National Cancer Institute

Molecular Characterization of Screen-Detected Lesions

NCI Board of Scientific Advisors
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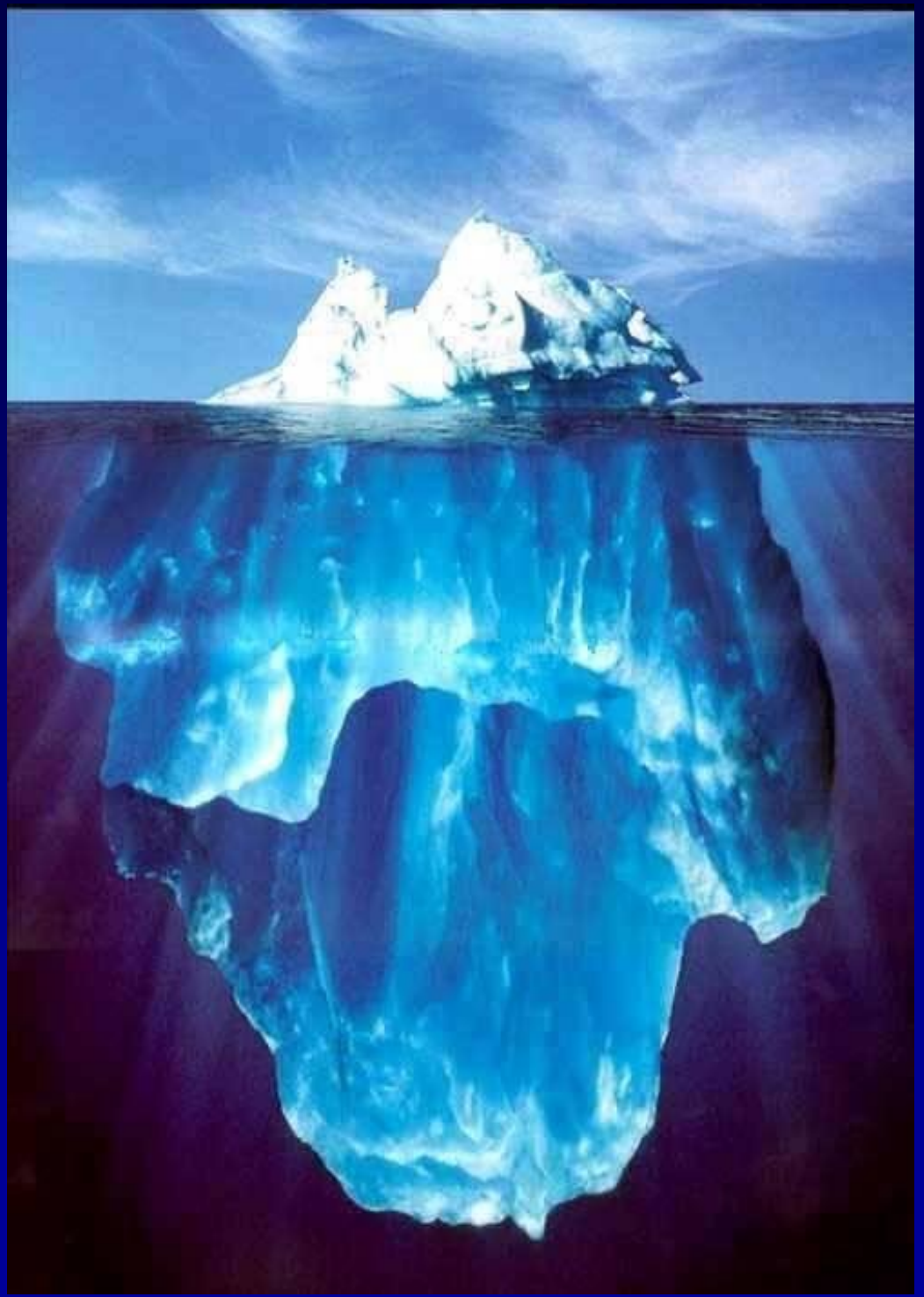
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health



Current Challenges with Screening and Early Detection

- **Phenotypically distinguishing between lesions that are likely to progress and those that are indolent and require no immediate treatment**
- **Predicting whether lesions that are detected by sensitive screening tests are indolent (hence, not requiring immediate treatment) or progressive and potentially life-threatening**

