CHAPTER SIX

Business Plan and Operations

RAND evaluated twelve repositories, which were grouped into three general sectors: government, academia, and industry (see Chapter Two, Table 2.1). The first category, government, includes two repositories funded by and operated by federal agencies, one repository contracted by a federal agency, and three repositories funded through cooperative agreements with a federal agency. The second category, academia, includes repositories at three major academic medical centers that are funded through Specialized Center Grants (P50s) from NCI, and one repository at a major academic medical center that houses both NCI-funded resources and institute-funded programs. The third category, industry, includes two private companies that operate biospecimen repositories. Different business models are represented within each category, including tissue banking versus prospective collection and distribution, networks versus individual sites, and centralized versus decentralized collection, storage, and bioinformatics systems.

Government Repositories

Six of the repositories evaluated for this study were categorized as government repositories. TARP and AFIP are government-sponsored and government-operated resources. CHTN, EDRN, and Philadelphia Familial Breast Cancer Registry are funded through Cooperative Agreements with NCI. NHLBI contracted out the operation of

its Biological Specimen Repository to BBI-Biotech Research Laboratories, a private company. CHTN and EDRN have a small core staff of government employees who facilitate coordination within the respective networks.

Of the government repositories evaluated, all but one were established primarily for the purpose of research. AFIP is foremost a diagnostic referral center and secondarily a tissue bank. AFIP does not seek out specimens for collection and banking; it is sent specimens, unsolicited, from pathologists for diagnostic purposes. AFIP serves as a referral center for pathologists in need of a secondary expert opinion. After AFIP renders a diagnosis, the specimen is stored in its repository (some specimens are returned to the submitting institution upon request). Although its primary function is in the area of diagnosis, AFIP pathologists do conduct some epidemiological research, particularly in clinical pathological correlations.

Academic Repositories

The academic repositories included in this evaluation were all partially government sponsored, usually with funding through a variety of granting mechanisms. All of the academic repositories operate one or more of the SPOREs. In addition to its Breast SPORE, Duke University has a Brain SPORE. Mayo Clinic has a Prostate SPORE, and also collects breast, ovary, intestine, pancreas, heart, brain, skin, bone, kidney, and bladder tissue. In addition to its Breast and Ovarian SPOREs, UAB has a Brain SPORE and a new Pancreas SPORE, is one of the Biomarker Validation Laboratories for EDRN, and serves as the Southern Division of CHTN. UPMC has a Lung SPORE and is also participating in CPCTR and EDRN.

The SPOREs are funded through Specialized Center Grants (P50s) from NCI. University of Pittsburgh HSTB receives most of its funding from NIH, NCI, the Department of Defense, and the State of Pennsylvania. In addition, small amounts of funding are provided by sponsored corporate relationships. A small part of the funding for

the biospecimen repositories at Duke University and the Mayo Clinic also comes from private sources.

Industry Repositories

RAND evaluated two industry repositories, Ardais and GCI. Ardais operates as a tissue bank and distribution service. GCI has a dual business model. It operates a fee-for-service tissue bank and distribution center that works primarily with the pharmaceutical industry to collect specimens for drug development, and it also participates in collaborative research with pharmaceutical and biotech companies and academic and government institutions. Collaborations with academic medical centers and government institutions are done on a non-profit basis. GCI and Ardais are privately funded, although Ardais has some public grant money for research projects.

Repository/Collection Site Relationships

How repositories arrange for the collection of specimens varies depending upon the business model. All of the academic repositories collect specimens almost exclusively from their on-site and associated medical facilities; hence, no formal agreements are necessary. The Mayo Clinic Prostate SPORE has gone outside of its hospital system to obtain specimens on rare occasions if there is a specific need that cannot be met otherwise.

