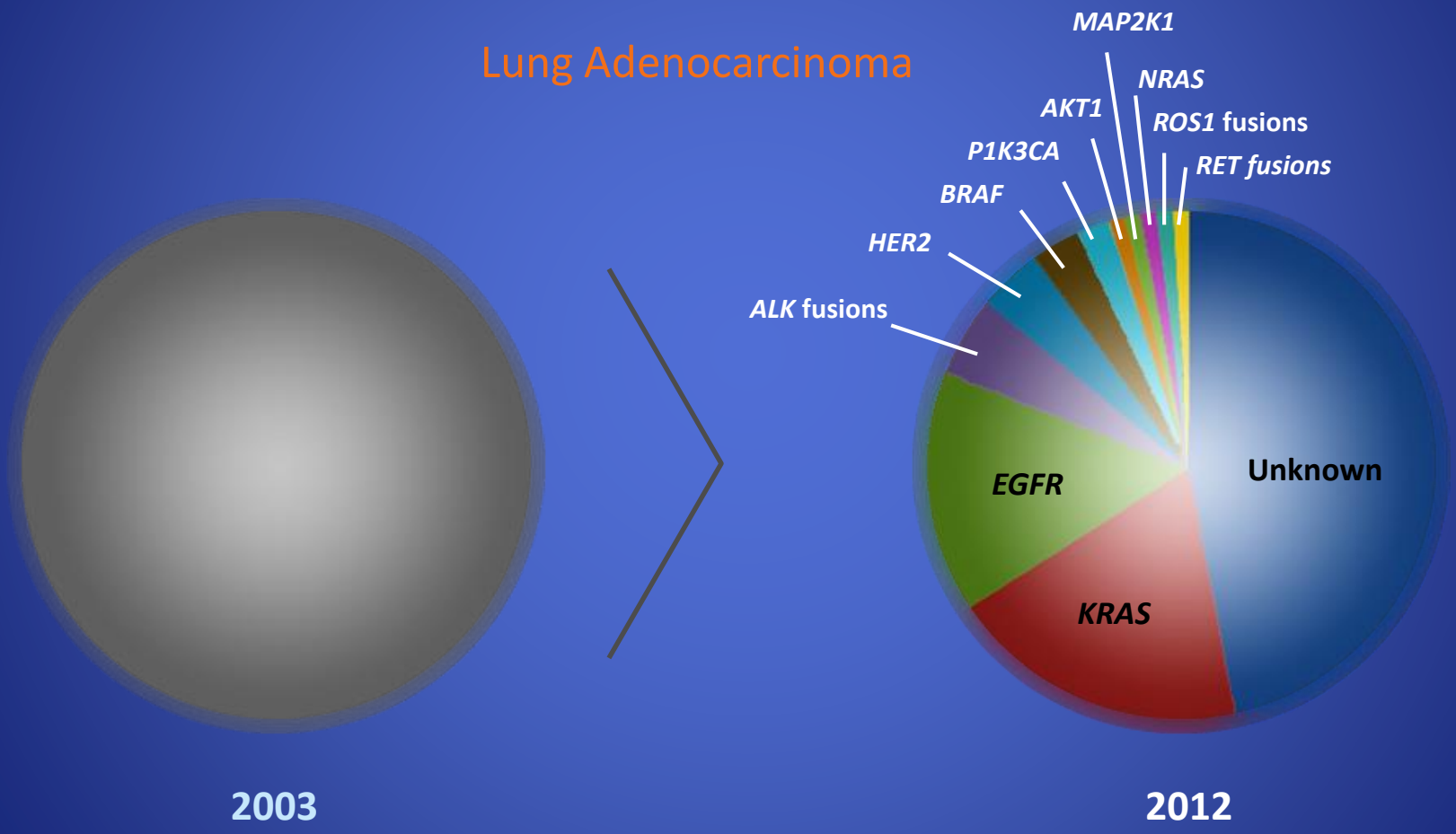
DNA CHANGES: Captured by Genomic Profiling



THERAPEUTIC OPTIONS FOR THE PATIENT WITH ADVANCED CANCER

- **CHEMOTHERAPY** - ***TARGET RAPIDLY DIVIDING CELLS***
- **IMMUNOTHERAPY** - ***PATIENT'S IMMUNE CELLS ATTACK CANCER***
- **TARGETED THERAPY** - ***BIND "DRIVER MUTATIONS" IN A CANCER CELL TO HALT GROWTH AND SPREAD***
- ***DRIVERS FOUND BY GENOMIC PROFILING***
- **COMBINATIONS OF THE ABOVE**

GENOMIC PROFILING CLASSIFIES CANCER BY DRIVER MUTATIONS



Modified from Pao and Hutchinson, Nature Medicine. 2012; 18:349-351.

