Next Generation Cohort Studies and Biobanking: How Cloud Technology is Accelerating Translational Research

The California Teacher's Study (CTS) team are collecting and managing blood and saliva samples for future biomarker research

By James V. Lacey, Jr., PhD

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About the Author

Dr. Lacey is an Associate Professor in Cancer Etiology at the City of Hope and serves as Principal Investigator for the *New Biospecimens to Enhance Research in the California Teachers Study* project within the California Teachers Study. Dr. Lacey received his PhD from the Horace H. Rackham School of Graduate Studies of the University of Michigan. After completing a postdoctoral fellowship at the National Cancer Institute (NCI), Dr. Lacey was an Investigator in the NCI's Division of Cancer Epidemiology and Genetics from 2001 to 2009. He joined the faculty at City of Hope in 2009; his primary research interest is the epidemiology of breast, uterine, and ovarian cancers.

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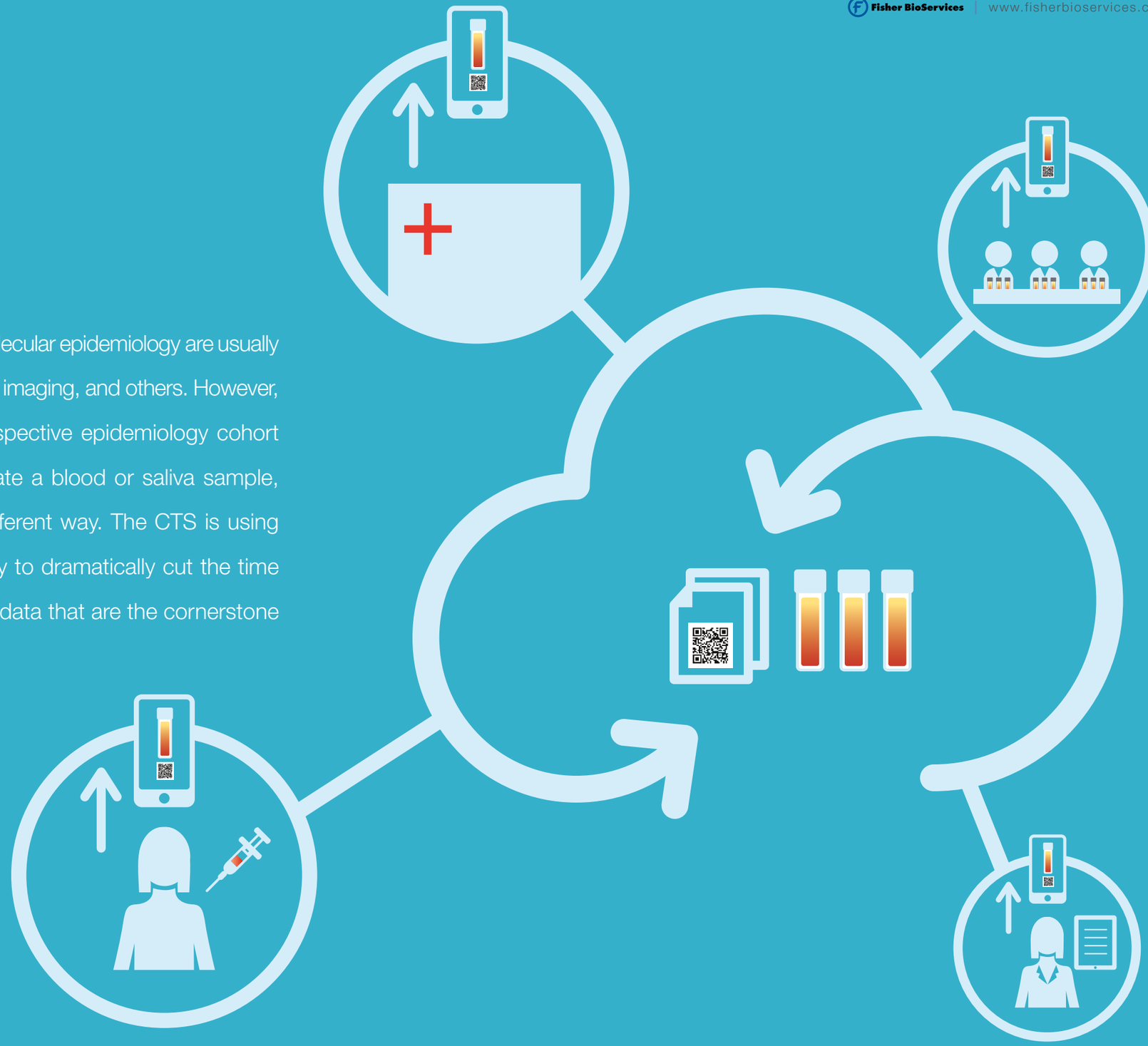
Introduction

Cutting edge technology and innovations in molecular epidemiology are usually associated with the lab: new assays, robotics, imaging, and others. However, the California Teachers Study (CTS), a prospective epidemiology cohort study that is asking its participants to donate a blood or saliva sample, is applying cutting edge technology in a different way. The CTS is using mobile devices and cloud-based technology to dramatically cut the time and cost of managing the huge amounts of data that are the cornerstone of epidemiological studies.



