The National Mesothelioma Virtual Bank (NMVB)

Project Report: September 01, 2010 – August 2014

Background:

The purpose of the National Mesothelioma Virtual Bank (NMVB) for Translational Research is to maximize the effectiveness of data and biospecimen collection for mesothelioma. The NMVB serves as a resource which allows researchers real time access to clinical data associated with tissue specimens from the registry, thus expanding scientific discovery and effective treatments to benefit the mesothelioma research and patient community. The NMVB is developed on well-established tissue banking models including the Cooperative Prostate Cancer Tissue Resource (CPCTR)[5-8] and the Pennsylvania Cancer Alliance Bioinformatics Consortium[11-12]. Drs. Becich, Dhir, Feldman and Melamed have collaborated on these efforts and have several publications together in the area of virtual tissue banks and the informatics tools required to make them scalable nationally[6-8, 12, 14, 15, 24, 25] . The experience and track record of collaboration between U Penn, U Pitt and NYU will ensure that the NMVB will provide large numbers of specimens with accurate quality control and standardized pathologic review, and detailed quality controlled outcome data to enable biomarker validation studies.

Methods:

I. Operations of the NMVB:

The PI at each site (Pass–NYU, Feldman–U Penn and Becich–U Pitt) is responsible for the local operations, including identification of cases from pathology records (by data managers or bank technologists), retrieval of tissue blocks and tracking of specimen inventory (by bank technologists, data managers, and/or histotechnologists), characterization of pathology material (by NMVB pathologists), extraction of clinical data from office and electronic' charts and electronic databases including hospital information systems and tumor registry databases (by medical abstractionists and clinical data managers), and finally data entry into a comprehensive database (by data managers). The data at each site are exported to a central database after de-identification. The specimens, however, physically remain at each site, resulting in a "virtual tissue bank". The administrative processes of the bank are handled by the central database personnel, who manage tracking of requests and queries to NMVB and oversee the application process. The "virtual tissue bank" model has been successfully used by two similar NCI supported cooperative resource, one focused on breast cancer, the Cooperative Breast Cancer Tissue Resource (CBCTR)[9-10], and another focused on prostate cancer, the Cooperative Prostate Cancer Tissue Resource (CPCTR)[5-8]. Thus, we have now been able to adapt and enhance the model for NMVB[14, 15]

II. Organizational Structure:

a) NMVB Steering Committee Roles and Responsibility:

This project is a cooperative mechanism with a governing NMVB Steering Committee (NMVB SC), composed of Drs. Becich, and Dhir from U Pitt; a patient advocate (Mary Hesdorffer from the Mesothelioma Applied Research Foundation), four members from accruing sites (Michael Feldman, MD from Abramson Cancer Center of University of Pennsylvania and Jonathan Melamed, MD/Harvey Pass, MD from NYU,); and 2 members from the CDC/NIOSH including the Program Coordinator. The role of the NMVBSC will be to oversee and guide NMVB's development and ongoing activities.

The NMVB SC can add additional members by a majority vote of the existing committee members. The committee meets in person (on average) at least twice a year. The committee holds monthly teleconferences and also as needed. The meetings are aimed at coordinating the activities of the participating sites, establishing new policies and priorities, and reviewing progress. At its initial meeting, and at subsequent anniversaries of that meeting, the Committee will elect a chairperson (who cannot be the CDC Program Coordinator). The Chair will be responsible for coordinating the Committee activities, for preparing meeting agendas, and for scheduling and chairing meetings. Dr. Becich is the current chair of this committee.

The Steering Committee acts as the governing body of the NMVB developing operating policies, which must be implemented at each participating site. NMVBSC has approved a Manual of Operations (see appendix A) for establishing uniform procedures to accession, process, and distribute tissue, uniform quality control methods and rules for access to the clinical and outcome data associated with the accrued cases. The Steering Committee will determine priorities for applications' final approval based on the recommendation of the Research Evaluation Panel (REP, see http://www.mesotissue.org/REP.html). Steering Committee review of operating procedures of the participating sites will be performed in order to insure that they are compatible with the overall goals and policies of the NMVB, and the CDC/NIOSH, to define specific quality control and tissue processing procedures, to establish procedures for effective communication and other network policies as needed.

The CDC Program Coordinator's role will be to coordinate, assist, and facilitate, but not to direct the activities of NMVB. The Program Coordinator will attend and participate as a voting member of the Steering Committee (CC). The Program Coordinator will act as a resource for information about CDC activities and will advise on the acceptability of the SC policies to the CDC/NIOSH. The Program Coordinator may review the activities of awardees for compliance with operating policies developed by the Steering Committee. The CDC/NIOSH may add others to the Steering Committee and invite guests to the face to face meetings.

Any disagreements that may arise on scientific/programmatic matters (within the scope of the award) between award recipients and the CDC/NIOSH may be brought to arbitration. An arbitration panel will be composed of three members: one elected by the coordinating committee (with the CDC Program Coordinator not voting) or by the individual awardee in the event of an individual disagreement, a second member selected by the CDC/NIOSH, and the third member selected by the two prior selected members. This special arbitration procedure in no way affects the awardees' right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR Part 50, Subpart D and HHS regulation at 45 CFR Part 16.

b) Research Evaluation Panel (REP) guides NMVB utilization:
The REP is initially composed of the PI of the NMVB, Michael J. Becich, MD PhD, Dr. Joseph Testa, PhD of Fox Chase Cancer Center, Dr. Brooke Mossman, PhD from University of Vermont, Michele Carbone from the University of Hawaii, a patient advocate, Courtney Broaddus University of California, San Francisco Chief, Division of Pulmonary and Critical Care Medicine San Francisco General Hospital and Ainsley Weston, a designee of the CDC under the cooperative mechanism guiding this proposal. Dr. Becich will Chair the REP. Drs. Mossman, Carbone, and, Testa are respected members of the mesothelioma research community and responsible for determining the importance of the proposed studies, the areas of weakness that require improvement, and for developing the recommendation to the Coordinating Committee. The REP review will be scientifically rigorous, but the written review does not need to result in a lengthy document. Since the written review will be primarily for internal documentation and to guide discussions with the investigators, it can even be in 'bullet' form if it makes the preparation easier.

