NCI Best Practices for Biospecimen Resources

Technical and Operational Best Practices
(Real-World Perspective)

Martin L. Ferguson, Ph.D.
2007-11-05
Outline

• Introduction and Perspective
• Examples
• Issues Encountered and NCI Best Practices
• Conclusion
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Introduction and Perspective

- **The Cancer Genome Atlas (TCGA) pilot project**
  - 3 year pilot project of the NCI and NHGRI to comprehensively catalog the molecular changes associated with cancer.
  - Three different cancers: brain, ovarian and lung
  - Biospecimens obtained from a network of retrospective collections at multiple academic medical centers.
  - Large scale molecular analysis – 10 platforms, each doing every case in common.
    (RNA and micro-RNA profiling, copy number variation, translocation analysis, epigentics, and sequencing.)
  - Clinical data integrated with molecular data.
  - Integrated data sets made available to the broad research community.
Introduction - Not in scope for this presentation

- Other important factors that impact biospecimen access:
  - Human subjects policies, IRB approvals, HIPAA
    - Re-contacting and re-consenting of living patients
  - Material Transfer Agreement, Intellectual Property, Authorship
  - Informatics
    - Extraction and transfer of associated clinical data
    - Process data
    - Standards compliance (caBIG™)
  - Costs
Introduction - TCGA Goals & Biospecimen Quantity and Quality

- **500 individual cases successfully yielding molecular profiles**
  - Estimated 35% histological + molecular QC failure = 760 cases
  - Statistical power vs. financial constraints
  - Preferably from 2 collections to minimize variability
- **Germline DNA source for every case**
- **Frozen samples with at least 200 mg of tumor tissue per case**
  - DNA + RNA from each sample, enough for all 11 sites
  - No WGA
- **At least 80% of each sample composed of viable tumor cells on histologic assessment**
  - No LCM
Introduction - TCGA Operational Overview

Clinical site biorepositories

Biospecimen Core Resource

Single central facility

- Biospecimen Inventory
- Pathology Verification
- Molecular Analyte Production & QC

Clinical Annotation & caBIG™ conversion

Data Center
Integrated Clinical Data and Molecular Profiles

Analytical Platforms
11 sites

Aliquots

Clinical site biorepositories

Clinical Data

Tissue

Clinical Data

Tissue

Clinical Data

Tissue
Introduction - Sample Selection Process – on paper

- Request for Information issued to identify interested biorepository custodians
  - ~75 responses
- Follow-up phone calls to clarify/verify data provided
- Site visits to institutions with estimated sufficient sample sets
  - Did not include “audit” level review – i.e. going into freezers or databases
- Determination of source’s willingness to donate samples and participate in TCGA

- Conclusion: TCGA needs could be met by 2 collections per cancer
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Examples - Real numbers from beginning ops

- All logged sample number dropped 95 – 99%

<table>
<thead>
<tr>
<th></th>
<th>Repository 1</th>
<th>Repository 2</th>
</tr>
</thead>
<tbody>
<tr>
<td># Frozen samples logged in collection</td>
<td>5000+</td>
<td>1200+</td>
</tr>
<tr>
<td># Samples meeting spec upon detailed (non-physical) review</td>
<td>1392</td>
<td>120</td>
</tr>
<tr>
<td># Samples meeting physical specs</td>
<td>174</td>
<td>18</td>
</tr>
</tbody>
</table>

Before full pathology review
Examples -
Top 5 Sources of GBM Failure

- Matched normal germline DNA controls (blood or other) lacking
- Insufficient tumor cellularity in samples
  - Tumor cellular composition too low
  - % necrosis too high
- Specimen size too small
  - Insufficient tissue to generate minimum required amount of DNA/RNA for all analyses
- Molecular quality insufficient
  - QC failure of DNA or RNA
  - Insufficient amount
- Tumor not primary disease
  - Samples derived from recurrent, i.e. previously treated GBMs (confounding issue: Rx-related effects)
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Best Practices - Lessons Learned

- Quality of existing sample sets are typically overestimated by biobanks
- Collection of control samples is not routine in existing protocols
- Anatomic site-matched normal controls may be impossible to acquire
- Histologic quality does not guarantee molecular quality
- Data are lacking to define quality parameter cut-points accurately
  - How does cellular composition affect genomics profiling?
  - Necrosis?
  - Yields of DNA, RNA per weight by tissue?

- Biospecimen research is needed to understand effects of tissue variables on analysis data from different platforms
Best Practices - Specimen Collection and Processing

- Tissue collection protocols need to start at the beginning
  - Surgical / OR staff, biopsies, pre-op, consent
- Handling appropriate for specimen type and study design
- Minimize collection and processing time
- Standard Operating Procedures
  - Quality management system
  - Document all protocols
  - Training programs
- Tag all specimens with human + machine readable labels
  - Alphanumeric code
  - Barcode / RFID
Best Practices - Collecting and Managing Clinical Data

- Relevant clinical data
  - Longitudinal data, clinical follow-up, outcomes
  - CTMS: patient tracking, study calendars, electronic data capture
- Relevant epidemiologic data
- Informatics system for tracking all aspects of collection, processing and distribution
  - caBIG™

✓ Comply with privacy rules and human subjects regulations
Best Practices - Monitoring and Storage

- **Inventory tracking system**
  - Check in / check out, log all handlings
- **Store specimens in a “stabilized state”**
  - Appropriate temperature
    - Aliquots
  - Minimize thawing and refreezing
- **Disposal according to SOPs**
  - Monitor and document storage equipment
    - Temperature tracking critical
Best Practices - Record Keeping

- **IRB protocol governing collection**
  - Informed consent
    - Version year, tiered, permitted uses, re-contact OK
  - Exemptions
- **Subject vital status**
  - Material Transfer parameters
  - Date of Collection
    - Archived specimens prior to the era of molecular medicine
    - Prior to HIPAA Privacy Rule (April 14, 2003)
Best Practices - Packaging and Shipping

- Packaging procedures
- Records of specimen distribution
- Shipping procedures
  - Appropriate temperature
  - Length of time
  ✓ Shipping container electronic tagging
    ✓ Temperature, orientation
- Train personnel
Best Practices - Biosafety Procedures

- Identify risks and hazards
  - Infectious, Radiation, Chemical
- Record exposure incidents
- Provide treatment
- Indemnification agreements
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Conclusions

• Garbage In -> Garbage Out
• Make the up-front investment in samples – it will be worth it
  • Tissue Banking is the protocol. Too often it is considered a sideline
  • Treat your donors like clinical trial participants.
    Track participants over time to get data: clinical follow-up / outcomes
• Do histopathology review (and molecular QC) prior to deposition
  • Categorize your samples
  • Discard what should be discarded
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