1 About the California Teachers Study

About the California Teachers Study

Female teachers have historically had higher rates of breast and other cancers, and in 1995, the State of California funded a study to investigate possible reasons. Eleven researchers from four California universities and research institutions partnered with the California State Teachers Retirement Systems (CalSTRS) to create the California Teachers Study (CTS). A total of 133,479 female active or recently retired public school professionals—primarily teachers and administrators—completed a questionnaire about their lifestyle, their family history, and their medical history.

CTS

133,479 current and former public school teachers or administrators

The CTS team includes investigators from four California institutions: City of Hope, the University of Southern California (USC), the University of California Irvine (UCI), and the Cancer Prevention Institute of California (CPIC). The CTS team is led by Dr. Leslie Bernstein, Director of the Division of Cancer Etiology and the Dean for Faculty Affairs at the City of Hope Comprehensive Cancer Center and Beckman Research Institute. Each site contributes specific expertise: Dr. Hoda Anton-Culver leads the team at UCI, Dr. Dennis Deapen leads the team at USC, and Dr. Pamela Horn-Ross leads the team at CPIC.

Questionnaires for CTS participants:

Health History + Factors related to breast cancer

The primary objective of the CTS was to investigate breast cancer, but the study has always maintained a broad emphasis on other cancers and on women's health overall. The baseline questionnaire in 1995 included detailed sections on diet, physical activity, smoking, height, weight, medication use, reproductive history, cancer screenings, family history, and environmental exposures. Four additional follow-up questionnaires have since been sent; in 1997-1998, a short questionnaire collected data on secondhand smoke, exposure to radiation, pregnancy history, and dietary patterns. In 2000-2001, participants were asked about stress, social support, memory and cognition, overall health, and medication use. The 2005-2006 mailing updated many of the items on the baseline questionnaire, while the most recent, in 2012-2013, included questions on sleep patterns, medical history, medication use, physical activity, vitamins and supplements, medical imaging and screening, and personal care practices. To date, the CTS team has published more than 100 research papers on breast, lung, ovarian, colorectal, uterine, thyroid, pancreatic, and other cancers. Numerous research projects on non-cancer outcomes, such as heart disease and stroke, are also underway.

2 New Biospecimens for New Research

New Biospecimens for New Research

A number of previous CTS projects have collected blood and saliva samples in order to compare DNA from women with cancer to DNA from a matched (same age, ethnicity, and other factors) group of women without cancer, to look for genetic differences. Because a person's genetic code—i.e., their germline DNA—does not change over time, genetic variations can be efficiently studied using samples that are collected from cancer survivors *after* their cancer has been diagnosed.