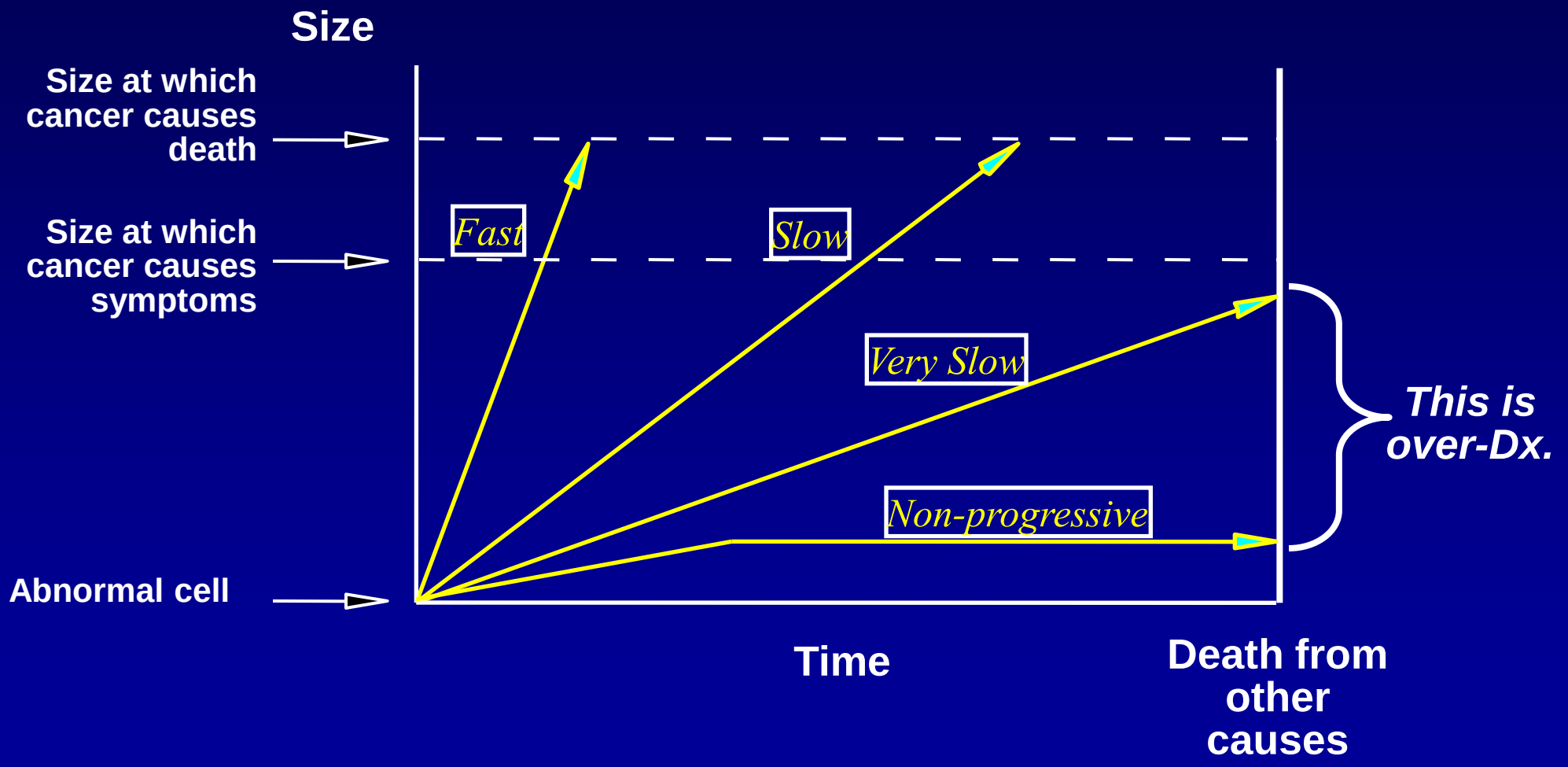
Increase in cancer incidence (particularly early stages), but no change in mortality indicates overdiagnosis

Requirements for Overdiagnosis

- Existence of a silent disease reservoir
- Activities leading to its detection (particularly screening)