The remainder of repositories tend to draw from a mix of community hospitals and academic medical centers for the bulk of their collection. Many of the regional divisions of CHTN have agreements with several community hospitals to enable them to provide researchers with a broad range of samples. For example, the Eastern Division has agreements with several sites to collect specimens, including six community hospitals, two eye banks, and an organ procurement organization. The collection model at Ardais has been designed to be flexible in size, scalable, and deployable at multiple sites. Ardais cur-

rently has arrangements with three academic medical centers (Duke University, Beth Israel, University of Chicago) and one hospital (Maine Medical Center) that serve as collection sites. GCI has over 700 collection sites in the United States, and has collected specimens from sites in Belgium, Poland, Tunisia, Vietnam, and India. GCI has made arrangements at the institutional level as well as with individual doctors through its Physician Network™.

The contractual agreements between collection sites and repositories are negotiated on a case-by-case basis. One repository may have different agreements with different collection sites. CHTN has negotiated agreements with some collection sites that provide some funding up front and then reimbursement for certain services or milestones. It also has fee-for-service agreements with some of its sites. GCI reimburses collection sites on a cost basis.

Repository Operations

CHTN, EDRN, the Breast and Ovarian CFRs, and NHLBI all have a coordinating body that oversees the general operations of the repositories and sets procedures and policies. GCI and Ardais have scientific advisory boards. A CHTN coordinating committee consisting of an NCI representative plus two representatives from each CHTN division sets the general operating procedures and policies for the network. Procedures are designed to enhance throughput rather than storage, since the CHTN was not designed for banking. A quality assurance subcommittee sets general standards for the pathology procedures and has developed a procedure manual that is used at all CHTN sites. Issues of quality control are discussed on a continuing basis, and criteria are modified as necessary. In addition, CHTN continually assesses researcher needs for services such as laser capture micro-dissection (LCMD) and tissue microarrays and adds new services when sufficient demand exists. CHTN has other subcommittees, including a marketing, development, and operations subcommittee, a quality assurance subcommittee, and a strategic planning subcommittee.

EDRN has a steering committee that coordinates the work of the consortium and provides major scientific management oversight. It is made up of the network's principal investigators and NCI staff and is responsible for developing and implementing protocols, designs, and operations.

The Breast and Ovarian CFRs, of which Philadelphia Familial Breast Cancer Registry is a member, has a steering committee, which is its official governing body. The steering committee is responsible for developing the core protocols for biospecimen collection, the core instruments for the collection of epidemiological and clinical data, and policy and procedures. The Breast and Ovarian CFRs also has an advisory board, which is an independent, multidisciplinary panel of senior cancer researchers that evaluates requests from researchers for use of the CFRs' resources. The advisory committee makes recommendations on research priorities to the steering committee, which ratifies the recommendations, based on the feasibility of providing the requested resources. The Breast and Ovarian CFRs also has a publications working group that oversees all issues associated with publications.

NHLBI has a DCC. The DCC for the LAM Registry performs its daily operations based on direction provided by its steering committee, data and safety monitoring board, and the NHLBI program office. In addition, a tissue repository committee provides direction to the DCC in regard to biological specimen distribution.

Lessons Learned

Many of those interviewed indicated that when discussions with a medical facility about becoming a participating collection site first begin, it is most productive to talk to pathologists and surgeons rather than administrators. That is, it is important to have "buy-in" up front from the people who will be directly working with the repository. It is also important to have someone involved from the beginning that understands every aspect of the process. Ultimately, it is necessary to establish good working relationships with all levels of collection site staff.

CHTN Eastern Division suggested caution when setting up collections from institutions that are already collecting tissue for other repositories—not only because of competition for specimens, but to minimize redundancy resulting from a specimen from one tissue source being divided up between different repositories. Researchers may unknowingly receive redundant samples if they have submitted requests to multiple repositories.

BBI, which operates the NHLBI repository, suggested that it is important for the repository to be involved in the design phase of a research effort. Storage experts can help determine the best procedures to use and can be helpful in identifying correct equipment, proper shipping techniques, and labeling.