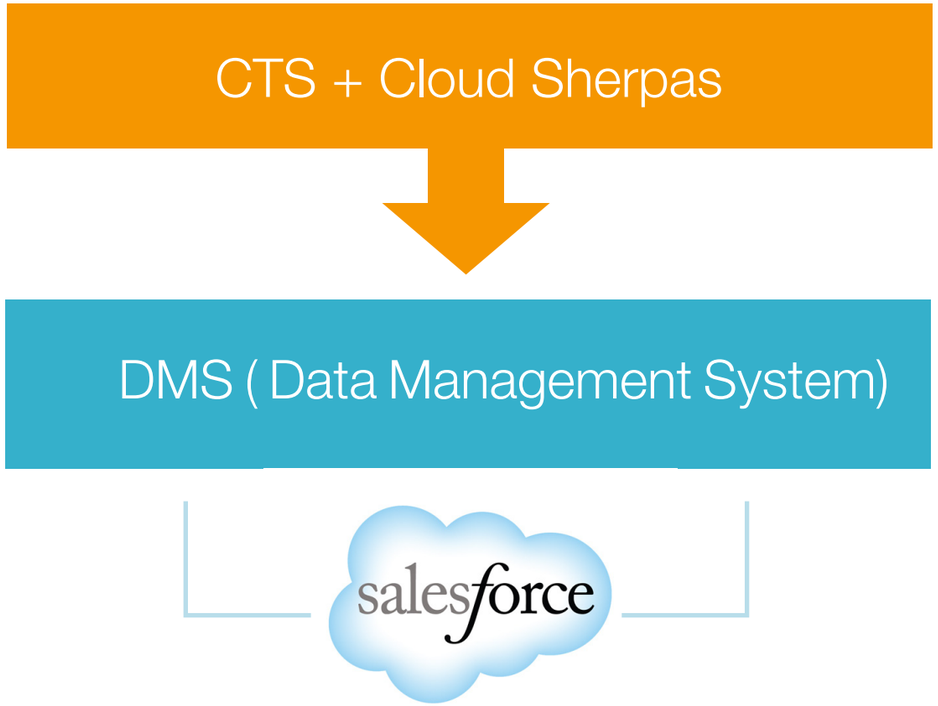
One exciting area of medical research is the search for new biomarkers that can be used to detect cancer earlier or to identify persons who are at higher risk of developing cancer. A biomarker is anything in the body that can be measured and that might indicate the presence of some biological phenomenon, such as disease or exposure to a particular agent. Pinpointing changes in hormone levels, certain proteins, or inflammatory markers that occur during the early stages of cancer can provide important clues about new avenues for early detection, prevention, and even treatment. However, biomarker research requires more than DNA. Finding and verifying (validating) biomarkers generally requires biospecimens that are collected *before* a person develops cancer. Thus, pre-diagnostic biospecimens are especially valuable, and the CTS is collecting large numbers of pre-diagnostic specimens to use in the search for cancer's early molecular and physiologic changes.

3 More than Just Drawing Blood – A Mobile App for Sample and Data Collection

More than Just Drawing Blood – A Mobile App for Sample and Data Collection

Collecting, storing, and tracking thousands of biospecimens and related data is no easy task. Most studies use standard desktop software to manage data and track study activities and convert participants' responses into analyzable data, a system that has not changed much in the past 30 years. Unfortunately, those methods are not very efficient, and they often do not scale up well enough to accommodate the needs of complex projects that collect thousands of samples in a short time.

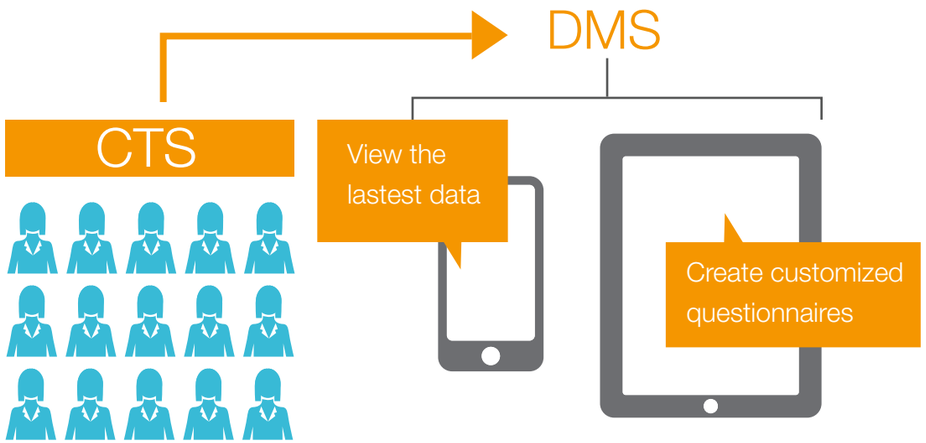
The CTS team realized that new approaches would be needed to manage, coordinate, and standardize the many moving pieces of this complex protocol. The "Aha!" moment for the team came when they realized that the core processes at play between research team members and potential specimen donors are remarkably similar to the process between sales personnel and their customers. Given this similarity, the CTS team developed a novel Data Management System (DMS) based on a sales-related platform, Salesforce.com.



Salesforce.com is a customer relationship management, or CRM system; CRM platforms are widely used in sales and other industries because they efficiently manage and track customer interactions and transactions. The CTS team worked with Cloud Sherpas, a cloud advisory and technology services company, to build the DMS on the Salesforce.com platform. The result was a system that manages the recruitment, scheduling of appointments, sample tracking, and other participant data in an integrated manner.

More than Just Drawing Blood – A Mobile App for Sample and Data Collection

Using the internet, mobile phones, and tablets, the CTS team can access the DMS anytime, view the latest data in real time, and even create customized questionnaires that incorporate each participant's individual data. The system includes extensive security and validation tools, all of which are under the team's direct control, to protect the privacy and confidentiality of the data and ensure that all operations are standardized across all sites. For the CTS, this novel DMS has reduced overall data management expenses, increased productivity, and shortened the data pipeline from months or years to days.



