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

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Abstract

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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Introduction

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 sub-classification 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 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 (i.e. cryopreservation and 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)-PCR, can be used to rapidly assess clinical samples with low-input FFPE-derived DNA [15]. In many next generation sequencing 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 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 vs. whole exome vs. whole genome analysis) will need to be established and eventually standardized as next generation sequencing 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 used in many of the comprehensive genomic studies performed to date. Though the integrity of DNA appears to be maximally preserved, snap freezing of samples must be performed soon after biopsy or resection, particularly to limit degradation of the more labile RNA used in gene expression profiles, as well as proteins that may be directly assayed. It should be noted that freezing of tissue alters morphology at the expense of preservation and may complicate any histopathological correlations to genomic data. Prioritization practices for procurement and handling of frozen samples in a surgical pathology laboratory have been summarized[10].

The logistical complexities of collecting and storing fresh or fresh-frozen tissue specimens hinder their routine use in clinical biobanking and subsequent genetic testing. At present, frozen biorepositories are more closely tied to a focused clinical research setting within established tissue procurement core facilities predominantly located at large academic medical centers[10]. These banks vary considerably in organization, management, and in what materials and data that are stored, and they may or may not be integrated with patient medical records in the local healthcare system. Thus, the use of frozen specimens in clinical biobanking presents a challenging and expensive undertaking even for the largest academic medical institutions and renders most of these specimens an impractical medium for diagnostic purposes in precision medicine. This is also challenging at the level of the cooperative groups, since specimens from both academic and community-based practices participate in clinical trials with biomarker assessment objectives. The scarcity of banked frozen tissue for rare malignancies limits their inclusion for retrospective analysis. Nevertheless, many centers will continue to bank frozen samples as part of their biospecimen repository and these samples will continue to provide a valuable source through which genetic studies can be made. The practical sustainability of this model over the long term, however, has yet to be fully examined, with the recent explosion in genomic sequencing likely taxing this arrangement even more.

Molecular Fixation: FFPE Coming of Age?

Formalin-fixed paraffin-embedded (FFPE) samples constitute the mainstay of anatomical pathology and remain the gold standard for morphologic and immunohistochemical assessment of tissue, and it is estimated that over 20 million blocks are constructed each year [18] [19]. FFPE specimens are stable at room temperature and easily stored. These readily derived and easily accessible specimens form the basis upon which surgical pathology reports are issued, and as such, are often well-characterized with combined histopathologic and clinical annotations with follow-up data. It follows then that FFPE blocks retained in surgical pathology libraries represent an invaluable repository of clinical genomic data for both prospective and retrospective cohort studies. In fact, FFPE blocks are currently the most common type of tumor specimens banked and evaluated for clinical and translational trials conducted by cooperative groups.

However, it is well known that formalin fixation alters and fragments nucleic acids and proteins[20, 21]. Formaldehyde reacts with nucleic acids and proteins through reactive hydroxymethyl intermediates that give rise to mixtures of DNA, RNA, and proteins covalently cross-linked by methylene bridges, as well as individual and cyclic nucleobase derivatives through deamination[22, 23]. These chemical modifications present challenges to sample extraction and recovery, and they have the potential to compromise downstream molecular genetic testing. Methylene crosslinks within DNA inhibits polymerase chain reaction (PCR) amplification and other enzymatic manipulations[24]. And since many formalin-induced transitions occur in methylated CpG dinucleotide sequences, fixation may confound the methylation status of tumor samples and their interpretation in certain assays[25].