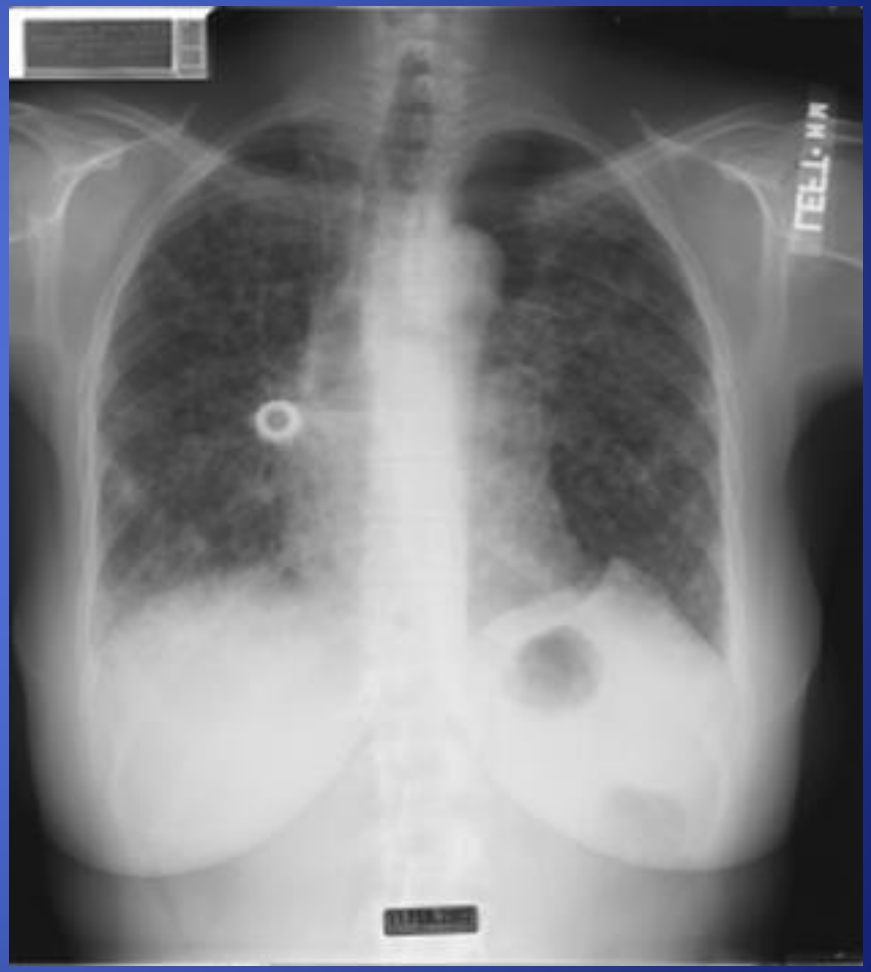
Genomic Profiling Identifies Gene Targets To Personalize Therapy

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)
EGFR L858R	Erlotinib Gefitinib Afatinib	Cetuximab Lapatinib Panitumumab

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)
ALK EML4-ALK fusion	Crizotinib	None
TSC2 splice site 3285-1 G>A	None	Everolimus Temsirolimus

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)
BRAF V600E	None	Vemurafenib Trametnib Dabrafenib