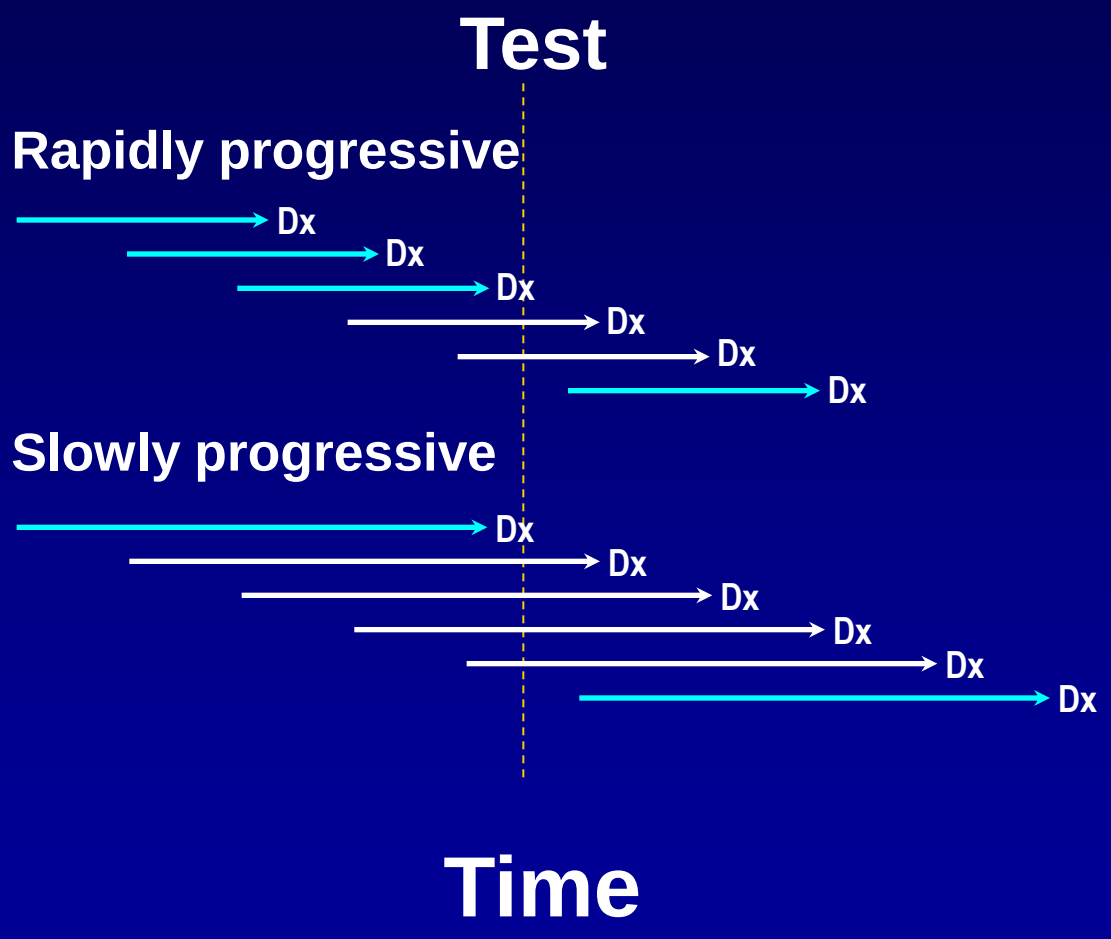
From G. Welch and W. Black, JNCI 2010

The Heterogeneity of Cancer Progression

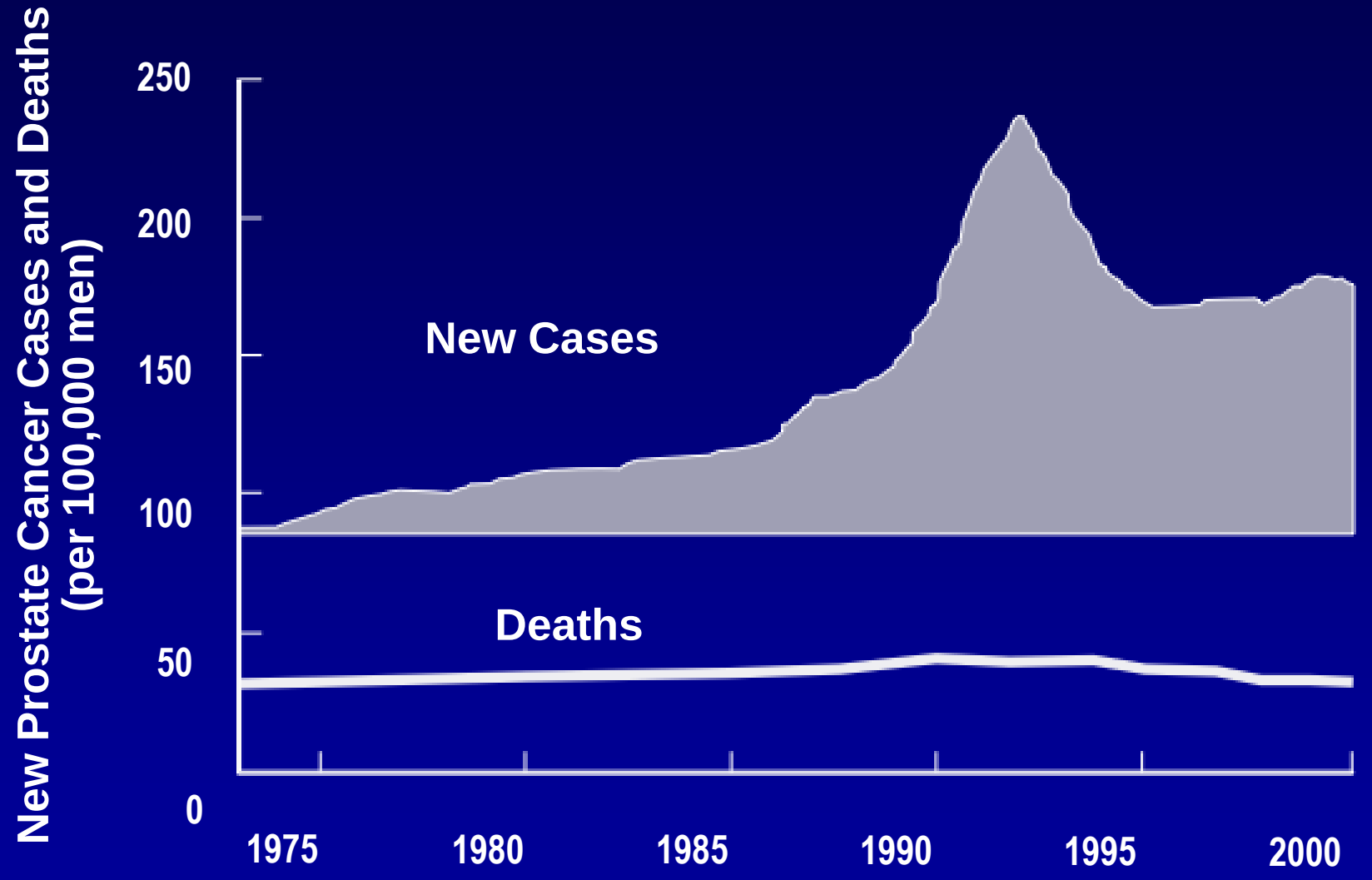


(Courtesy of H. Gilbert Welch, Dartmouth)

Length Biased Sampling