The REP considers these factors:

- Importance: What is the importance of the basic question(s) being addressed, without respect to study design problems?
- Areas Requiring Improvement: Identify weaknesses and list recommendations for modifications; and

Decision/Recommendation:

- The study should receive requested biospecimens(tissue and data, or TMA)
- The study should receive requested biospecimens if the identified weaknesses are corrected, or
- The study should not receive NMVB biospecimens

We have identified a statistician, Roger Day, PhD, to work with the REP to provide input on the statistical veracity/feasibility of the study proposed by the investigator if recommended by the REP during review of requests from researchers. \To date the REP has received over twenty research requests and all but one has been unanimously approved. This has all been handled to date by e-mail coordinated by the U Pitt team.

c) NMVB Working Group
Each site has designated specific personnel to participate in monthly NMVB Working Group meetings for the purpose of continuing to monitor and increase accruals to the resource; discuss Letters of Intent 'in-process';

reporting requirements, data collection and entry, provide administrative updates and a forum for questions and answers.

III. Human Subjects Protection: Regulations and Informed Consent:

The specimens and information collected by the NMVB are used for human subjects research and all applicable laws and regulations as well as ethical requirements are observed. While all specimens and clinical data are coded for de-identification purposes, a link to the participant/subject is maintained for the purpose of ongoing follow-up, and therefore the local sites and their protocols for handling of NMVB materials and information have all required and obtained full board approval from the local Institutional Review Boards (IRBs). Each of the sites maintains its own database of specimens and clinical and follow-up information in a secure manner, thus assuring local control of patient confidentiality. Each site strips patient identifiers from data that is provided to the central database ensuring that only de-identified data exists in the overall resource, and that only de-identified and HIPAA compliant data linked to specimens may be provided to investigators. In the case of prospectively collected specimens and data, all sites obtain written informed consent before collecting patient specimens or data for the resource. Researchers using the resource still need to obtain IRB approval at their own institutions for each project that uses NMVB material. Because data is de-identified, most projects require only an expedited IRB review. Local sites are all in compliance with their institutional HIPAA policies.

a) Description of proposed involvement of human subjects: There are two types of involvement of human subjects and their tissue and blood samples in this proposal. The Tissue Resource has IRB approval for collecting tissues using both these mechanisms.

b) Obtaining tissues from patients with consent for tissue banking:These are patients who have signed the tissue banking consent form, which is a form separate from the surgical consent form.This allows these tissues to be banked and stored with appropriate patient identifiers. The signed consent form also gives the Health Science Tissue Bank (HTSB) the ability to extract additional information and data from the currently existing medical record archives. The signed consent form also provides the HTSB the ability to obtain follow-up data, if and when necessary. The tissue resource has designed this consent form with extensive input from the clinical colleagues and the Institutional Review Board of the University of Pittsburgh. The consent form currently utilized allows us to include all patients who present to the participating University of Pittsburgh Medical Center (UPMC) Health System institutions.

c) Documentation of Consent: The consent obtained in the physician's office by the nursing/ medical staff is a signed consent form. Copies of this consent form are faxed to the health science tissue bank and sent via interoffice mail to the resource and stored. In addition, a copy of this consent form is made a part of the patient's clinical records.

d) Anonymized collections of tissues: This mechanism applies to tissue materials harvested from excess diagnostic patient materials, in which signed consent is not available. The IRB approval for this tissue banking mechanism restricts the bank to collecting research tissues, to be used for research after appropriate diagnostic evaluation. These materials are stored with just the pathology report. This provides details about the disease process as well as basic demographic information. There is, however, no information available regarding patient identifiers available to the Resource as well as any data other than the pathology report. Some of the specimens to be evaluated fall into this category.

e) Research subject's rights and right to withdraw from the study**:** Patients have the right to choose not to take part in this protocol and are assured that refusal to participate will involve no penalty or loss of rights to which they are entitled. Patients may also withdraw from this study at any time without penalty or loss of other benefits to which they are entitled. At such time the patient decides to withdraw, a patient of their legal representative will need to contact in writing the NMVB or the Institutional Review Board for Biomedical Research. When the request for withdrawing a patient's samples from this study is received, all samples will be disposed of according to University and Federal Policy.

f) Risks to Subjects: The primary risks in the "Universal consent" lie in obtaining the blood sample. Our consent form states, "… If you are having a surgical procedure, you have been explained the risks and benefits of your surgical procedure for which there are existing intravenous lines in place to draw blood from; your blood sample will be drawn from this line. If no lines are in place, or if you are an outpatient volunteer, a needle-draw will be used. The needle puncture of your vein to obtain the blood sample may result in pain and soreness, bruising, and rarely infection. This procedure will be performed by individuals trained and experienced in obtaining blood samples so as to minimize these risks…" This standard language is included in all patient consent forms at UPMC-HS and adequately covers the physical risk involved in this program. The tissue material obtained from surgical excess tissues is a by-product of the surgical procedure. The risk is that of the surgical procedure. There is no additional risk because of the banking protocol.

We believe with the extensive knowledge our team has gained over the past 20 years of tissue banking that there are minimal other risks to the patients involved in these studies. The only other major concern is the confidentiality of patient information related to their disease and clinical information. We have a "best practices" philosophy for protecting patients who consent to have their materials included in the tissue resource and constantly refine and update our procedures to minimize risks. We have in place state of the art computer system and have an informatics infrastructure with multiple layers of fire walling to prevent inappropriate access to patient's confidential information.

The procedures we have in place for minimizing breaches in confidentiality include anonymization of all patient materials. Codification of all stored materials is performed and the "codes" are only available to the tissue bank team. Investigators using materials and requesting additional information on a sample will do this via a pathology tissue bank "honest broker" (someone not involved as a collaborator in the study who has administrative access to the database). Firewalls, security procedures and physical security measures (high security locks and limited physical access methodologies) are employed to ensure confidentiality of data. The materials obtained from our organ procurement agencies are also stored and provided for research using the above protocols to help safeguard confidentiality.

Computer terminals that have access to the NMVB database are password protected and automatically locked from user access after 15 minutes of inactivity. Currently, the clinical data is linked with patient identifiers however a new version of the database is undergoing beta testing and is designed to separate patient identifiers from the clinical data itself. Access to be identifying information would then be available only to the research team. The offices for the database manager, biostatistician and programmer are secured each evening and patrolled by the hostile security department. All hard copy of research records are locked in one of two dedicated, secured filing cabinets within our administrative offices.

The database resides on a secure hospital server that undergoes nightly backup. Access to the database is limited to the database manager, biostatistician, database programmer and investigators. The database manager accesses the database from within the department offices. Data quality is monitored regularly during weekly meetings. At these meetings, ongoing improvements the database are discussed and new concerns or issues related to the database are addressed. The primary biostatistician, database manager and database representative attend these meetings. Approximately every other year, a random sample of 50 to 100 records is identified from the database for quality assurance purposes. The hospital medical records are then requested and re-entered into an empty database. A detailed point-by-point comparison is then made to the actual data in the database.