Despite these technical considerations, FFPE has proven to be a robust sample source for sequencing and transcriptome analysis. Indeed, many studies have explored the utility of next-generation sequencing on FFPE samples [26, 27]. Hadd *et al.* assessed the targeted sequencing capability of FFPE samples and reported 99.6% concordance of variant calls between two different NGS sequencing platforms (Illumina GAIIx vs Ion Torrent PGM), and an accuracy of 96.1% against traditional Sanger sequencing[28]. Spencer *et al.* demonstrated similar results obtained through an in-depth pair-wise comparison of fresh-frozen and formalin-fixed tissues using targeted NGS, with >99.99% concordance of base calls between the paired samples and a 96.8% match in the single-nucleotide variants that were detected[25]. Of most importance, the error rate, library complexity, enrichment performance, and coverage variability lacked statistical significance between the sample groups. A low frequency of nucleotide transition artifacts attributed to formalin fixation was noted, although these high-quality discrepant base calls were statistically indistinguishable from the frozen sample data[25]. Recently, rapid whole-exome sequencing (WES) from archived FFPE and frozen tissue tumor material was examined in a prospective clinical trial to guide the treatment of a patient, demonstrating the comparable utility of FFPE clinical samples in a proof-of-concept precision medicine case[29]. Together, these studies provide convincing evidence that formalin-fixed specimens are a reliable source for clinical-grade NGS, spanning a broad spectrum from single-gene to whole exome sequencing.

Addressing the effects of formalin-fixation on specimens and next generation molecular assays is an area of renewed interest and active investigation. For example, it has been demonstrated that pretreatment of sample DNA by uracil DNA glycosylase (UDG) may mitigate formalin-induced sequencing artifacts[30]. Other approaches include post-sequencing bioinformatic measures as a means to identify and filter out such changes, and filtering mechanisms may be adjusted given variations in FFPE clinical specimens across institutions with collection, processing, and storage conditions[28]. This will be especially important for prospective cohort studies that utilize blocks of considerable sample age (>10 years) and unknown fixation conditions. Realizing the value of formalin blocks, The Cancer Genome Atlas (TCGA) recently established the Formalin-fixed Paraffin Pilot Project (FPPP) to optimize DNA and RNA extraction methods from FFPE samples for whole-exome sequencing, copy number profiling, RNA sequencing, and other platforms (http://cancergenome.nih.gov/researchhighlights/leadershipupdate/FPPP_Roy_Tarnuzzer). To that

end, an FFPE Analysis Working Group composed of Memorial Sloan Kettering and Oregon Health and Science University is tasked to further define best practices and limitations of FFPE-derived DNA and RNA for molecular diagnostics.

Additionally, FFPE samples can be examined by a variety of other molecular techniques that complement sequencing, transcriptome, and pharmacogenetic analysis[31]. Proteomic analysis from formalin-fixed tissues has been exhaustively studied through immunohistochemistry, as well as more direct methods of protein detection by isotope labeling, mass spectrometry, and nuclear magnetic resonance spectroscopy (though limitations do exist, such as with quantification of kinase networks and phosphoprotein analysis, a niche where fresh/frozen tissue is superior [32]). Surprisingly, polar metabolites have been directly identified from FFPE-archived tumor specimens using targeted mass spectrometry[33]. Flow cytometry-based techniques have been developed to isolate pure populations of tumor cells from FFPE samples for array-based comparative genomic hybridization (aCGH) and whole exome next generation sequencing[34]. In addition, laser capture microdissection (LCM)[35] can be utilized to isolate specific regions of tumor, surrounding matrix, and/or subcellular organelles. For example, LCM can be employed to isolate nuclei[36] for single cell sequencing. The leading edge of invasive tumors and/or the desmoplastic response can be microdissected to investigate regional molecular changes associated with tumorigenesis. These “micro-procurements” may offer the ability to provide spatial relationships to genetic alterations from banked specimens with limited bias, and they will be integral to understanding of functional genomics.

Though fresh/frozen tissue has long been regarded as the traditional specimen for tissue banking and most molecular testing, current data clearly illustrate that FFPE samples are reliable sources for next generation sequencing. This, coupled with widespread availability and detailed clinical annotations, ensures that FFPE specimens will assume a primary role in clinical molecular genetic testing of tumors (Table 1). Further, it has been demonstrated that specimens from other commonly used pathology fixatives are amenable to NGS. For instance, sequence information obtained from archived fine needle aspirate (FNA) smears fixed by methanol or ethanol are indistinguishable from FFPE tissue [37]. Hence, next generation sequencing will bridge molecular testing and continue the vital clinical workflow relationships between surgical pathology and cytology.