U.S. Prostate Cancer Incidence vs. Mortality Over-Diagnosis



From . Welch, *"Should I Be Tested for Cancer?"*, 2004

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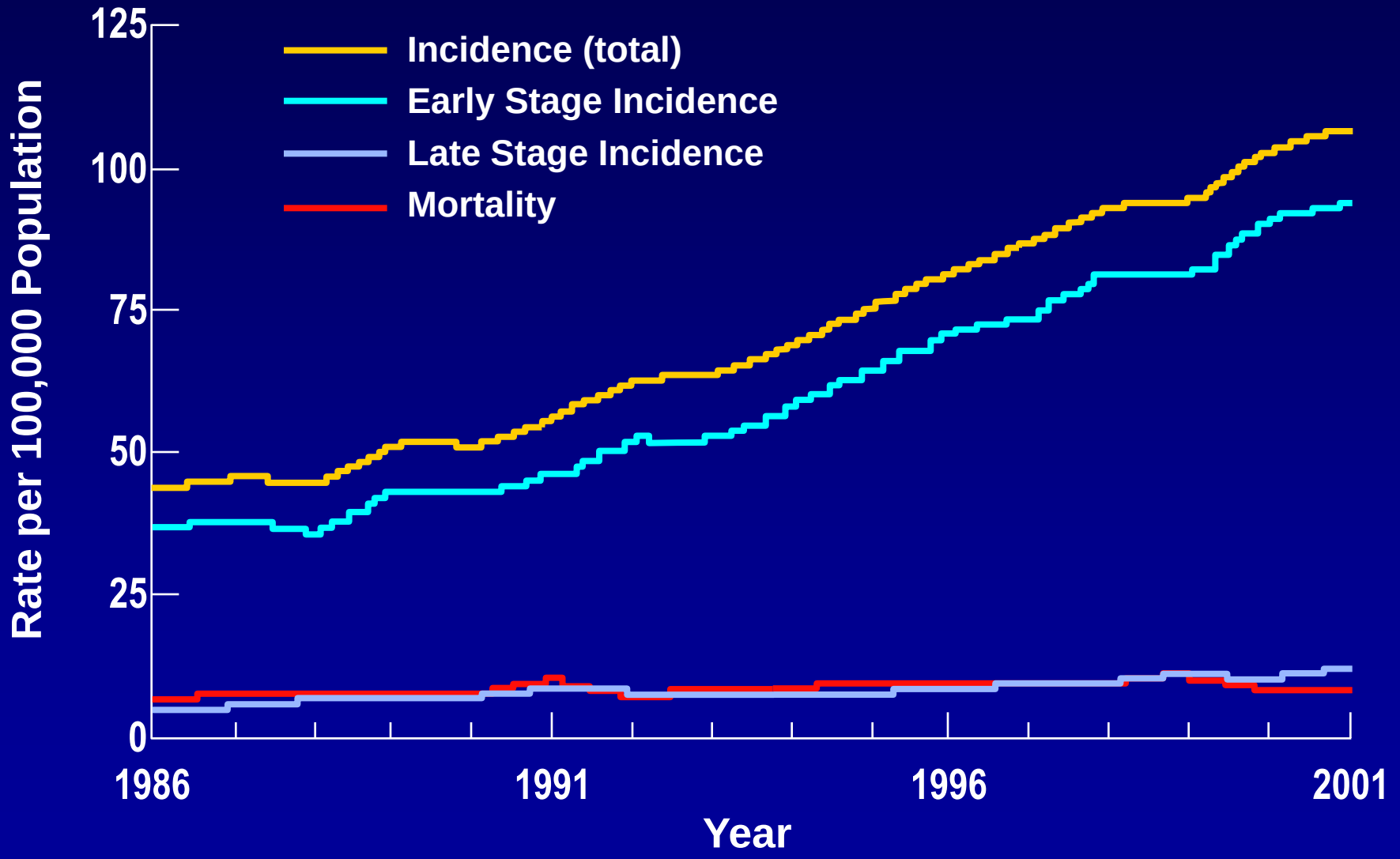
Evidence of Melanoma Overdiagnosis in the Medicare Population