IV. Biospecimens Collection:

a) Prospective Case Collection at NYU/U Penn/U Pitt: Prospective case collection will continue to occur at a new case accrual rate in excess of 80 cases per year at the four sites (approximately 20 cases per site/yr). We are attempting to collect excess material from these surgical resections for paraffin blocks and as much material as possible for fresh frozen tissue. We also collect blood and urine and process the blood into serum, plasma and buffy coat (for genomic studies). Prior cases that go back for second surgery for metastatic disease that are already consented will also be available for collection. The rate of metastatic surgery is unknown at the current time. These consented cases will also be cross checked with our historical paraffin material already contributed to the NMVB project to find any overlap so that a more complete data collection on these historic paraffin cases can be obtained for cases we have already contributed.

b) Retrospective Case Collection at NYU/U Penn/U Pitt: All sites now have a HIPPA waiver authorization to obtain clinical outcomes information on the over 1000 additional paraffin cases that we have already verified have available material for NMVB at the three collection sites. Given the short median survival of mesothelioma patients (<1 yr) and the age of most our currated paraffin cases (>3 yr old), the IRB has granted us a HIPPA waiver so that we may get clinical outcome data.

c) Control samples of other thoracic malignancies: Controls will be required for comparison studies. Penn's Thoracic oncology group as well as U Pitt's Lung SPORE collects over 400 lung carcinomas per year. These thoracic malignancies and the associated biosamples will be made available to the NMVB for investigators seeking to undertake early detection studies using biomarkers of disease. In addition, at U Pitt there is a donor lung collection that can be made available upon request.

d) Biospecimen and Data Quality Assurance (QA)/Quality Control (QC): Each biospecimen in the repository has undergone individual pathology verification. In addition, slides created for QA/QC at the time of triage of the specimen are stored along with whole slide images of appropriate areas. We also perform molecular quality testing as needed using the Agilent bio-analyzer for evaluating RNA integrity (18S/28S ribosomal RNA ratios).

Data managers and tumor registrars specified in the honest brokers plan at each site review and extract clinical data for NMVB cases. The data is accrued in part from the tumor registries of the hospitals. Additional in-depth clinical information is obtained by direct review and extraction of information from patient charts, from consultation with outpatient referring physicians, and from direct patient questionnaires/interviews as specified in our IRB and consent. Staff perform quality assurance audits of the clinical data at regular intervals at each site (resulting in independent repeat review of 10% of the material), and these audits are thereafter reviewed by the overall resource quality assurance manager.

V. Resource Sharing Plan

The CDC has a policy of requiring public release in a timely fashion of the rich data sets generated during these projects. Access to these data sets will benefit the entire research community. Drs. Becich, Dhir and the NMVB team have strong track records of sharing data. Some notable examples include:

I. Sharing of full gene expression datasets for expression profiling experiments through the SPOREs program, the Director's Challenge effort and the Pennsylvania Cancer Alliance Bioinformatics Consortium.
II. Tissues from the University of Pittsburgh have been shared with over 47 other investigators through the Cooperative Prostate Cancer Tissue Resource as well as over 87 other collaborators (outside of UPCI and U Pitt) through their Health Sciences Tissue Bank.
III. The Cooperative Prostate Cancer Tissue Resource and Pennsylvania Cancer Alliance Bioinformatics Consortium.
IV. The team has also made cDNA and RNA samples from expression array studies available to researchers from outside institutions through caARRAY and the PCABC website.

VI. Data Sharing Plan:

As stipulated by the RFA and according to NIH and CDC policy, each funded institution will make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication. Drs. Becich, Feldman, Melamed and Pass have long track records of sharing reagents and data with qualified researchers. Tissue samples have been shared with multiple institutions including the Food and Drug Administration. Tissue microarrays developed by the have been shared dozens of researchers nationally.
In the framework of the consortium, we would propose to share data and resources in the following manner:

I. Clinical and pathology parameters of our patient cohort will be provided in a de-identified fashion through our website as described in our Manual of Operations
II. To facilitate inter-institution collaborations we will provide de-identified list of the clinical/pathology parameters of our patient cohorts and pending approval from our respective tissue usage committees release samples to qualified collaborators based on review by the Research Evaluation Panel.
III. Data will also be deposited on a secure web-accessible data warehouse such that qualified participants can readily access the information. Infrastructure is in place for this as demonstrated by the PCABC and the NMVB databases. Finally all data will be shared via caBIG compliant mechanisms as they mature so they can broadly be shared with the cancer research community as the NMVB database is a re-architected tool initially based on caTISSUE CAE and will employ other caBIG tools in the future.
IV. Sharing and release of data from the NMVB will be timely, involve raw as well as analyzed data sets and our plan will be in collaboration with the CDC and NIOSH who will participate in the Steering Committee governing the NMVB.

VII. Intellectual Property: Research Resources and Intellectual Property Plan:

The University of Pittsburgh is a public institution devoted to teaching, research, and service. One aspect of its mission is the application of knowledge to problems of general public interest. Technology transfer, as a beneficial outcome of teaching and research, is an application of knowledge that responds to many societal needs. The University recognizes and supports technology transfer and intellectual property development activities as an integral component of its mission, and asserts that the guiding principle governing the conduct of these activities shall be the service of its mission. The objectives of the technology transfer and intellectual property development activities of the University shall be: to facilitate the efficient transfer of knowledge and technology from the University to the private sector in service of the public interest; to support the discovery of new knowledge and technology and to attract resources for the support of University programs; to provide services to the University faculty and staff to facilitate their efforts to carry out the University's mission; and, to promote local and national economic development.

It is the University of Pittsburgh's policy that inventions made by its employees are owned by the University. Once a disclosure has been made to the Office of Technology Transfer, the office works with the inventor to determine the most appropriate protection and commercialization strategy. We follow the NIH Guidelines for Research Tools – namely, if the disclosure covers a form of research tools, we prefer to license the tools on a non-exclusive basis. In cases where the tool would not make it to the marketplace unless an exclusive license is provided, we require our exclusive licensee to allow us to provide the tools to other research institutions or to make the tools widely available to the research community.

If the strategic partnership encounters difficulties, we will consult the CDC and NIOSH for assistance. The NMVB consortium's strategic partnership has provided draft copies of MTA's and Intellectual Property agreements between collaborating institutions and letters of collaboration countersigned by all relevant parties. This document describes the IP issues and provides applicants with all rights necessary to perform activities required by the research plans. The NMVB strategic partnership recognizes that certain research activities may result in inventions and that the Universities are entitled to protect such inventions through patenting and licensing activities in accordance with the Bayh-Dole Act, 35 USC § 200 et seq. and the implementing regulations, 37 CFR Part 401 ("Bayh-Dole Act).