Lung Ca Patient Treated With an EGFR Inhibitor

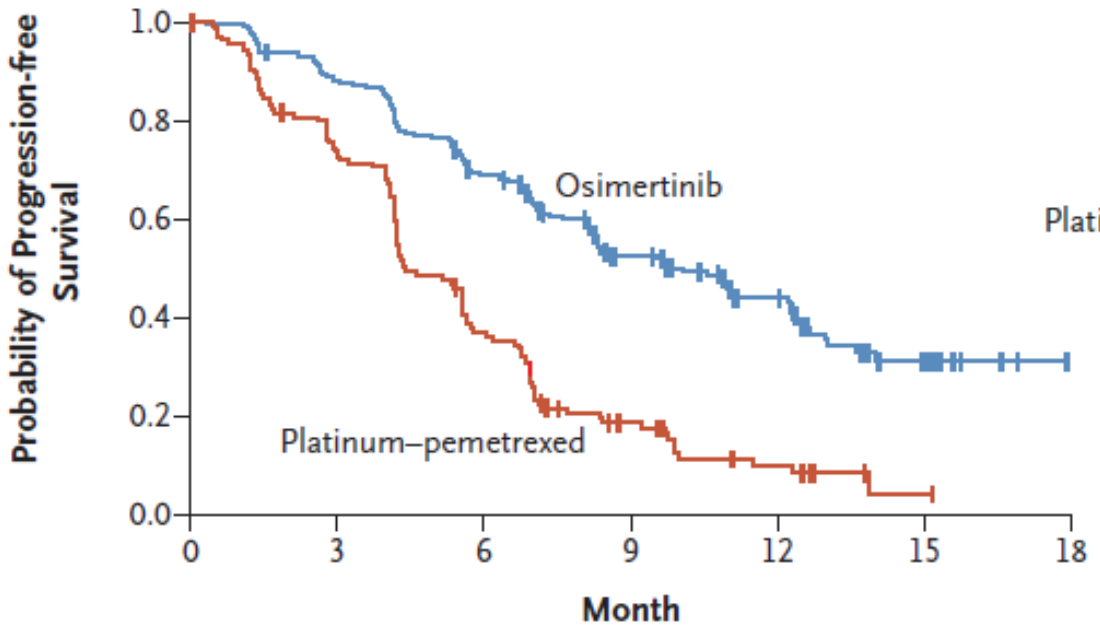


6 FEB 2002

13 FEB 2002

TARGETED THERAPY VS. CHEMOTHERAPY IN LUNG CANCER

A Patients in Intention-to-Treat Population



No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

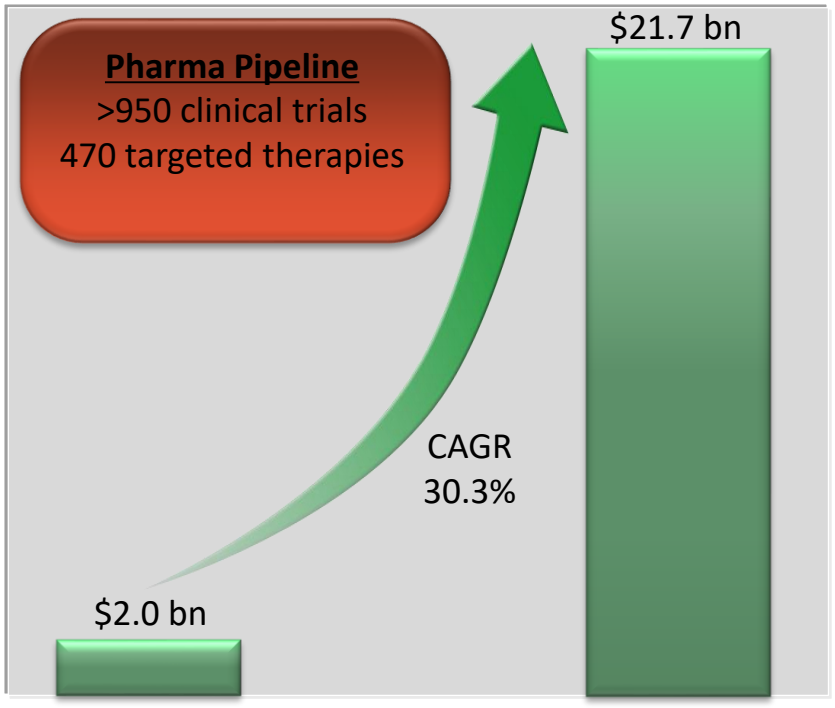
	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