Tumor Heterogeneity and Sample Bias: A Major Concern

Considerable genomic and phenotypic variation exists not only between cancer types, but also between individuals who have the same type of cancer (intertumoral heterogeneity) and within individual tumors (intratumoral heterogeneity). Heterogeneity is further extended between primary tumors and metastatic lesions in the same case (intratumoral vs. intrametastatic heterogeneity). Thus, spatial and temporal heterogeneity are intrinsic features of tumor growth and progression[38].

New experimental approaches and deep sequencing of tumors have provided considerable insight into the phenomenon of tumor heterogeneity[39]. NGS has demonstrated marked genetic heterogeneity within a variety of hematopoietic and solid tumors, including acute

myeloid leukemia (AML)[40], chronic lymphocytic leukemia/lymphoma (CLL)[41], B-cell lymphoma[42], breast carcinoma[43–45], glioblastoma multiforme[46], renal cell carcinoma[47, 48], pancreatic tumors[17, 49, 50] and oropharyngeal squamous cell carcinoma[51].

The mechanisms of heterogeneity have been reviewed and are largely a result of genetic instability, epigenetic alterations, and cancer stem cell plasticity that result in clonal expansion[52–54]. Additionally, it was recently revealed that PTEN loss in human T-cell acute lymphoblastic leukemia (T-ALL) can be influenced by the tissue microenvironment, suggesting that intratumoral heterogeneity is even more complex than previously thought, and that it can exist independent of cancer genotype[55].

Tumor heterogeneity obviously poses a major impediment to tumor banking and personalized oncology[56], particularly in the genomic assessment of clinical samples. Biopsy captures—even multiple cores taken from a block—may represent only a fraction of the complete genomic landscape of a tumor. Bias due to heterogeneity and sampling can misguide genetic interpretation and alter the molecular classification of the tumor[12], with profound effects on prognosis and delivery of appropriate targeted therapy. Sequencing data from genomic profiling can also be misleading since the genomic profile of the most abundant cell type within a given tumor specimen may not necessarily reflect the biological activity of minor clones or the tumor as a whole. For instance, sequencing analysis of triple negative breast carcinomas has demonstrated that metastatic tumors can arise from a minority proportion of cells within the primary lesion[57].

Treatments such as radiation and certain forms of chemotherapy that damage DNA may also influence genomic heterogeneity of recurrent or metastatic lesions. This will be of importance in clinical settings as it may indicate a requirement for new biopsies to ascertain the post-therapy genomic status of a patient's tumor[53, 58]. For instance, it has been established that relapsed cases of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) are associated with the emergence of novel genetic variants after therapy, suggesting that clonal evolution is driven in part by resistance to chemotherapy [40, 59].

Measuring clonal dynamics throughout the course of the patient's care through serial tumor sampling, single cell sequencing[43], and deep sequencing[60] (for example, after therapy-associated relapse or treatment resistance[61] or with the development of metastatic disease) will provide the most current genomic profile by which individualized treatments or clinical trial enrollment can be modified as necessary. In many instances, however, the usefulness of the primary lesion will be retained since profiling the escape mutations in metastatic or recurrent lesion for alternative or combination drug targets will rely on comparison with the original tumor sample[62] [63]. It is becoming increasingly clear that in order to have effective clinical utility, biobanking of any specimens, including frozen tissue, must now encompass multiple sampling of primary tumors, metastatic lesions, and post-treatment samples[64].