Results:

Summary of NMVB's Accomplishments (09/01/2010 to 09/29/2014:

NMVB has collected 259 cases in its shared repository available for research and is queryable from the website (www.mesotissue.org). During the period (09/01/2010 – 09/29/2014) the University of Pittsburgh has collected 200 prospective and 59 retrospective cases. At each institution, surgical resected specimen along with blood products (serum, plasma, RBC, buffy Coat, whole blood) have also been collected from prospectively banked mesothelioma patients. In addition, The NMVB is also providing three distinct tissue microarray for biomarker testing from each of the collaborating institutes. We have implemented the open access Tissue Microarray Data Exchange Specification[23, 24] which allows the NMVB to share and merge data with other tissue microarray (TMA) files or link to data contained in external biological databases[24]. This makes the NMVB research resources unique and extremely valuable. The users of NMVB can utilize the web interface for public query of summary data on the cases that were available, to prepare requests, and to receive tissues. Most importantly, from 09/01/2010 – 09/29/2014 during the period of suspension of funding we received 20 specimens request through NMVB letter of intent (LOI) process that have been reviewed by the REP, approved by the Steering Committee and shipped to the investigators. We have provided 579 serum samples, surgical resected mesothelioma specimens (Fresh Frozen 109 and paraffin tissue 566) and 118 TMA slides. This is quite an extraordinary accomplishment for the NMVB team which continues to have an impact on the broader community.

Tissue Microarray for Mesothelioma Research Community:

Both New York University and the University of Pittsburgh have each provided a Tissue Microarray and the University of Pennsylvania has designed four TMA's to facilitate identification of markers differentially expressed in primary mesothelioma lesions as well as metastatic lesions. For these six TMA's, either Microsoft excels files or whole slide images are readily available to download directly from the NMVB website.

NMVB Database:

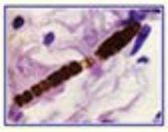
The NMVB is a virtual biospecimen registry with robust biomedical informatics support to facilitate basic science, clinical, and translational research. It protects patient privacy by disclosing only de- identified data. The database provides researchers real-time access to richly annotated specimens and integral information related to mesotheliomas.

The NMVB database architecture is based on three major components: (a) common data elements (based on CAP protocol and NAACCR standards), (b) clinical and epidemiologic data annotation, and (c) data entry and query tools. These tools work interoperably to standardize the entire process of annotation. The NMVB tool is based upon the caTISSUE Clinical Annotation Engine, developed by the University of Pittsburgh in cooperation with the Cancer Biomedical Informatics Grid (caBIG, https://cabig.nci.nih.gov/tools/cae). This application provides a web-based system for annotating, importing and searching mesothelioma cases. The underlying information model is constructed utilizing Unified Modeling Language (UML) class diagrams, hierarchical relationships and Enterprise Architect (EA) software.

The workflow for entering data into the virtual bio-repository has been as follows:

1) The local (physical) tissue bank identifies cases appropriate for inclusion in the Consortium's virtual bio-repository (warehouse).
2) The local (physical) tissue bank pre-processes data on these cases. The most important component of pre-processing is de-identification. All de-identification occurs at the local banks. No identifiable data is sent to the virtual bio-repository (warehouse).
3) De-identified data are entered into the warehouse through a web site. The data entry web site uses dropdown lists of values and other user interface features to constrain the data entry so that all values conform to the established common data elements.
4) The local (physical) banks label each case with de-identifiers. This number is used to link the information in the warehouse to the cases in the local banks. The linkage codes are stored locally, using appropriate electronic and physical safety measures. Only the local banks have access to these linkage codes.
5) The warehouse contains very minimal demographic data and complies with all HIPAA requirements.
6) Access to the data entry application is controlled by user name and password. Cases entered into the virtual bio-repository are scanned for logical errors (e.g. first recurrence before diagnosis etc.).
   The NMVB Project required a mechanism for making Mesothelioma cases searchable via a web interface. The University of Pittsburgh project team met this requirement using the NMVB Data Tool. The NMVB tool, available at the project website (https://www.data.nmvb.org/mvb) offers the following functionality:
   - A summary view of the data in the database, available to the general public (See Figure-1).
   - A query interface (see Figure 2) that allows a user to specify query parameters using any of the data elements in the system and returns a statistical summary of the cases and specimens that match the query. The results page shows the number of cases, specimens and blocks in the database that match the query criteria of the investigator as well as general statistics on a limited number of data elements. (Results that look just like the ones shown in **Error! Reference source not found.**, but the numbers indicate the number of matches.) This view islikely to be most valuable to investigators who are preparing a grant application or otherwise evaluating whether the resource has sufficient biospecimens to fulfill particular experimental requirements.
   - A query interface for authorized users (See Section 4.12 for information about user accounts and authorization.) This user interface is similar to the publicly available one (See Figure-2) but the results are displayed in more detail, as individual records. By default the system displays a patient's gender, race, and vital status along with data about asbestos exposure and the site and histology of the specimen(s) in the repository. An investigator may redefine that view to see a display of any data of interest.
   - A data entry interface for authorized users. This interface, to be released as part of the NMVB 2.0 software application at the end of March, 2008, allows an Honest Broker at one of the collection sites to enter all of the de-identified data that is stored in the central NMVB repository. This interface allows no free-text data; rather, by displaying the standard values for each common data element the system ensures that the data standards are maintained. (See Figure-3)

National Mesothelioma Virtual Bank



Home Statistical Query **Username:** **Password:** Login

Virtual Bank Totals:

Number of Cases	1166	100%
Number of Specimens	1416	100%
Number of Blocks	1147	100%

Specimen Availability

Lymph Node Cases		
Paraffin	27	4.19%
Bulk Frozen	0	0%
Fresh Frozen	1	0.16%
Glass Slides	9	1.4%
None	607	94.25%
Metastatic Cases		
Paraffin	29	4.45%
Bulk Frozen	0	0%
Fresh Frozen	7	1.08%
Glass Slides	16	2.46%
None	599	92.01%
Resected Cases		
Paraffin	362	24.88%
Bulk Frozen	108	7.42%
Fresh Frozen	360	24.74%
Glass Slides	315	21.65%