MOK TS, ET AL. NEJM 2016

Targeted Cancer Therapies are Exploding

EGFR AURKA KRAS CDK4
SRC DDR2 CCND1
ERBB3 DNMT3A HGFR RET
GNAQ BRAF FBXW7
CDK6 BRCA1 NOTCH1 STK11
MET KDR
TSC1 TNF VEGF/VEGFR MAP2K1
IGF/IGFR family HER2 PTEN
PIK3CA FLT3 CDKN2A FGFR1
TSC2 AKT1 PIK3CA
IGF1R NF1 RAF1 GATA3



Progress in molecular biology continues to underpin explosive growth in the number of targets, targeted therapeutics, and their utilization

Source: Tufts Center for the Study of Drug Development

[1] *Worldwide dollars spent on targeted oncology drugs*

Potential State Role

Genetic Testing

-Mandate that insurers cover the cost for testing of any individuals who meet national testing guidelines for hereditary cancers

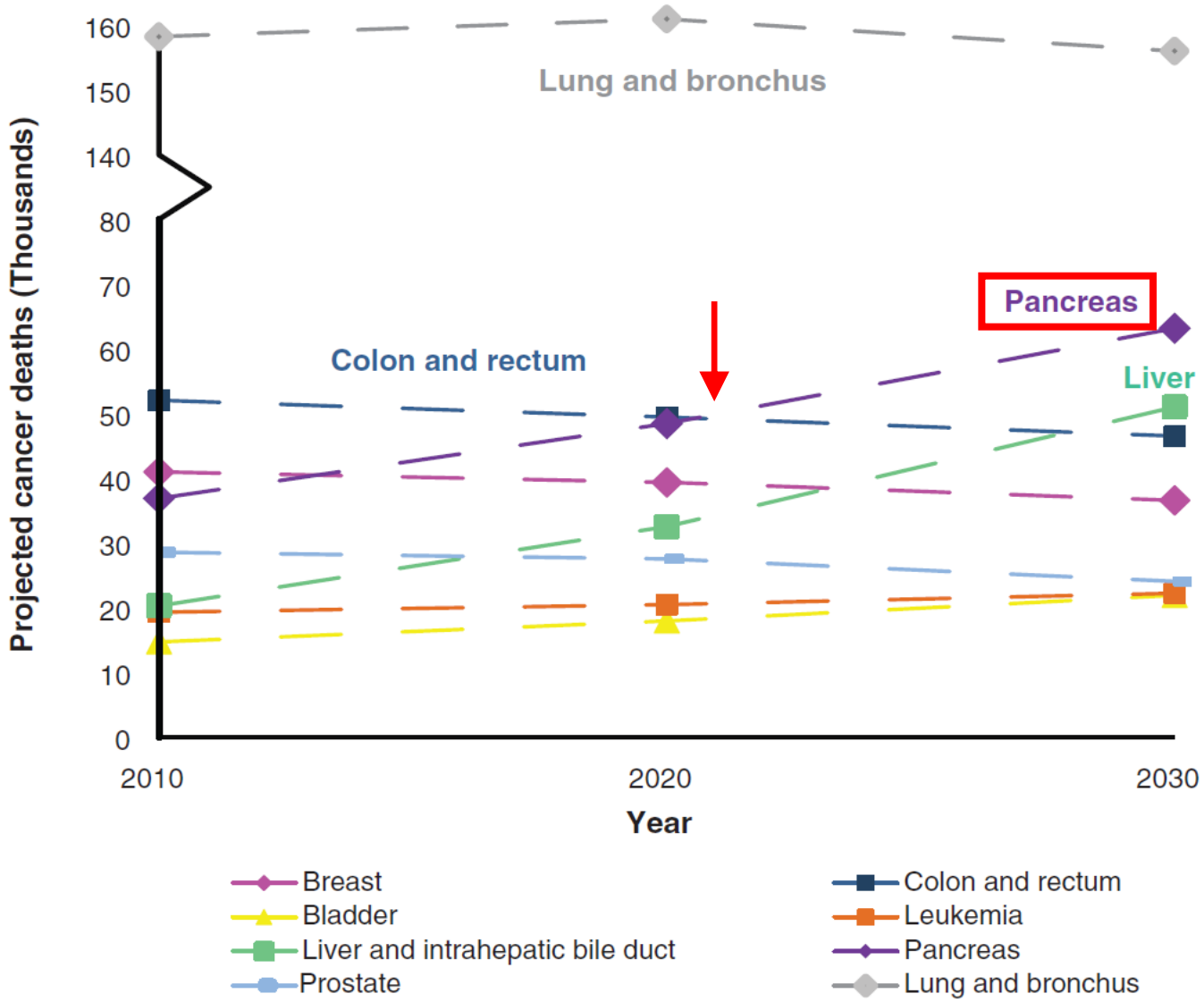
Genomic Testing

-Mandate that insurers cover the cost of at least one "Genomic Profile" for each patient with advanced, incurable cancer.