Good communication between the repository and collection site was also considered vital. At CHTN Eastern Division, collection site personnel function as an extension of CHTN staff and are integrated into repository processes. There are contractual requirements for monitoring, reporting, and interaction, and there is often daily contact between CHTN and collection site staff. Ardais staff are in continuous contact with collection site staff, and formal meetings are held on a regular basis. GCI has one full-time staff member whose sole responsibility is to communicate with collection sites. Establishing and maintaining close working relationships with surgeons, pathologists, nurses, and other relevant staff at the collection sites is a **best practice**.

Repository Model

Banking Versus Prospective Collection

Most of the repositories evaluated did both prospective collecting of specimens and banking of specimens. Philadelphia Familial Breast Cancer Registry, NHLBI, AFIP, and the UAB Breast and Ovarian SPOREs are only involved in banking. Both of the industry repositories, Ardais and GCI, are primarily involved in banking but have done some prospective collecting. CHTN primarily conducts pro-

spective collection and distribution of biospecimens and does limited banking. This prospective procurement model enables CHTN to closely tailor specimen preparation to individual researcher requests and needs. Combining banking to collect and maintain a ready supply of tissue with prospective collection to meet researcher needs is a **best practice**.

Centralized Versus Decentralized

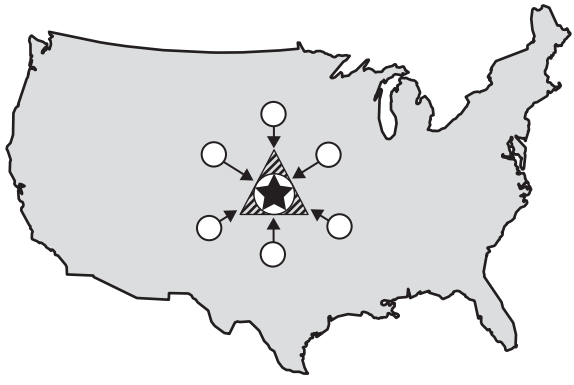
CHTN, EDRN, the Breast and Ovarian CFRs (of which the Philadelphia Familial Breast Cancer Registry is a member), and University of Pittsburgh HSTB are decentralized resources deployed through a distributed physical network of geographically dispersed tissue centers that are coordinated and supported by a centralized bioinformatics and data management system networked across the country (see Figure 6.1, A). Their specimens are stored at geographically dispersed sites. CHTN has six regional divisions, located at academic medical centers that collect specimens at those centers and from satellite sites that include community hospitals, eye banks, and organ procurement organizations. Specimens are stored for short periods of time (usually four to six weeks) at each regional site until they are distributed to researchers. The data and information regarding these specimens are maintained in a centrally located bioinformatics and data management system that is accessible by members of the repository network. Each collection/storage site also maintains its own bioinformatics and data management system that links to the centralized system. The bioinformatics systems for CHTN, EDRN, and University of Pittsburgh HSTB are only accessible by repository personnel. Members of the Breast and Ovarian CRFs can upload data to the bioinformatics system, but only staff at the Informatics Center at the University of California, Irvine, have access to download information.

NHLBI, AFIP, Ardais, and GCI have a decentralized collection model but maintain their storage and distribution of specimens and their bioinformatics system at one physical location (Figure 6.1, B).

Figure 6.1
Centralized and Decentralized Repository Models

A. Decentralized Collection and Storage with Centralized Bioinformatics/Data Management

B. Decentralized Collection with Centralized Storage and Bioinformatics/Data Management



C. Centralized Collection, Storage, and Bioinformatics/Data Management

TARP also has a decentralized collection model with the bioinformatics system and storage maintained at one physical location, but it sends its tissue microarrays to CHTN Eastern Division for distribution to users. Duke University Breast SPORE, Mayo Clinic Prostate SPORE, and the UAB Breast and Ovarian SPOREs have centralized collection, storage, and bioinformatics systems and data management (Figure 6.1, C). These centralized bioinformatics systems have various levels of access. For example, Ardais's system is directly accessible by its customers, but the bioinformatics systems at all of the SPOREs and at GCI are accessible by repository personnel only.