National Mesothelioma Virtual Bank
Home
Statistical Query
Username:
Password:
Login
Clear
Get Statistics
Case
Disease Information
Epidemiology Data
Anatomic Pathology
Genotypes Data
Staging
Therapy
Therapy
Therapy Type
Surgery
Radiation therapy
Chemotherapy
Hormone therapy
Therapy Months After Diagnosis
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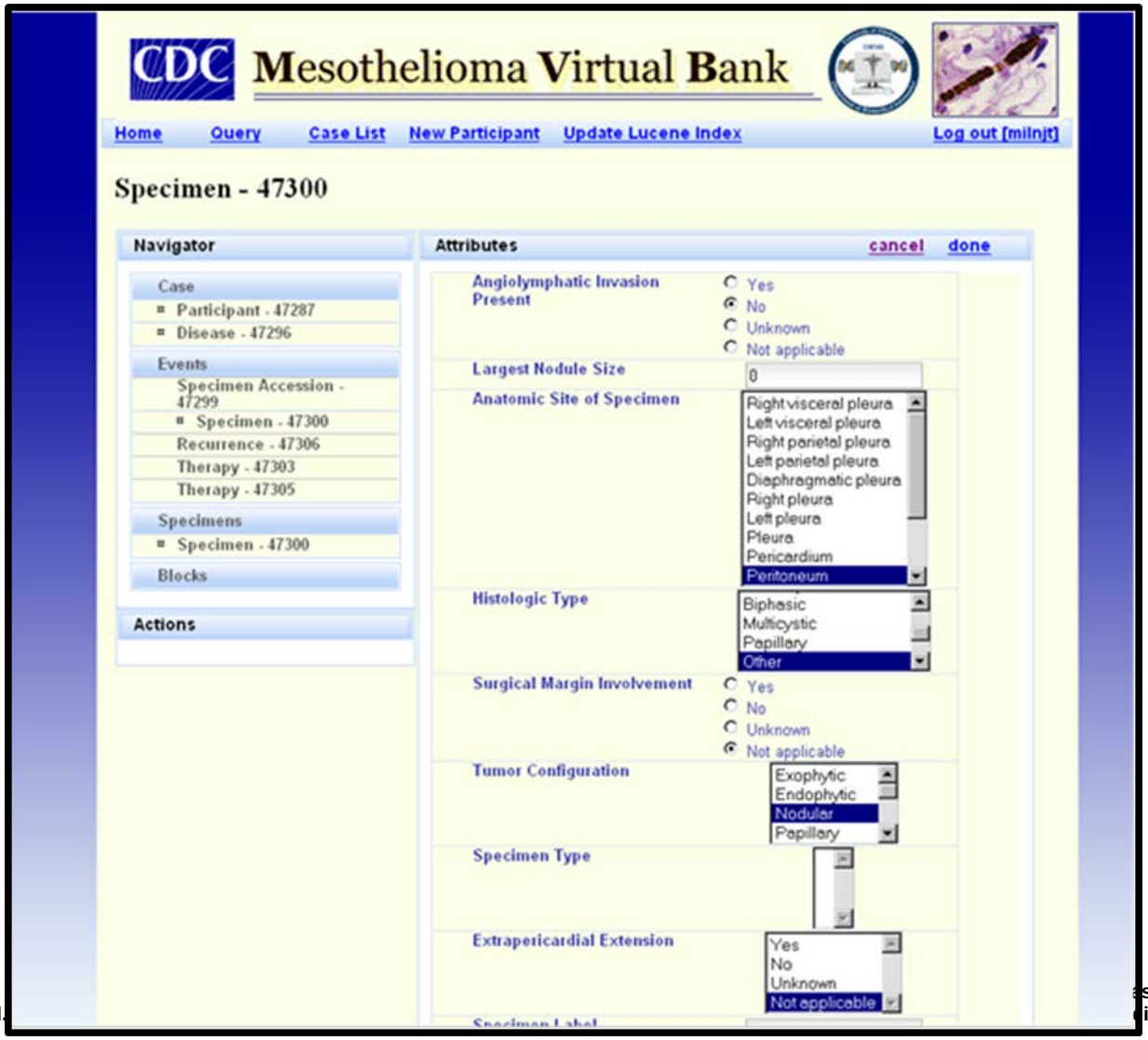

Figure 2. as they are collected. ived.

Marketing the Resource:

Marketing and outreach strategies targeted to the mesothelioma research community will: continue to

a) Publicize the availability of the NMVB to prospective users,
b) Solicit input from the research community about how to maximize the effectiveness of the NMVB
c) Inform the research community of advances facilitated by the NMVB

Advertising Methods: NMVB uses various media for advertising the availability of the tissues and services available to the research community. The list of methods will include, but are not be restricted to:

A. The NMVB website with links to the, e.g., NIH, NCI, OBBR, NCBI and CGAP websites: It is designed and hosted by the UPCI with input from the CDC and the NMVBCC. The website includes general information about the mesothelioma resource, information about the type of specimens available, a searchable database of the cases, and forms for making tissue requests and inquiries. Web Trends software is used to provide access-log analysis for the NMVB website. This software will continue analyze the log files created by the Web server and will provide invaluable information on how users access the Website. Web Trends will provide statistical information as well as graphs that show trends, usage, and much more. Customized reports are generated to compare specific activities among multiple time periods. These reports help to:

   - Measure both quality and quantity of visitors.
   - Count how many users visit the site daily and find out whether that number is growing or shrinking.
   - Learn which paths visitors follow when they browse our Web site.
   - Find out which countries, cities, and states the users connect from.
   - Determine the most active day of the week and hour of the day.

   Reports are automated so that they can be updated weekly, and stored in HTML on a Web server accessible to the Internet. The addresses of the reports will not be published beyond the members. The URLs will not be referred to by any publicly accessible Web sites.

B. E-mailings to potential users: E-mails are sent to investigators that have published articles in mesothelioma research in the recent past and cancer research coordinators. The e-mail addresses are available in the address for reprint requests, cancer research societies, and the NIH Reporter database. E-mails will also be sent to investigators that have received or applied for Meso Foundation research grant funding, have attended or presented at the Meso Foundation's annual International Symposium and/or are otherwise included in the Meso Foundation's database of approximately 300 mesothelioma-interested investigators. The e-mail addresses of pharmaceutical companies and other industrial enterprises will be obtained by web search and other methods. A mechanism to be deleted from any mailing list will be offered to each e-mail recipient.
   a) We have developed an e-mail contact list for the funded investigators in the area of mesothelioma
   b) We have developed an e-mail marketing list of hundreds of researchers who have published on mesothelioma from PubMed
   c) We actively update these lists and provide quarterly e-mails marketing NMVB
C. Word of mouth, especially at the Meso Foundation's annual symposium, the International Mesothelioma Interest Group's every other year meeting, and other research meetings.
D. Posters and podium presentations at research meetings, presenting scientific and practical aspects of the mesothelioma resource collection.*
E. Booths at research meetings, in conjunction with other NCI resources, or as stand-alone booths.