Regulatory Guidelines for Next Generation Sequencing in the Clinic

Significant infrastructure and the collective expertise of many diverse stakeholders—including hospital administration, clinicians, molecular genetic pathologists, scientists, and bioinformatics specialists—will be required for the implementation of next generation sequencing in clinical laboratory settings. Regulatory issues governing clinical laboratory testing include many technical and quality management aspects such as test method validation, quality control and assessment, proficiency testing, and reference calibration[16]. Recently, the College of American Pathologists (www.cap.org) and the New York State Department of Health have published standards for accrediting laboratories that perform clinical next generation sequencing, and similarly, standards for an accreditation program for biorepositories have been developed[65]. In addition, to further address these issues, in 2011 the Division of Laboratory Science and Standards (DLSS) of the Centers for Disease Control and Prevention (CDC) and the American College of Medical Genetics established a national workshop (Next Generation Sequencing – Standardization of Clinical Testing, or Nex-StoCT) to identify principles and develop guidelines for assuring quality practices relevant to the use of next generation sequencing in clinical tests[66]. As discussed below (Table 1), since the concept of biobanking is poised to move from collection and curation of tissue specimens only, to collection and curation of tissue specimens and associated genomic information, issues related to the quality of NGS data are now squarely a component of biobanking.

Biospecimen Banking Paradox: The Genomic Data Challenge

Advances in next generation sequencing have now outpaced our current understanding of cancer biology. A vital component to the revolution in genomic profiling lies not only in the banking of tissue but also in the structuring and analysis of the massive knowledge bases of genomic data generated from these samples. NGS instruments have now exceeded the capability of producing more than 100 gigabases (Gb) of reads in a given day[67], prompting the question, how do laboratories, clinicians, and biobanks contend with such massive amounts of sequencing data? The use of high throughput genomic profiling for precision-based medicine will also require extensive metadata to accompany sequenced specimens. This may include a patient's personal profile, clinicopathological data with associated proteomic profile, molecular imaging, and other studies. Together, these data will become the core of modern day biospecimen banks (Figure 1)

How will these heterogeneous sources of information be compiled and where will the collection be stored? Will the clinical metadata be arranged in external sidecar files, or will everything, including the raw sequencing data of the specimen, be dumped into a single container format? How will the data be compressed to allow for real-time access over web services? How will this information be secured, and what software interfaces will be required for storage, transmission, and retrieval of information to and from the biobank information management system (BIMS)[68], laboratory information management systems (LIMS), and the patient's electronic medical record (EMR)? These and other questions must be addressed as institutions begin modernizing tissue banks to address emerging research and patient care paradigms. In an apparent paradox, the infrastructure for tissue banking as

developed for the collection and storage of patient specimens may assume primary importance for banking of the *genomic data* obtained from tissue samples rather than the tissue samples themselves. Newly generated sequencing data from current biopsies will be cross referenced in real-time to previously archived molecular data from prior patient samples in order to further guide patient care and determine what clinically actionable options are available. This analogy holds true to how an existing surgical pathologist examines a new case under the microscope and compares it with previous slides[16].

How will data be selectively anonymized, accessed, and shared by researchers for scientific studies and the development of clinical trials within and across different institutions? As biobanks assume more and more of a role as a repository and custodian of genomic profiles, the notion of data ownership and access becomes more contentious. There is a critical need to establish working groups to address this complex interplay between a patient's genomic sequence and those who have access to it.

Banking in the Clouds

Many cancer-specific and pharmacogenomic reference databases have been and are being concurrently developed across a multinational consortia of academic, managed care, industry, and government agencies[69, 70]. One of the most difficult conundrums in all of this will be finding effective ways for clinicians, researchers, and other vested parties to easily access and share information from these well-annotated reference databases, and answering the question of how this information will be rapidly integrated and continuously monitored within the electronic medical record system of patients. Cloud-based computing has surfaced as a viable platform for large-scale next generation sequencing analyses and data banking. Identified variants are reviewed against a variety of powerful web-based informatics tools such as The Database of Short Genetic Variation (dbSNP)[71], the Catalog of Somatic Mutations in Cancer (COSMIC)[72], and the 1000 Genomes Catalog of Human Genetic Variation[73], the NHLBI Exome Server[74], the Genome in a Bottle Consortium/Genome Comparison and Analytic Testing (<http://www.bioplanet.com/gcat>) [75], and the recently published, cloud-based Literome by Microsoft, which will automatically extract a variety of genomic information published and posted in PubMed abstracts[76]. However, all of these databases differ in the way data are curated, and they vary considerably in editorial oversight. Accessing and using these knowledge bases as reference material poses concern for standardization of bioinformatics workflow, validity, and regulatory issues when utilized in the context of analyzing clinical NGS cases today, and will similarly impact emerging biobanking paradigms. For instance, variant calls that seem insignificant today might very well be significant once more data is compiled. It is clear that the capability to sequence, search, and make decisions has outstripped the material to which we have access in the database.

