Genetic Testing and Tissue Banking for Personalized Oncology: Analytical and Institutional Factors

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Personalized oncology, or more aptly precision oncogenomics, refers to the identification and implementation of clinically actionable targets tailored to an individual patient's cancer genomic information. Banking of human tissue and other biospecimens establishes a framework to extract and collect the data essential to our understanding of disease pathogenesis and treatment. Cancer cooperative groups in the United States have led the way in establishing robust biospecimen collection mechanisms to facilitate translational research, and combined with technological advances in molecular testing, tissue banking has expanded from its traditional base in academic research and is assuming an increasingly pivotal role in directing the clinical care of cancer patients. Comprehensive screening of tumors by DNA sequencing and the ability to mine and interpret these large data sets from well-organized tissue banks have defined molecular subtypes of cancer. Such stratification by genomic criteria has revolutionized our perspectives on cancer diagnosis and treatment, offering insight into prognosis, progression, and susceptibility or resistance to known therapeutic agents. In turn, this has enabled clinicians to offer treatments tailored to patients that can greatly improve their chances of survival. Unique challenges and opportunities accompany the rapidly evolving interplay between tissue banking and genomic sequencing, and are the driving forces underlying the revolution in precision medicine. Molecular testing and precision medicine clinical trials are now becoming the major thrust behind the cooperative groups' clinical research efforts.
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Genomic profiling of tumors has revolutionized our ability to decipher the complexities of cancer biology, rapidly expanding our understanding of the dysregulated processes and mechanisms associated with tumorigenesis and metastasis. Compared with earlier approaches that could analyze genetic alterations serially, on a gene-by-gene basis, massively parallel sequencing (also referred to as next-generation sequencing, or NGS) can now scan the entire genome with even greater sensitivity, simultaneously detecting numerous genetic changes potentially underlying malignancy. Advances in sequencing technologies and refinements in bioinformatic processing have now enabled the high-throughput detection of the full spectrum of clinically actionable genomic alterations, including nucleotide substitutions, insertions/deletions (indels), copy number alterations, translocations, and/or chromosomal rearrangements.[1] Indeed, major large scale collaborative sequencing initiatives, such as The Cancer Genome Atlas (TCGA)[2] (http://cancergenome.nih.gov) and the International Cancer Genome Consortium (ICGC)[3] (http://icgc.org), have been cataloguing these genetic changes, leading to the subclassification of many common cancers based on their molecular or genotypic profile.[2,4–6]

With advances in genome sequencing technology now outpacing Moore's law,[7] an apparent paradigm shift in genetic testing and personalized medicine has emerged. Once thought to be limited to research, genomic profiling of tumors is rapidly evolving towards point-of-care clinical testing. Central to this phenomenon in genomics-driven cancer medicine[8] is the structuring of tissue procurement and tumor banking—and subsequent elucidation

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and management of the associated genomic data—as a routine part of patient care.[9] The importance of tissue procurement and tumor banking as a routine part of patient care has never been greater, as an increasing number of ongoing and planned clinical trials by cancer cooperative groups utilize integral biomarkers for patient selection.

Institutional experiences and current recommendations for integrating procurement and banking of biospecimens for research and its evolution towards personalized medicine have been reported by a number of academic medical centers.[10] Though dated, additional best practices for successful research biobanking have been summarized by the Office of Biorepositories and Biospecimen Research (http://biospecimens.cancer.gov/bestpractices/) and the International Society for Biological and Environmental Repositories (http://www.isber.org). However, there are a number of practical and current issues central to both tissue banking and contemporary genomic sequencing analysis, at the institutional and the cooperative group level, that have emerged in the last several years that are not adequately addressed by existing guidelines. Specifically, banking paradigms must respond to the need to obtain not only tissue specimens, but also the associated genomic information.

TISSUE ACQUISITION AND STORAGE

Research biobanking paradigms are well established. However, one of the key issues with biospecimen repository management in clinical settings is deciding what specimens are collected (tissue, aspirates, blood, or a combination thereof) and how they are stored. The current approach used by most laboratories, analogous to umbilical cord blood banking,[9] is collecting specimens now for the uncertain probability that they will be used to direct patient care at a later time. In essence, banked tissues serve as an insurance policy against molecular diagnostics and treatment modalities yet to be envisioned. An important question raised from this discussion is whether multiple tissue samples should be banked over a course of the patient's diagnosis and treatment. With the growing field of pharmacogenomics,[11] the ability to review genetic alterations longitudinally across baseline, treatment, and recurrence time points may be essential for generating the data needed to establish predictive response or resistance to therapy.

The most important preanalytical consideration, for both research and clinical biobanking, occurs at the time of tissue acquisition and procurement, beginning with the biopsy or resection tissue sample. In some instances, intraoperative consultations by pathologists may prove increasingly useful by providing the surgeon with immediate information concerning the nature of the tumor specimen. Decisions made by the surgical pathologist in the operating room or grossing room are critical to the success of tumor banking and the downstream pipeline in molecular analysis. Fine-needle aspirations and core biopsies present even more technical challenges. Will samples be divided for parallel archiving (ie, cryopreservation and formalin-fixed paraffin embedding [FFPE])? How will this be implemented, and are decision algorithms in place for dealing with such limited specimens that might need to be shared across multiple tests for diagnosis? Have sources of potential sample bias and sampling bias been identified for tissue banking and analysis?[12,13]

Sample adequacy for tumor content will need to be assessed at the time of procurement and again on processed blocks. In both cases, it is vital to select representative tumor areas that will likely generate the best possible results. A sufficient mass of viable tumor nuclei must be cored, since inadequate amounts of high-quality template DNA are prone to sequence-dependent amplification errors, diminished read depth, and decreased library complexity, all of which negatively impact NGS sensitivity and specificity.[14] Preanalytical quality and quantitative tools, such as quantitative functional index (QFI)-polymerase chain reaction (PCR), can be used to rapidly assess clinical samples with low-input FFPE-derived DNA.[15] In many NGS laboratories, libraries for whole genome (WGS) or whole exome (WES) sequencing generally start with 100 ng or more of total DNA (~500,000 cells) from a representative sampling of a specimen.[16] Selecting areas with necrosis and high stromal background may diminish sample yield and quality metrics, and must be avoided if possible.

Growing knowledge of the dynamic clonal evolution of cancer illustrates the necessity of adequate tumor sampling for proper clinical management of the patient. Indeed, genetically evolved metastatic subclones have been found within a primary carcinoma.[17] Comprehensive geographic sampling of known primary tumors (as well as metastatic lesions) and high-depth sequencing are needed to effectively characterize the mutational load of tumor specimens. Criteria standards incorporating tumor sampling, quality, and clonality assessment across different genomic sequencing platforms and depth of coverage (targeted v whole exome v whole genome analysis) will need to be established and eventually standardized as NGS assumes a more central role in clinical diagnostic testing.

FROZEN TISSUE

Fresh/frozen tissue from surgical biopsies is considered the preferred specimen for most molecular diagnostic assays, and these specimens have been