It will be the responsibility of the NMVB CC along with Meso Foundation to implement any outreach efforts, under supervision of the Coordinating Committee. Formal advertising for the NMVB resource began in March 2008 and will continue through 2016.

Discussion:

A. Outreach and Resource Development - Patient Advocates, Other Stakeholders: To accelerate scientific advances and ultimately benefit patients, the NMVB requires a model built on growth and sustainability. Developing and managing appropriate relationships with the public-at-large, the patient advocacy community, and other key stakeholders about the importance of this endeavor, enable prolonged support for this resource to occur. In this regard, the NMVB will interface with these populations including the underserved and minority populations to increase their understanding and appreciation for this essential resource. Increased education and awareness among those outside of the research community will allow for resource development activities, including the attainment of non-federal funds to support NMVB. The NMVB will utilize various approaches to interface with these populations. The goals of the outreach efforts will include: 1) awareness of the NMVB resource, 2) education about the function NMVB and how it is operated, 3) providing information about scientific advances facilitated by NMVB. 4) listening and learning from the affected communities about the disease especially through active participation at the International Symposium on Malignant Mesothelioma (Meso Foundation sponsored annual meeting).

The methods utilized to interact with the non-research community will include, but not be limited to:

In parallel to the website for the research community described above, information for a non-scientific audience will be maintained as part of the Meso Foundation's website. The layperson website will contain, in plain language, background information on tissue banks and specific information about the NMVB resource, including member organizations and updates on research projects supported by the resource. The website will include a number of downloadable educational tools. The website will also contain links to the websites of partnering mesothelioma science and advocacy organizations, and to other informational websites about mesothelioma.

1) Informational mailings – Letters and/or emails will be distributed to the various populations listed above. Content will be tailored to the target population to ensure that the information is clear and relevant.
2) Articles in society or foundation newsletters – Foundations that serve the mesothelioma community (e.g. Meso Foundation) will be asked to include an announcement that the NMVB is being developed in their newsletters. Regular updates regarding the NMVB and the research and researchers it supports will be prepared and published in their print and electronic newsletters as well.
3) Meetings or seminars – Groups interested in mesothelioma will be invited to host a representative of the NMVB for a lecture, which may provide background information about NMVB or updates on specific research projects.
4) Word of mouth.

B. Mesothelioma Applied Research Foundation/ NMVB Connection:

To date, Meso Foundation has funded over $7.6M in competitive research awards to 76 different projects. This is a significant event in mesothelioma research which is currently markedly underfunded based on the continuing increase in families affected by this fatal yet preventable disease. Meso Foundation also holds an annual research and advocacy symposium, called the International Symposium on Malignant Mesothelioma (see http://www.curemeso.org). This event will play a major annual role in promoting the collaboration between Meso Foundation and NMVB.

Together, with NIOSH, the NMVB consortium working in collaboration with the Meso Foundation will publicize the availability of this resource to prospective users; not only with a sound marketing plan but through extensive interaction with its members. This will allow us to effectively communicate effectively about the resource to the scientific community, and to the patients whose lives are affected by this deadly disease. Moreover, the NMVB cooperative group in collaboration with will seek additional resources in the form of collaborations, services, and funding to further the goals of the mesothelioma community by creating a model national resource for translational research.

There is a close connection between the NMVB and Meso Foundation funded investigators. Meso Foundation's funding and its scientific expertise will help promote and "subsidize" high level scientific use of the resource as follows: Meso Foundation encourages its funded investigators to utilize the NMVB in their research. The Call for Applications and grant advertising, as well as the grant application itself, includes a description of the NMVB and how it can assist investigators in their research. This is also be discussed at Meso Foundation's annual

Symposium (see above), which all Meso Foundation-funded researchers are required to attend, and which many other investigators attend as well. Following the careful, peer-reviewed scrutiny that Meso Foundation applies in awarding its grants, the NMVB provides facilitated access to the resource by Meso Foundation-funded researchers. They receive expedited review of requests to use the NMVB, and at no cost they have direct access to materials already in the bank, as well as enhanced collections from the main sites of materials not already in the bank which they need for their research. Meso Foundation will require its funded investigators who are using the NMVB to report on such use in their quarterly progress reporting.

C. Resource for the Clinical Science Community: Our NMVB cooperative group has established a process for qualified applicants to access information in the database and to request available samples for use in legitimate research. Together, with NIOSH, the NMVB consortium, working in collaboration with Mesothelioma Applied Research Foundation, will continue to publicize the availability of this resource to prospective users; not only with a sound marketing plan but through extensive interaction with other stakeholders including the International Insulators Union and representatives from the legal community, namely The Simons Foundation. This will allow us to effectively communicate about the resource to the scientific community, legal teams, and most importantly to the patients whose lives are affected by this deadly disease as well as to those tradesman and women who remain disproportionally susceptible.
Indeed, the Simons Foundation provided the financial support to establish the Mesothelioma Specialty Care Center at the University of Pittsburgh Cancer Institute's which provides an 'all-in-one' approach to patient care. A specialized nurse coordinator assists each mesothelioma patient by acting as a liaison to the various components of care; treatment plan, ontology, radiology, social services, insurance, scheduling appointments and providing follow-up.

Conclusion

The NMVB has exceeded all previously reported Specific Aims; met accrual targets, provided rare specimens with highly annotated data to over 20 investigators, advanced the body of knowledge through publications, expanded the network of affiliated academic health centers, and has been instrumental in bringing stakeholders together. The team of dedicated professionals associated with the NMVB is committed to continuing this important work.