The shift towards whole exome and whole genome analysis will generate even larger data sets that will need to be managed and interpreted in a clinically relevant timeframe. Bioinformatics specialists must develop innovative computational approaches for data compression, storage, retrieval, and analysis. This task is imperative in order to overcome the data bottleneck that threatens the success of precision medicine. Of note, the NIH Big

Data to Knowledge (BD2K) initiative has been established to address major challenges in using complex datasets, so called “Big Data.” (<http://bd2k.nih.gov/index.html#sthash.2U7zh7Oq.dpbs>)

Medicolegal and Ethical Issues in the Era of Personalized Medicine

The accelerating pace of sequencing technology and genomic discoveries is revolutionizing the way pathologists diagnose and oncologists treat their patients, and has also raised many legal, ethical, and financial concerns[77]. Next generation sequencing encompassing germline DNA or whole genome sequencing can readily identify an individual. Further, mutations unrelated to the banked tumor specimen but to hereditary cancer syndromes or many non-cancer diseases will be known. These findings not only impact the patient, but also his or her immediate family members. Emerging from this scenario is the question: To what extent is genetic data returned to patients and/or clinical trial participants? The return of these genetic results poses a number of controversial situations for the patient and clinician[78].

Importantly, the Genetic Information Nondiscrimination Act (2008) prohibits the improper use of genetic information for employment and health insurance, but does not apply to life insurance, disability, or long-term care insurance providers [79]. In 2010 the Patient Protection and Affordable Care Act was enacted, prohibiting health insurers from denying coverage or charging higher premiums on the basis of pre-existing conditions [80]. These are important steps towards ensuring patient privacy and informed consent regarding genomic analysis of banked tissue specimens.

Consent and IRB review form the legal framework for successful tissue biorepositories in the era of genomic profiling. Considerations for these requirements have been summarized, including a detailed description of requirements needed for consent documentation as well as best practice guidelines for the banking of tissue samples[16].

Moving Forward with Personalized Oncology: the Importance of the Network Groups

The genomic landscape of the more common forms of human cancer has been drafted, identifying scores of novel cancer genes. These cancer-associated genes have largely now been classified into one or more of a dozen cell signaling pathways, which have been broadly grouped as processes regulating cell survival, fate, and genome maintenance[81]. Although a few genes are mutated at high prevalence, the majority of cancer genes exhibit mutation frequencies of 2–20%[1]. An analysis by the Broad Institute recently reported that an average of 2,000 tumors for each of 50 tumor types would be required in order to identify mutations within this intermediate frequency range[82]. In order to comprehensively define driver genes at 1% frequency within a particular tumor subtype, it has been suggested that 10,000 biobanked samples for each of the more common cancers be sequenced [83]. It is clear from these projections that the sequencing and cataloguing of many tumors with matched normal samples will be required in order to achieve the required statistical power to reliably identify and act upon rare cancer mutations that would otherwise never be detected.

The abundance of high-quality FFPE specimens enabled by biobanking across multiple centers carries the leverage to achieve these genomic sequencing goals.

At this stage, how comprehensively should the cancer genome of these and subsequent banked clinical cases be sequenced? Whole-genome sequencing provides a more complete picture of the genomic landscape of tumors from which potentially actionable targets might be ascertained, but is very expensive when performed at the depth of coverage required for clinical use[58]. Whole exome or targeted gene panels are considerably less expensive and have a much faster turnaround time for analysis. Although these approaches may be more suited for clinical diagnostics initially, the limited scope of these panels significantly reduces the genetic profile of the tumor specimen and will constrain the use of potential therapeutic targets. This is a pressing issue, as the decisions made today will likely structure the capacity and usefulness of genomic databases in the future.

