Molecular Characterization of Screen-Detected Lesions

NCI Board of Scientific Advisors
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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
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The Heterogeneity of Cancer Progression

- **Size at which cancer causes symptoms**
- **Size at which cancer causes death**
- **Abnormal cell**

**Time**

**Death from other causes**

- **Fast**
- **Slow**
- **Very Slow**
- **Non-progressive**

*This is over-Dx.*

(Courtesy of H. Gilbert Welch, Dartmouth)
Length Biased Sampling

Rapidly progressive

Slowly progressive

Test

Time

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

New Prostate Cancer Cases and Deaths
(per 100,000 men)

New Cases

Deaths

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


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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?
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

- 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

NIH Programs
- EDRN
- TMEN
- NCATS
- PLCO
- PROSPR
- BETRNet

Consortium for Molecular Characterization of Screen-Detected Lesions

Molecular/Cellular Characterization Laboratories

Coordination and Data Management Group (CDMG)

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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 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
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

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Serum (pre-Dx)</th>
<th>Plasma (pre-Dx)</th>
<th>Red Cells (pre-Dx)</th>
<th>Buffy Coat</th>
<th>Whole Blood</th>
<th>Buccal Cells/DNA²</th>
<th>Tumor Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>3924</td>
<td>3870</td>
<td>4018</td>
<td>3270</td>
<td>3106</td>
<td>2131</td>
<td>1058</td>
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<tr>
<td>Screen-detected</td>
<td>1448</td>
<td>1399</td>
<td>1466</td>
<td>1170</td>
<td>1053</td>
<td>NA</td>
<td>496</td>
</tr>
<tr>
<td>Interval</td>
<td>123</td>
<td>121</td>
<td>123</td>
<td>90</td>
<td>88</td>
<td>NA</td>
<td>41</td>
</tr>
<tr>
<td>Others³</td>
<td>2353</td>
<td>2350</td>
<td>2429</td>
<td>2010</td>
<td>1965</td>
<td>NA</td>
<td>521</td>
</tr>
<tr>
<td>Lung</td>
<td>1570</td>
<td>1202</td>
<td>1589</td>
<td>1060</td>
<td>1051</td>
<td>870</td>
<td>436</td>
</tr>
<tr>
<td>Screen-detected</td>
<td>268</td>
<td>82</td>
<td>262</td>
<td>197</td>
<td>159</td>
<td>NA</td>
<td>97</td>
</tr>
<tr>
<td>Interval</td>
<td>141</td>
<td>57</td>
<td>138</td>
<td>84</td>
<td>94</td>
<td>NA</td>
<td>17</td>
</tr>
<tr>
<td>Others³</td>
<td>1161</td>
<td>1063</td>
<td>1189</td>
<td>779</td>
<td>798</td>
<td>NA</td>
<td>322</td>
</tr>
<tr>
<td>Breast (F)⁴</td>
<td>1984</td>
<td>1930</td>
<td>1972</td>
<td>1803</td>
<td>1583</td>
<td>1687</td>
<td>807</td>
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<tr>
<td>Melanoma⁴</td>
<td>636</td>
<td>625</td>
<td>645</td>
<td>619</td>
<td>505</td>
<td>494</td>
<td>NA⁵</td>
</tr>
<tr>
<td>Pancreas⁴</td>
<td>357</td>
<td>348</td>
<td>345</td>
<td>262</td>
<td>217</td>
<td>24</td>
<td>NA⁵</td>
</tr>
</tbody>
</table>

**Note:**
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.

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<table>
<thead>
<tr>
<th></th>
<th># of Cases</th>
<th>% of Cases with Tumor Tissue Available(^1)</th>
<th>% of Cases with Serum, Urine and Sputum Available(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen detected</td>
<td>CT Arm</td>
<td>649</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>CXR Arm</td>
<td>279</td>
<td>56%</td>
</tr>
<tr>
<td>Interval</td>
<td>CT Arm</td>
<td>44</td>
<td>26%</td>
</tr>
<tr>
<td></td>
<td>CXR Arm</td>
<td>137</td>
<td>24%</td>
</tr>
<tr>
<td>Others(^2)</td>
<td>CT Arm</td>
<td>367</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>CXR Arm</td>
<td>525</td>
<td>13%</td>
</tr>
<tr>
<td>Total lung cancers</td>
<td>CT Arm</td>
<td>1060</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>CXR Arm</td>
<td>941</td>
<td>25%</td>
</tr>
</tbody>
</table>

Note:
1. Approximate percentages.
2. Never screened and post-screening cases.
## Available PCPT Biospecimens by Arm and Detection Mode

<table>
<thead>
<tr>
<th>Arm</th>
<th>Detection mode</th>
<th># of prostate cancer cases¹</th>
<th>% of Cases with pre-Dx serum available²</th>
<th>% of Cases with WBC/DNA available²</th>
<th># of cases with prostatectomy tissue available³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride</td>
<td>For cause⁴</td>
<td>435</td>
<td>~95%</td>
<td>~60%</td>
<td>149</td>
</tr>
<tr>
<td></td>
<td>End of study biopsy</td>
<td>368</td>
<td>~95%</td>
<td>~60%</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>803</td>
<td>~95%</td>
<td>~60%</td>
<td>222</td>
</tr>
<tr>
<td>Placebo</td>
<td>For cause⁴</td>
<td>571</td>
<td>~95%</td>
<td>~60%</td>
<td>186</td>
</tr>
<tr>
<td></td>
<td>End of study biopsy</td>
<td>576</td>
<td>~95%</td>
<td>~60%</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>1147</td>
<td>~95%</td>
<td>~60%</td>
<td>306</td>
</tr>
</tbody>
</table>

Notes:
2. Estimated percentage of cases with specimens available.
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.

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