Bibliography and References Cited:

1. Clausen KP, Grizzle WE, Livolsi V, Newton WA Jr, Aamodt R. Special communication. The Cooperative Human Tissue Network. Cancer 1989 Apr 1;63(7):1452-5.
2. LiVolsi VA, Clausen KP, Grizzle W, Newton W, Pretlow TG 2d, Aamodt R. The Cooperative Human Tissue Network. An update. Cancer 1993 Feb 15;71(4):1391-4.
3. Grizzle WE, Aamodt R, Clausen K, LiVolsi V, Pretlow TG, Qualman S. Providing human tissues for research: how to establish a program. Arch Pathol Lab Med 1998 Dec;122(12):1065-76.
4. National Biospecimen Network Blueprint - http://www.ndoc.org/about_ndc/reports/pdfs/FINAL_NBN_Blueprint.pdf
5. Cooperative Prostate Cancer Tissue Resource website - http://www.prostatetissue.org
6. Melamed J, Datta MW, Becich MJ, Dhir R, Orenstein, JM, Silver S, Fidelia-Lambert M, Kadjacsy-Balla A, Macias V, Walden PD, Bosland MC, and Berman JJ. The Cooperative Prostate Cancer Tissue Resource (CPCTR): A Specimen and Data Resource for Cancer Researchers. Clin Cancer Res. 2004 Jul 15;10(14):4614-21.
7. Patel AA, Gilbertson JR, Parwani AV, Dhir R, Datta MW, Gupta R, Berman JJ, Melamed J, Kajdacsy-Balla A, Orenstein J, Becich MJ, and the Cooperative Prostate Cancer Tissue Resource. An Informatics Model For Tissue Banks – Lessons Learned From The Cooperative Prostate Cancer Tissue Resource. NEED REFERENCE.
8. Patel AA, Kajdacsy-Ball A, Berman JJ, Bosland M, Datta MW, Dhir R, Gilbertson J, Melamed J, Orenstein J, Tai KF, Becich MJ. The development of common data elements for a multi-institute prostate cancer tissue bank: The Cooperative Prostate Cancer Tissue Resource (CPCTR) experience. BMC Cancer 2005, Aug 21;5(1):108
9. Cooperative Breast Cancer Tissue Resource website - http://cbctr.nci.nih.gov/index.html
10. Glass AG, Donis-Keller H, Mies C, Russo J, Zehnbauer B, Taube S, Aamodt R; Cooperative Breast Cancer Tissue Resource. The Cooperative Breast Cancer Tissue Resource: archival tissue for the investigation of tumor markers. Clin Cancer Res. 2001 Jul;7(7):1843-9.
11. Pennsylvania Cancer Alliance Bioinformatics Consortium website - http://pcabc.upmc.edu
12. Patel AA, Gilbertson JR, Showe LC, London JW, Ross E, Ochs MF, Carver J, Lazarus L, Parwani AV, Dhir R, Mohanty SK, Beck JR, Liebman L, Garcia FU, Prichard J, Wilkerson M, Herberman RB, Becich MJ and the PCABC. A Novel Cross-Disciplinary Multi-Institute Approach to Translational Cancer Research: Lessons Learned from Pennsylvania Cancer Alliance Bioinformatics Consortium (PCABC). Cancer Informatics 2007:3, 255-274 (2007). e-pub = http://la-press.com/journals.php?pa=abstract&content_id=272 and see appendix J.

13. NIH Roadmap websites - http://nihroadmap.nih.gov/ and http://nihroadmap.nih.gov/clinicalresearch/overview-networks.asp
14. Mohanty SK, Mistry AT, Amin W, Parwani AV, Pople AK, Schmandt L, Winters SB, Milliken E, Kim P, Whelan NB, Farhat G, Melamed J, Taioli E, Dhir R, Harvey I. Pass HI and Becich MJ. The development and deployment of Common Data Elements for tissue banks for translational research in cancer – an emerging standard based approach or the Mesothelioma Virtual Tissue Bank (in press, BMC Cancer).
15. Amin W, Pople AK, Schmandt L, Mohanty SK, Winters SB, Farhat G, Whelan NB, Milnes JT, Schneider A, Miranda L, Valdiviseo F, Feldman M, Pass HI, Melamed J, Dhir R, Parwani AV, Becich MJ. National Mesothelioma Virtual Bank: Standards Based Biospecimen and Clinical Data Resource to Enhance Translational Research. Submitted, BMC Cancer.
16. Fleming ID, American Joint Committee on Cancer., American Cancer Society., American College of Surgeons.: AJCC cancer staging manual, 5th edition. Philadelphia: Lippincott-Raven; 1997.
17. NAACCR Data Standards for Cancer Registries - http://www.naaccr.org/index.asp?Col_SectionKey=7&Col_ContentID=122
18. The CAP Cancer protocols: Checklist for prostate gland - http://www.cap.org/apps/docs/cancer_protocols/prostate04_pw.pdf
19. Winget MD, Baron JA, Spitz MR, Brenner DE, Warzel D, Kincaid H, Thornquist M, Feng Z: Development of common data elements: the experience of and recommendations from the early detection research network. Int J Med Inform 2003, 70(1):41-48.
20. The NCICB's Cancer Data Standards Repository (caDSR) - http://ncicb.nci.nih.gov/core/caDSR
21. Pass HI, Stevens EJ, Oie H, Tsokos MG, Abati AD, Fetsch PA, Mew DJ, Pogrebniak HW, Matthews WJ. Characteristics of nine newly derived mesothelioma cell lines. Ann Thorac Surg. 1995 Apr;59(4):835-44.
22. Abati,A., Sanford,J., Fetsch,P. and Pass,H. Detection of aneuploidy in mesothelioma cell lines by fluorescence in situ hybridization (FISH), Diagn.Cytopathol., *16:* 375-377, 1997.
23. Berman, J. J., Edgerton, M. E., and Friedman, B. A. The tissue microarray data exchange specification: a community-based, open source tool for sharing tissue microarray data. BMC Med Inform Decis Mak, 3: 5, 2003.
24. Berman JJ, Datta M, Kajdacsy-Balla A, Melamed J, Orenstein J, Dobbin K, Patel A, Dhir R, Becich MJ: The tissue microarray data exchange specification: implementation by the Cooperative Prostate Cancer Tissue Resource. BMC Bioinformatics 2004, 5(1):19.
25. Datta MW, Dhir R, Dobbin K, Melamed J, Becich MJ, Orenstein JM, Kajdacsy-Balla AA, Bosland MC, Patel A, Macias V, Berman JJ, and the Cooperative Prostate Cancer Tissue Resource. Prostate cancer in patients with low initial screening serum PSA values: Results from the Cooperative Prostate Cancer Tissue Resource. J Urol 2005 May, 173(5);1546-51.
26. The National Mesothelioma Virtual Bank website http://www.mesotissue.org
27. Dhir R, Patel AA, Winters SB, Bisceglia MA Swanson D, Aamodt R and Becich MJ. A multi-disciplinary approach to honest broker services for tissue banks and clinical data: a pragmatic and practical model (in press, Cancer).
28. Becich, MJ, Patel AA, Jukic DM. The digital future of histopathology: where we are today and where we are heading. The Bulletin of The Royal College of Pathologists July Issue 131(27-31) 2005.
29. Becich, M.J. Patel A.A. and Jukic D.M. A Diagnostic Virtual Microscope System for Whole Slide Robotic Imaging: The Value of Virtual Slides for the Practice of Pathology. Gu, J. and Ogilvie, R.W., Eds., Virtual Microscopy and Virtual Slides in Teaching, Diagnosis and Research, Taylor & Francis, Boca Raton, 2005.
30. Fine JL, Grzybicki DM, Silowash R, Ho J, Gilbertson JR, Anthony L, Wilson R, Parwani AV, Bastacky SI, Epstein JI, Jukic DM. Evaluation of whole slide image immunohistochemistry interpretation in challenging prostate needle biopsies. Hum Pathol. 2008 Jan 29; [Epub ahead of print].
31. Gilbertson JR, Ho J, Anthony L, Jukic DM, Yagi Y, Parwani AV. Primary histologic diagnosis using automated whole slide imaging: a validation study. BMC Clin Pathol. 2006 Apr 27;6:4.
32. Ho J, Parwani AV, Jukic DM, Yagi Y, Anthony L, Gilbertson JR. Use of whole slide imaging in surgical pathology quality assurance: design and pilot validation studies. Hum Pathol. 2006 Mar;37(3):322-31.
33. Clausen KP, Grizzle WE, LiVolsi V, Newton WA, Aamodt R. The Cooperative Human Tissue Network. Cancer 1989;63:1452-5.
34. LiVolsi VA, Clausen KP, Grizzle W, Newton W, Pretlow TG 2nd, Aamodt R. The Cooperative Human Tissue Network: an update. Cancer 1993;71:1391-4.
35. Grizzle WE, Aamodt R, Clausen K, LiVolsi V, Pretlow TG, Qualman S. Providing human tissues for research: how to establish a program. Arch Pathol Lab Med 1998;122:1065-76.
36. Grizzle WE, Sexton KC. Development of a facility to supply human tissues to aid in medical research. In: Srivastava S, Henson DE, Gazdar, A, editors. Molecular Pathology of Early Cancer. Washington, DC: IOS Press; 1999. p.371-83.
37. Qualman SJ, France M, Grizzle WE, et al. Establishing a tumour bank: banking, informatics and ethics. Br J Cancer 2004;90:1115-9.
38. Jewell S, Srinivasan M, McCart LM, et al. Analysis of the molecular quality of human tissue: an experience from the Cooperative Human Tissue Network. Am J Clin Pathol 2002;118:1-9.