Costs

Repository Costs

Most of those interviewed did not know the cost per sample for their repository to collect, process, store, and distribute tissue. CHTN estimates that it costs approximately $60 per sample shipped. This includes costs involved in collecting, processing, storing, and distributing each specimen. TARP also estimates that it costs $60 to produce and distribute each slide from a tissue microarray. The UAB Breast and Ovarian SPOREs estimate that it costs between $120 and $150 for tissue and data collection per patient, and has an annual operating budget of $80,000 to $100,000 to cover tissue collection and research services. The annual budget for the repository at AFIP is $3.2 million. Likewise, University of Pittsburgh HSTB estimates that it currently receives $2 to $3 million annually either directly or indirectly through grants, sponsored research agreements, and foundation/institutional support for its tissue bank and related informatics program. Ardais collects detailed activity-based costing information for all cases and samples accrued but declined to share that information publicly. GCI also declined to share this information. In many cases, the cost of running the repository was not well known, because the costs are split among multiple grants covering different portions of various personnel's salaries.

Costs to Researchers

CHTN charges academic researchers $20 per sample and charges commercial researchers $60 per sample for the initial processing of the tissue (e.g., snap frozen, paraffin embedded). CHTN uses itemized pricing based on the level of work involved, adding a surcharge for tissue processing in addition to the initial processing (e.g., an H&E slide costs an additional $7, an unstained slide costs an additional $5, and a touch preparation costs an additional $4.50). CHTN is attempting to recover its tissue processing costs. TARP, also moving toward cost recovery, charges academic researchers $40 per slide (TARP first must buy its specimens from CHTN for $20, and then CHTN charges $20 per array for distribution). TARP charges commercial researchers $120 per slide. Tissue microarrays produced by commercial businesses can cost $150 to $200 per slide for 80 to 100 cancer samples, whereas TARP arrays contain smaller cores and a much higher density of tissue samples (300 to 500 cancers).

Philadelphia Familial Breast Cancer Registry charges $1 per microgram of DNA. AFIP attempts to recover some of the processing charges. For example, it charges $2.50 per H&E slide. Other types of tissue processing at AFIP can be as much as $200 a slide depending upon the complexity of the request.

University of Pittsburgh HSTB provides researchers at the university with a small amount of tissue for pilot projects with the understanding that grant proposals will include money in the budget for the repository. There are currently approximately ten to fifteen grants that support the repository's activities. CPCTR, of which Pittsburgh is one of four participating locations, has a set fee structure: $40 per set of samples (four standard 5-micron or two 10-micron slides), $50 for RNA or DNA analysis, and $100 for a frozen tissue specimen not to exceed 0.2 gram. Additional slides cost $3 for a standard 5-micron slide; $4 for 3- to 4-micron slides; $5 for 10-micron slides; $10 for an 11- to 24-micron thick section on a slide; $20 for a 25-micron or thicker section (placed in a tube for polymerase chain reaction [PCR] analysis); and $4 for a slide with an H&E stained section. All charges are tripled for commercial researchers requesting material.

EDRN, NHLBI, and Duke University Breast SPORE provide samples free of charge. Mayo Clinic Prostate SPORE samples are free, although there is a nominal cutting fee if the researcher wants the laboratory to make sections. Samples from the UAB Breast and Ovarian SPOREs are free to members of the SPORE at UAB and are $50 (plus shipping) to all external researchers, both SPORE and non-SPORE members.

GCI negotiates the price per slide under each contract, although standard fees apply. The company declined to give its exact pricing schedule. On research collaborations with academic or government scientists, samples are provided at or near cost or sometimes for free. Ardais declined to publicly disclose pricing but does provide its partner medical center researchers with samples at cost or less.