- ✓ Reduced the overall DMS expense
- ✓ Increased the staff productivity
- ✓ Shortened the overall data pipeline time

The DMS includes all of the records of participants invited to provide a blood or saliva sample, and also allocates participants by location to the three institutions involved in specimen collection. The Cancer Prevention Institute of California is responsible for participants in the northern half of the state, City of Hope is responsible for the greater Los Angeles area and parts of the Central Valley, and the University of California Irvine is responsible for the southern-most areas, including San Diego and Orange County. The DMS facilitates every step of the process, from generating the recruitment letters to scheduling the appointments. Having all data management tasks in a single DMS ensures that all three of the study sites are using the same procedures and facilitates implementation and monitoring of compliance to study protocols. In addition, the study team can evaluate a whole range of performance and study metrics, in real-time, across all three study sites.

4 Addressing the Challenges with a Pilot Study

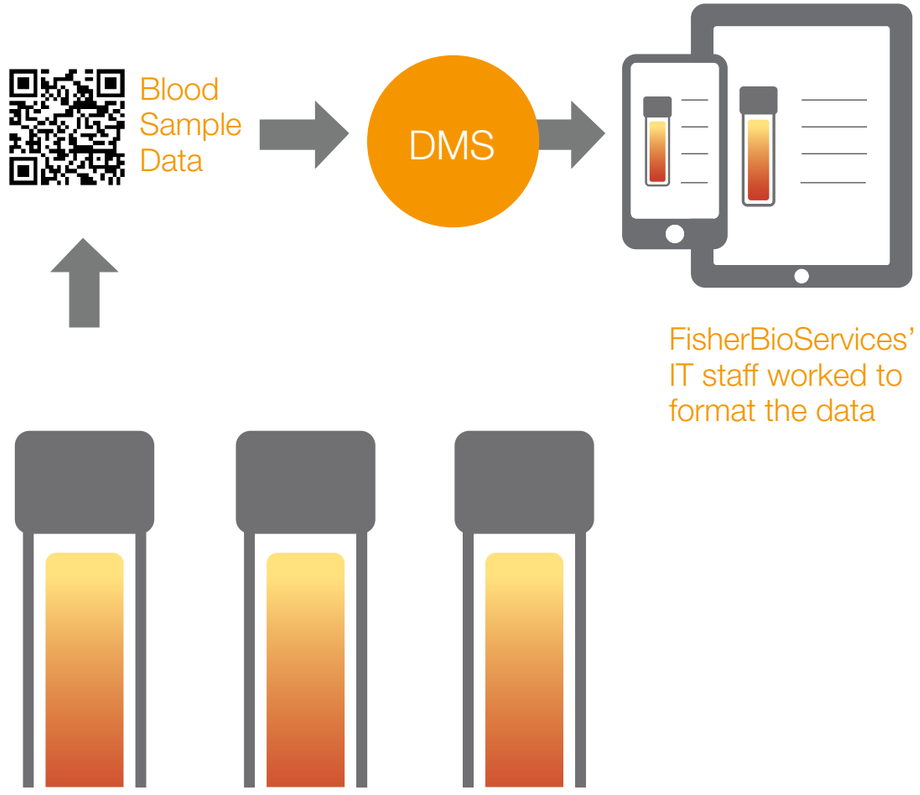
Addressing the Challenges with a Pilot Study

Building, testing, and implementing this new system required careful preparation and execution. Together, the CTS and our repository partner, Fisher BioServices, whose laboratory and biobank storage facility is in Rockville, Maryland, conducted a series of pilot studies to develop and validate the specific procedures and protocols for this project. In May and June of 2013, the pilot testing addressed a number of issues: collection and blood handling process, shipping and logistics, data transfer from the DMS to Fisher BioServices' inventory management system, and processing to maintain biochemical integrity.

To prevent sample deterioration and preserve the blood components for the broadest range of future research, the samples need to be kept cool and then processed within 24 hours of collection. Samples would be collected from all over California, under conditions that ranged from summer heat in Southern California to the snowy winters in Lake Tahoe.

Volunteers provided blood specimens, and the phlebotomists went through their activities—entering data into the mobile devices, scanning the QR codes, and uploading the data to the DMS. Fisher BioServices provided TrekView® temperature monitors to record the temperature of the blood tubes on a minute-by-minute basis, from the time of the collection until they arrived at the lab.