G. Welch, *BMJ*, 2005

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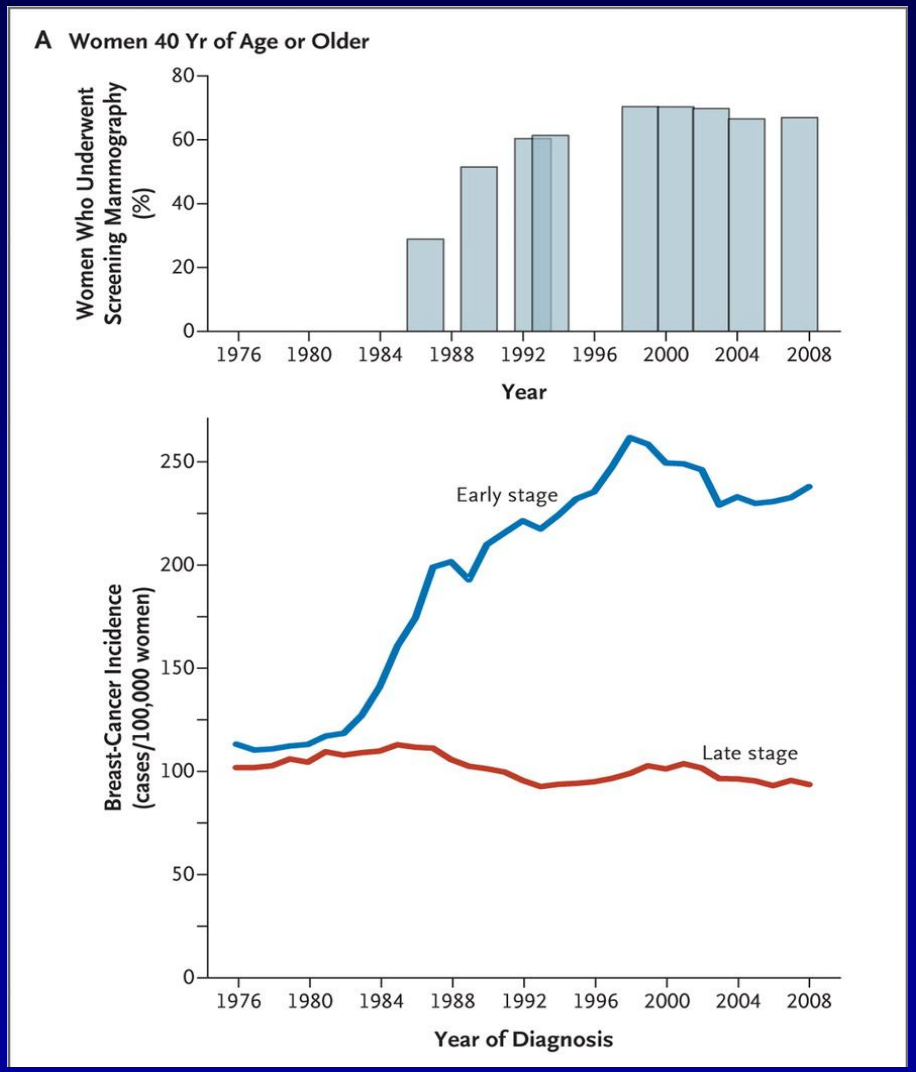
Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the U.S., 1976–2008



The NEW ENGLAND JOURNAL of MEDICINE

Bleyer A, Welch HG. N Engl J Med 2012;367:1998-2005.

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Key Biological Questions

- What molecular/cellular characteristics (genetic, epigenetic, cell physiology, signaling profile, metabolism, microenvironment, and immune reaction) define indolent versus progressor lesions that are detected by screening tests?
- Are there lineage relationships among indolent, interval, and malignant lesions?
- What kind of selective forces shape the evolution of a cancer during its progression to become invasive?
- What role does the tissue microenvironment play in modulating or determining the biological behavior of the screen-detected lesions?

DCP Workshop on Molecularly Defined Natural History of Cancer

- A two-day Think-Tank meeting was held on March 8-9, 2012 in Bethesda, MD to discuss the overdiagnosis issue

- The conclusion: it is critical to determine the molecular and cellular characteristics of both the lesion itself and its microenvironment that predict lesion's behavior.