NMVB Related and Supported Publications:

1. Amin W, Parwani AV, Melamed J, Raja F, Pennathur A, Valdevieso F, Whelan NB, Landreneau R, Luketich J, Feldman M, Pass HI, Becich MJ. National Mesothelioma Virtual Bank: A Platform for Collaborative Research and Mesothelioma Biobanking Resource to Support Translational Research, Lung Cancer International, vol. 2013, Article ID 765748, 9 pages, 2013. doi:10.1155/2013/765748.

2. Amin W, Srinivasan M, Song S, Parwani AV, Becich MJ. Use of Automated Image Analysis in Evaluation of Mesothelioma Tissue Microarray (TMA) from National Mesothelioma Virtual Bank. Pathology Research and Practice. 2014 February, 210(2) 79–82 PMID: 24359722.

3. Amin W, Kang HP, Egloff AM, Singh H, Trent K, Ridge-Hetrick J, Seethala RR, Grandis J, Parwani AV. An informatics supported web-based data annotation and query tool to expedite translational research for head and neck malignancies. BMC Cancer. 2009 Nov 13;9:396. PMID: 19912644 PMCID: PMC2780457.

4. Mohanty SK, Mistry AT, Amin W, Parwani AV, Pople AK, Schmandt L, Winters SB, Milliken E, Kim P, Whelan NB, Farhat G, Melamed J, Taioli E, Dhir R, Pass HI, and Becich MJ. The development and deployment of Common Data Elements for tissue banks for translational research in cancer - an emerging standard based approach for the Mesothelioma Virtual Tissue Bank. BMC Cancer. 2008 Apr 8;8:91. PMID: 18397527 PMCID: PMC2329649.

5. Pass HI, Lott D, Lonardo F et al. Asbestos exposure, pleural mesothelioma, and serum osteopontin levels. N Engl J Med. 2005 Oct 13;353(15):1564-73.

6. Zhang X, Shen W, Dong X, Fan J, Liu L, Gao X, Kernstine KH, Zhong L. Identification of novel autoantibodies for detection of malignant mesothelioma. PLoS One. 2013 Aug 19;8(8):e72458. doi: 10.1371/journal.pone.0072458. PMID: 23977302.

7. Newick K, Cunniff B, Preston K, Held P, Arbiser J, Pass H, Mossman B, Shukla A, Heintz N. Peroxiredoxin 3 is a redox-dependent target of thiostrepton in malignant mesothelioma cells. PLoS One. 2012;7(6):e39404. doi: 10.1371/journal.pone.0039404. Epub 2012 Jun 25.

Inclusion Enrollment Report

This report format should NOT be used for data collection from study participants.

Study Title: National Mesothelioma Virtual Bank Expansion: The "SPIRiT" of Collaboration

Total Enrollment: 1092 **Protocol Number:**

Grant Number: U24 OH009077-08

PART A. TOTAL ENROLLMENT REPORT: Number of Subjects Enrolled to Date (Cumulative) by Ethnicity and Race

Ethnic Category	Females	Males	Sex/Gender Unknown or Not Reported	Total
Hispanic or Latino	5	12	0	17 **
Not Hispanic or Latino	207	781	2	990
Unknown (individuals not reporting ethnicity)	44	100	2	146
Ethnic Category: Total of All Subjects*	256	893	4	1153 *
Racial Categories				
American Indian/Alaska Native	1	1	0	2
Asian	0	5	1	6
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	7	15	0	22
White	216	788	2	1006
More Than One Race	0	0	0	0
Unknown or Not Reported	28	76	**13**	117
Racial Categories: Total of All Subjects*	252	885	16	1153 *

PART B. HISPANIC ENROLLMENT REPORT: Number of Hispanics or Latinos Enrolled to Date (Cumulative)

Racial Categories	Females	Males	Sex/Gender Unknown or Not Reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	**0**	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0	**0**
Black or African American	0	0	0	0
White	5	5	0	10
More Than One Race	0	0	0	0
Unknown or Not Reported	0	7	0	7
Racial Categories: Total of Hispanics or Latinos**	5	12	0	17 **

The “Ethnic Category: Total of subjects” must be equal to the “Racial Categories: Total of All Subjects.”