Of equal concern will be the issue of parsing true clinical variants from miscalled genomic reads in the billions of sequenced nucleotides generated. Mutational heterogeneity of patients within a cancer type, particularly regional genomic heterogeneity, is a fundamental problem of large scale genome studies. Computational methodologies such as MutSigCV have been developed to address these issues[39]. Specimens will undoubtedly require replicate genome sequencing[84] as a confirmatory algorithm, independent of any sequencing approach, in order to increase reliability in identifying and validating bona fide sequencing variants of interest. Increased sequencing fidelity, improved bioinformatic algorithms, and the use of orthogonal detection platforms may also be required for cross validation in clinical molecular pathology laboratories as well.

With worldwide access to thousands of banked, high-quality FFPE specimens and plummeting sequencing costs, oncologists and pathologists are now in a position to make proposed systematic sequencing of large tumor populations a reality, shifting the narrative from ephemeral discussions toward an urgent medical need as the rapid evolution in genetic testing and personalized oncology continues to unfold. Coupled with technological advances in genome sequencing, FFPE tissue blocks will almost certainly form an essential cornerstone for molecular genetic testing.

As efforts to match specific driver mutations to targeted therapies gain momentum, it is anticipated that the cooperative group mechanism will be the ideal vehicle to conduct clinical trials based on molecular abnormalities, particularly for those that occur at low frequency. Already, studies such as the ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)(NCT02194738), Squamous cell lung master protocol (NCT02154490), and NCI-MATCH (Molecular analysis for Therapy Choice) are utilizing molecular analysis as the basis for treatment selection. These studies require common protocols for sample collection, storage, and shipping across academic and community sites. And, as indicated by the discussion above, these cooperative group biobanks will need expanded capacity for storage, clinical data collection, bioinformatics resources, and personnel. As the next generation of clinical investigations to improve outcomes for cancer patients is developed, it is imperative that the biobanking and molecular testing capacities of the cooperative groups are adequately supported.

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Figure 1. A Schematic For the Workflow in Precision Oncology

Revolutionary advances in genome sequencing technology have accelerated our understanding of the complexities of cancer biology, with profound changes in personalized genomic medicine. Next generation sequencing and other molecular technologies are being incorporated into the practice of surgical pathology to evaluate the molecular profile of tumor specimens in both primary and increasingly of recurrent or metastatic disease (inset). Categorization of genetic alterations allows for the identification of clinically actionable variants, which in turn can be used to better assess the prognosis and likelihood of patient benefit from targeted therapies. Combined with these technological advances in molecular testing, tissue banking has expanded from its traditional base in academic research and is assuming a pivotal role in directing the clinical care of cancer patients. Formalin-fixed paraffin-embedded (FFPE) tissue blocks are an abundant and robust sample source for molecular analysis and specimen banking. However, a currency shift towards the banking and analysis of genomic data is rapidly becoming the driving force for precision-based oncology.

Table 1

The Evolving Biobank in Personalized Oncology

BiobankRole	Advantages	Disadvantages
Traditional Frozen tissue of primary and paired normal samples	Amenable to DNA, RNA, and proteomic analysis	One time point, no longitudinal outlook Loss of morphology Expensive, laborious
Current Process Frozen tissue of primary and paired normal samples FFPE of many blocks at diagnosis FFPE of posttreatment lesions; multiple metastases Details of treatment	As above Tumor heterogeneity and clonality assessment Tumor heterogeneity and identification of escape mutations Required to understand response to therapy	As above Increased physical space and expense Requires massive institutional support How will information be collected Who will host and curate biobank?
The Future? As above Bioinformatics Banking extended to cloudbased genomic data storage and retrieval	As above Genotype correlated with phenotype Integrating functional genomics to evaluate: initial disease and response to therapy escape of therapy and resistance other empiric associations	As above Big-data challenges: Massive data storage and management Shared Access/Ownership Continuous data surveillance for patient as database grows (seeking clinically actionable variants discovered after entrance into biobank) Ethical considerations