Microenvironment and Tumor Progression

- Role of microenvironment in tumor progression is being demonstrated.
- Chromosomal instability, microsatellite instability, genome-wide aneupoloidy, loss or gain of whole chromosome or chromosome arms may accelerate progression.
- However, these studies are cross-sectional and do not address the dynamics of evolving lesions, especially in the context of screening.

Constitution of Tumor Microenvironment

Physiological Parameters [glycolytic pathway, hypoxia, ***acidic tumor microenvironment*** (acidic pH), etc.]

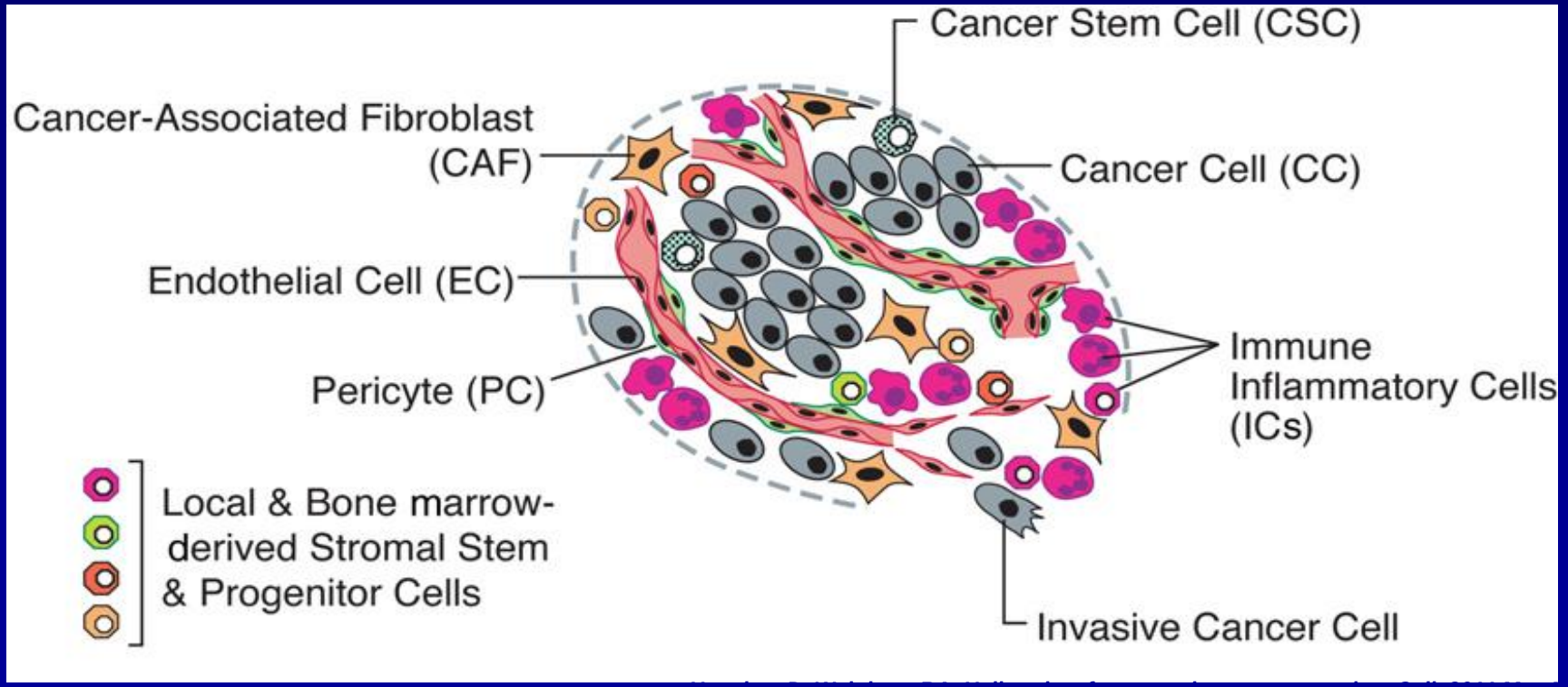
Malignant Cells (cancer cell, cancer stem cell, etc)

Vasculature and Stroma (endothelial progenitor cell, pericyte, bone marrow derived cell, etc)

Immune Response Cells (macrophages, mast cells, tumor-infiltrating lymphocytes, etc)

Extracellular Matrix (fibronectin, collagen, integrins, MMP, tetraspanins, etc)

Secreted Proteins (chemokines, growth factors, etc), including gradients



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Goal of This Initiative

To support a consortium of multidisciplinary research programs that undertake a comprehensive characterization of tumor cell and microenvironment components of screening-detected early lesions and missed interval cancers