PANCREATIC CANCER LACKS THERAPEUTIC OPTIONS

- **CHEMOTHERAPY**: ***TARGET RAPIDLY DIVIDING CELLS***
- ***IMMUNOTHERAPY - PATIENT'S IMMUNE CELLS ATTACK CANCER***
- ***TARGETED THERAPY - BIND "DRIVER MUTATIONS" IN A CANCER CELL TO HALT GROWTH AND SPREAD, DRIVERS FOUND BY GENOMIC PROFILING***
- ***COMBINATIONS OF THE ABOVE***

Projected Annual US Cancer Deaths



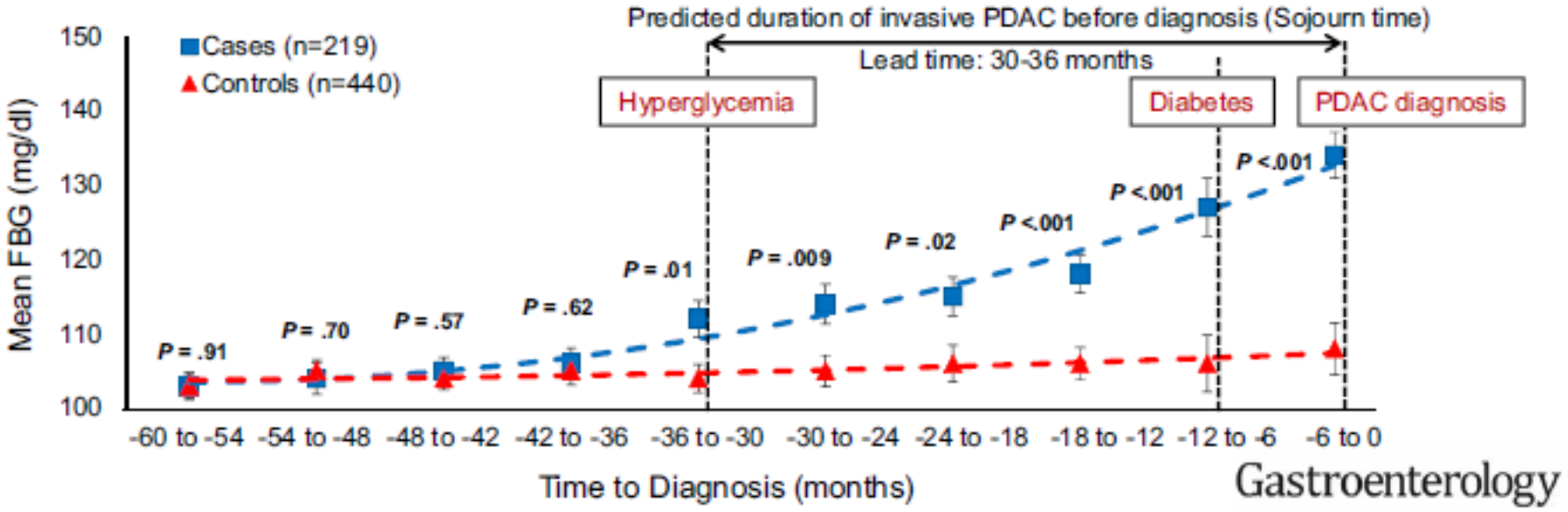
Rahib et al., Cancer Res 2014

Pancreatic Cancer

High-Risk Groups Under Study:

- **Hereditary Genetic/Familial: 10%**
- **Sporadic (no known cause): 90%**
  - **High-Risk: Age 50+ with new-onset diabetes mellitus (12 months)**

Fasting Blood Glucose Levels Provide Estimate of Duration and Progression of Pancreatic Cancer before Diagnosis



Early Detection Protocol in New-Onset Diabetes >50 yo