Although not often practiced, accurate determination of the actual costs of collecting, processing, storing, and distributing tissue samples combined with operating on a cost recovery basis (at least for the government and non-profit organizations) to financially sustain the repository is a **best practice**.

Developing and Adopting New Technologies

All the repositories evaluated claimed to constantly watch for new technologies to improve their processes. Some have regular meetings with staff to brainstorm the issue; others have more formal mechanisms, such as committees or workshops established to purposefully scan for improvements and new technologies.

Some of the repositories are actually involved in creating new technologies and techniques. TARP, for example, develops and promotes new tissue fixation and processing techniques. Duke University Breast SPORE developed a new surgical protocol to collect breast tissue because of increased difficulty obtaining sizable amounts of tissue given more focused breast surgeries. It developed a method of extracting a core from limited resection (e.g., lumpectomy) specimens without affecting the diagnostic ability of surgical pathologists.

University of Pittsburgh HSTB is developing technologies to improve the lifetime of specimens in storage. It has also developed a whole-slide imaging system that takes digital images of whole slides, compresses the files (10:1), and shares them over the Internet, allowing pathologists to evaluate samples without actually having the slide or microscope in front of them. Ardais developed new tissue handling and extraction methods that it supplies to the collection sites.

Continually assessing new technologies and creating a process flexible enough to develop and incorporate added-value technologies into the repository is a **best practice**.

Tracking of Sample Use

The majority of repositories track the number of samples distributed through their bioinformatics system.

Acknowledgments in Publications

All repositories request acknowledgment if their resource is used in research, although few have actual requirements or any form of enforcement. At the academic-based and commercial repositories, no acknowledgment is required, although someone from the repository often is listed as a co-author on the publication. Other forms of acknowledgment include mention in the methods section of the publication or in the acknowledgments section at the end of the publication. Most of the government repositories (CHTN, TARP, EDRN, the Cancer Family Registries, and AFIP) have stricter rules on acknowledgement. In each case, researchers must agree to the acknowledgment in order to receive specimens, and specific wording is suggested. For example, CHTN requires researchers to sign an Agreement for Use of Tissue to obtain samples, and part of that agreement suggests that a specifically worded acknowledgment be used in any resulting publication. EDRN requires acknowledgment and strictly checks for it when collaborators are up for review. AFIP provides a standard disclosure statement, which is detailed in AFIP

Regulation 360-1, "Publication or Oral Presentation of Papers of a Scientific, Technical, or Professional Nature."

Requiring specific acknowledgment of the repository and providing researchers with the specific language to use in publications is a **best practice** because it raises the visibility of the resource and may encourage future participation in and use of the resource.

Best Practices

1. Establish and maintain close working relationships with surgeons, pathologists, nurses, and other relevant staff at the collection sites. CHTN, Ardais, and GCI make concerted efforts to establish and maintain close working relationships with collection site staff.
2. Combine banking to collect and maintain a ready supply of tissue with prospective collection to meet researcher needs. CHTN, Duke University Breast SPORE, Mayo Clinic Prostate SPORE, and University of Pittsburgh HSTB are engaged in a combination of banking and prospective collection.
3. Accurately determine the actual costs of collecting, processing, storing, and distributing tissue samples to researchers, and operate on a cost recovery basis to financially sustain the repository. CHTN, TARP, AFIP, UAB, and University of Pittsburgh HSTB provided information about costs.
4. Continually assess new technologies and take measures to develop and incorporate new technologies into the repository. All the repositories evaluated are constantly evaluating new technologies to improve their processes.
5. Require acknowledgment of the repository and provide researchers specific language to use in publications to raise the visibility of the resource and encourage future participation in and use of the resource. Acknowledgment is required and specific wording is suggested by CHTN, TARP, EDRN, the CFRs, and AFIP. The remainder of the repositories request acknowledgment if their resource was used but do not require it.