NCI Best Practices for Biospecimen Resources

Technical and Operational Best Practices (Real-World Perspective)

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2007-11-05

NATIONAL CANCER INSTITUTE

Outline

OBBR Office of Biorepositories and Biospecimen Research

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

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Introduction and Perspective

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- **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

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- **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

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- **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

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Clinical site biorepositories

Clinical Data

Tissue

Clinical Data

Tissue

Clinical Data

Tissue

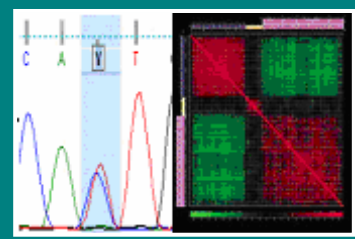
Biospecimen Core Resource

Single central facility

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

Clinical Annotation & caBIG™ conversion

Aliquots



Analytical Platforms

11 sites

Data Center

Integrated Clinical Data and Molecular Profiles

Introduction - Sample Selection Process – on paper

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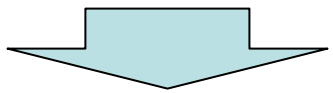
- **Request for Information issued to identify interested biorepository custodians**
  - ~75 responses
- **Follow-up phone calls to clarify/verify data provided**
- **Site visits to institutions with estimated sufficient sample sets**
  - Did not include “audit” level review – i.e. going into freezers 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

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- All logged sample number dropped 95 – 99%

	Repository 1	Repository 2
# Frozen samples logged in collection	5000+	1200+
# Samples meeting spec upon detailed (non-physical) review	1392	120
# Samples meeting physical specs	174	18

← Before full pathology review

Examples - Top 5 Sources of GBM Failure

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- **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

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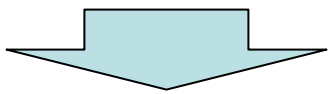
- **Quality of existing sample sets are typically overestimated by biobanks**
- **Collection of control samples is not routine in existing protocols**
- **Anatomic site-matched normal controls may be impossible to acquire**
- **Histologic quality does not guarantee molecular quality**
- **Data are lacking 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

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- **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

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- **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

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- **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

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- ✓ **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

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- **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

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

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Conclusions

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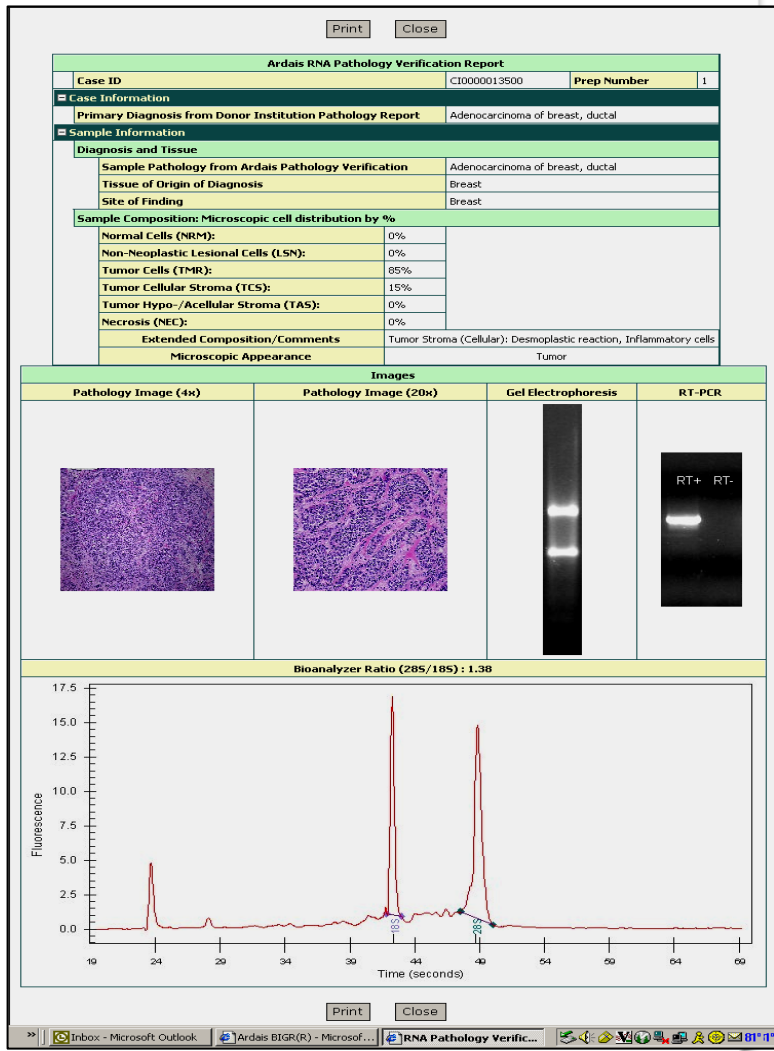
- **Garbage In -> Garbage Out**
- **Make the up-front investment in samples – it will be worth it**
  - Tissue Banking is the protocol.
    - Too often it is considered a sideline
  - Treat your donors like clinical trail participants.
    - Track participants over time to get data: clinical follow-up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



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