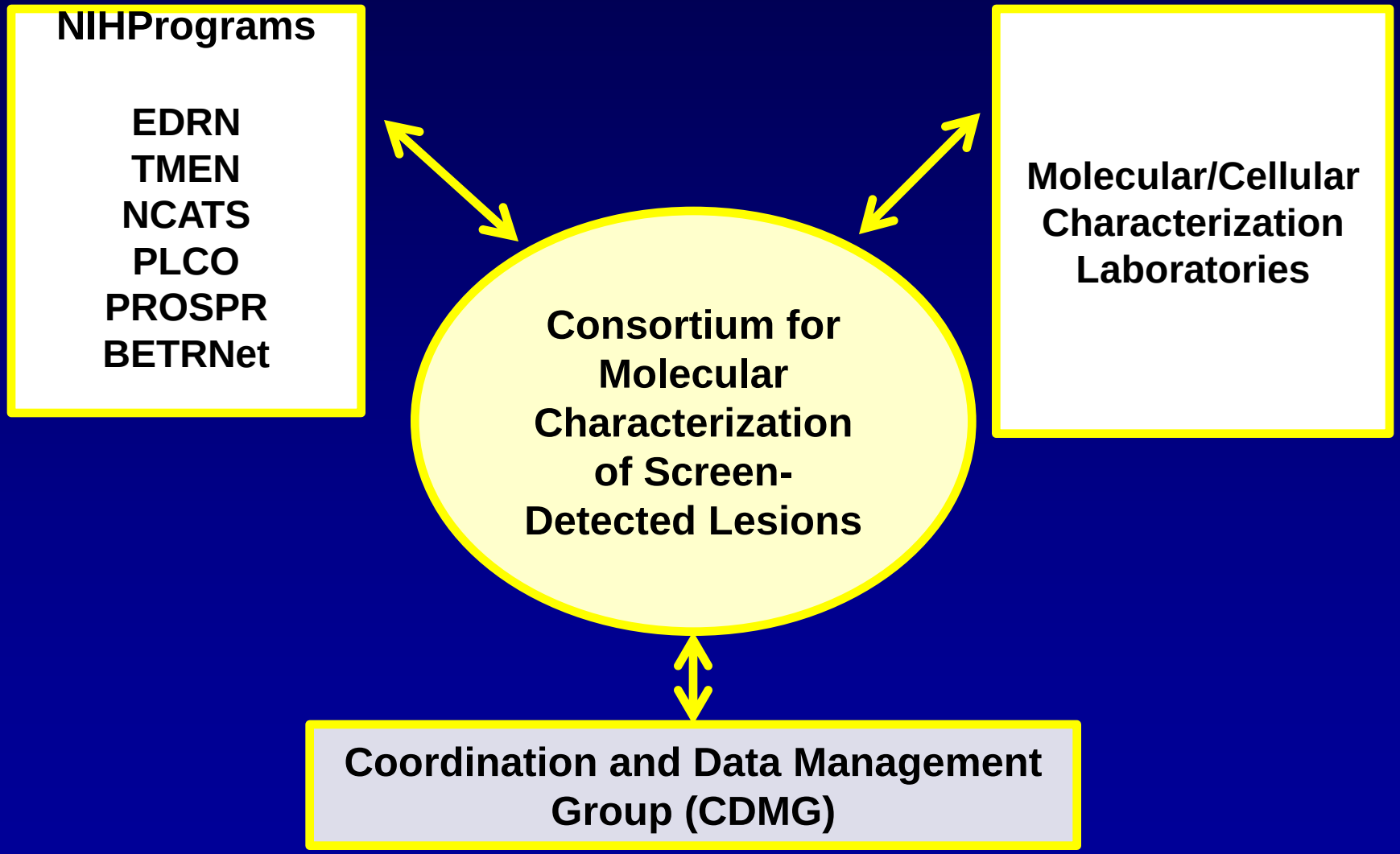
Types of Studies That Can be Undertaken (1)

- Molecular & cellular comparisons to determine whether a subset of screen-detected lesions shares features with aggressive interval cancers (missed by screening) that are likely to have progressing phenotypes
- Single cell analyses of tumor heterogeneity within lesions
- Phenotyping cellular components of lesions, including the tumor cells and surrounding microenvironment

Types of Studies That Can be Undertaken (2)

- Establishing novel mouse models, organoid cultures or patient derived xenografts from screening-detected lesions that maintain the original tumor architecture
- Systems approaches and modeling using experimental data (genomics, epigenomics, proteomics, imaging etc.) to define “disease dynamics”
- Sequential imaging together with molecular approaches to elucidate dynamic changes occurring during progressive disease

Organization Structure of the Consortium



Why Consortium?

- Uniform data collection, protocols, analyses
- Common Data Elements (CDEs) for serial sample collection and clinical annotation
- Reproducibility of data collection including verification and auditing
- Creation of a national resource for valuable samples of screen-detected and of interval cancers for future use
- Central management of IRB, material transfer agreements, and protocols

Portfolio Analysis

- Portfolio analysis yields a few funded grants in progression and microenvironment; however these studies are preliminary and not generalizable because the lack of appropriate annotation, e.g., screen- or symptom-detected lesions
- Keywords: indolent cancer and progression (3)
- Therefore, portfolio analysis fully supports the need for an early diagnosis initiative

Funding Mechanism and Budget

- Cooperative Agreement U01/U24 $5 M/yr of which $1.6 M supported by Breast Cancer Stamp Act Funds; Total Five Year $25 M
  - Breakdown: $4.5 M for U01 and $500 K for U24 per year;
  - Five-Year Total Cost: $25 M
- Allows NCI staff involvement in providing direction, cross talk, dissemination of information and assistance in meeting the programmatic goals
- Facilitates development of resources for biospecimens, reagent generation and dissemination of research tools and biologics
- NCI-DEA organized Special Emphasis Panel to review the application

Application Requirements

Applications will be required to:

- Include collaborative arrangement with existing or ongoing biospecimen networks or consortia as a partner on the application
- Clearly demonstrate the ability to procure appropriate specimens for the proposed study
- Be willing to share samples across the Consortium on cross-laboratory discovery and verification

Above requirements will be made part of the Notice of Grants Award (NGA)

Existing Resources

- Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)
- National Lung Screening Trial (NLST)
- Clinical and Translational Science Awards (CTSA)
- Canary-EDRN Prostate Active Surveillance Study (PASS) Cohort
- Specialized Programs of Research Excellence (SPOREs)
- DOD Specimen Banks (case-control specimens on prostate, breast, colon)
- VA Hospitals (archived specimens)
- Various Academic Autopsy Collections (Nebraska, Cornell, Johns Hopkins, etc.)

Number of Cases by Specimens Available for Selected Cancers in PLCO[1]

	Serum (pre-Dx)	Plasma (pre-Dx)	Red Cells (pre-Dx)	Buffy Coat	Whole Blood	Buccal Cells/ DNA[2]	Tumor Tissue
Prostate	3924	3870	4018	3270	3106	2131	1058
Screen-detected	1448	1399	1466	1170	1053	NA	496
Interval	123	121	123	90	88	NA	41
Others[3]	2353	2350	2429	2010	1965	NA	521
Lung	1570	1202	1589	1060	1051	870	436
Screen-detected	268	82	262	197	159	NA	97
Interval	141	57	138	84	94	NA	17
Others[3]	1161	1063	1189	779	798	NA	322
Breast (F)[4]	1984	1930	1972	1803	1583	1687	807
Melanoma[4]	636	625	645	619	505	494	NA[5]
Pancreas[4]	357	348	345	262	217	24	NA[5]

Note:

1. **Data as of January 31, 2013.**
2. **Buccal cells were collected from control arm only.**
3. **Others: Never screened and post-screening cases (and control arm for tumor tissue).**
4. **Detection mode for breast cancer, melanoma and pancreatic cancers is unknown.**
5. **Tumor tissue samples are not available for melanoma and pancreatic cancers.**

NLST Specimens and Screen Detected/Interval Cases

		# of Cases	% of Cases with Tumor Tissue Available[1]	% of Cases with Serum, Urine and Sputum Available[1]
Screen detected	CT Arm	649	65%	20%
	CXR Arm	279	56%	20%
Interval	CT Arm	44	26%	20%
	CXR Arm	137	24%	20%
Others[2]	CT Arm	367	21%	20%
	CXR Arm	525	13%	20%
Total lung cancers	CT Arm	1060	44%	20%
	CXR Arm	941	25%	20%

Note:
1. Approximate percentages.
2. Never screened and post-screening cases.

Available PCPT Biospecimens by Arm and Detection Mode

Arm	Detection mode	# of prostate cancer cases[1]	% of Cases with pre-Dx serum available[2]	% of Cases with WBC/DNA available[2]	# of cases with prostatectomy tissue available[3]
Finasteride	For cause[4]	435	~95%	~60%	149
	End of study biopsy	368	~95%	~60%	73
	All	803	~95%	~60%	222
Placebo	For cause[4]	571	~95%	~60%	186
	End of study biopsy	576	~95%	~60%	120
	All	1147	~95%	~60%	306

Notes:

1. Data from: Thompson et al., N Engl J Med. 2003 Jul 17;349(3):215-24. The influence of finasteride on the development of prostate cancer.
2. Estimated percentage of cases with specimens available.
3. Data from: Lucia et al., J Natl Cancer Inst. 2007 Sep 19;99(18):1375-83. Finasteride and high-grade prostate cancer in the Prostate Cancer Prevention Trial.
4. Number of cases in whom a biopsy was performed for a cause either during the study or at the end of study and cases who underwent another procedure such as transurethral resection of the prostate during the trial.