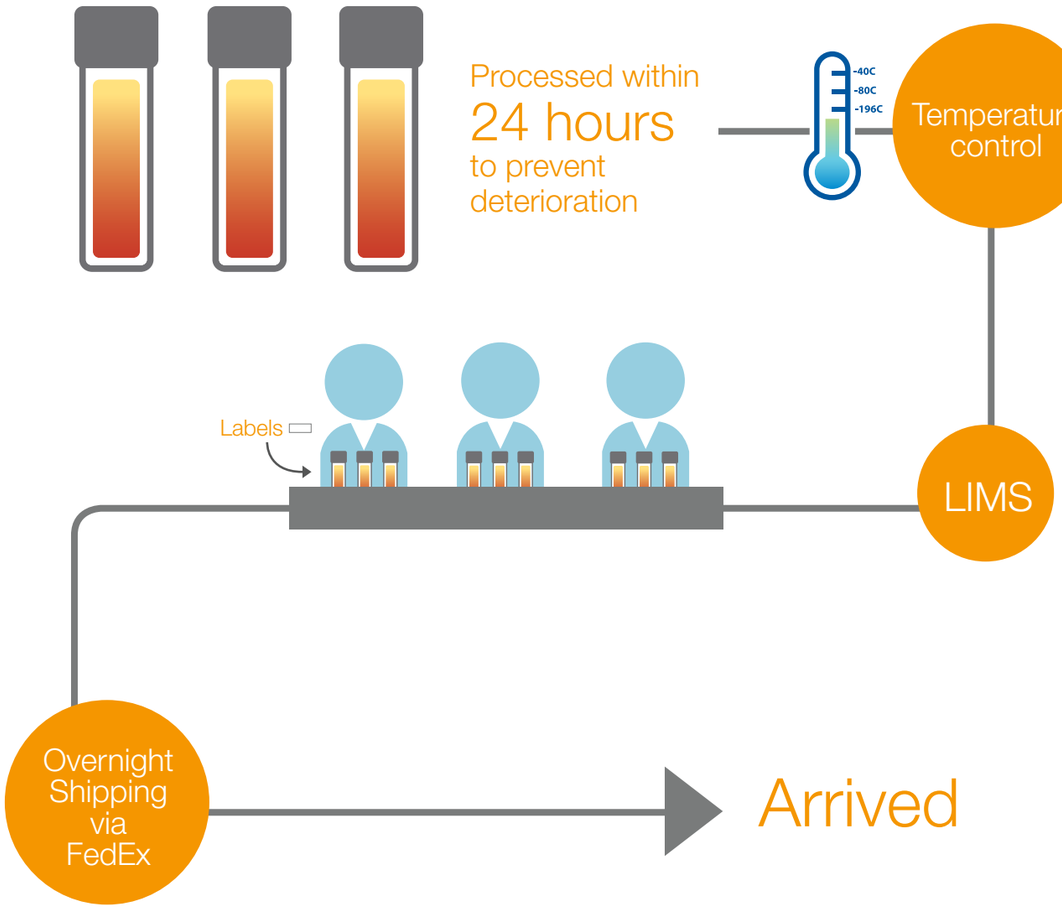
When some samples arrived too cold and others arrived too warm, Fisher BioServices recommended Cube® boxes, which use patented phase change panels to maintain temperature. Along with the Cube® box, Fisher BioServices provided a specific pre-conditioning protocol to cool the phase change panels and gel packs overnight and establish and maintain correct temperature. Testing confirmed that this approach worked, and now each phlebotomist uses a Cube® box to make sure that every tube of blood arrives at Fisher BioServices in optimal condition.



Addressing the Challenges with a Pilot Study

Each tube is labeled with a specimen identification number in the form of a QR code. Getting the correct barcode/QR code formats to work across all of the different settings—kit assembly and preparation at the Maryland facility, scanning during the collections in California, and then receipt and recording when the blood samples arrive the next morning in Maryland—also required extensive testing and retesting. Fisher BioServices' IT staff worked to format the data, and test and retest, to verify that the data up-loaded correctly into the various data fields in the inventory management system. The QR system now allows every parent and child vial to be quickly identified and tracked at any point in the process.

Fisher BioServices' inventory management system recorded and tracked the time points from the draw through the laboratory work flow to ensure the required timeline was met. Overnight shipping of samples via FedEx is routine for Fisher BioServices, and the change in time zone during the overnight flights from California to Maryland added a slight advantage. Nonetheless, laboratory staff at Fisher BioServices revised their receiving process to add a safety margin: Technicians arrive at work a little earlier and print and apply the labels to the child aliquot cryovials in advance. The lab is prepared for processing before FedEx arrives with the tubes.

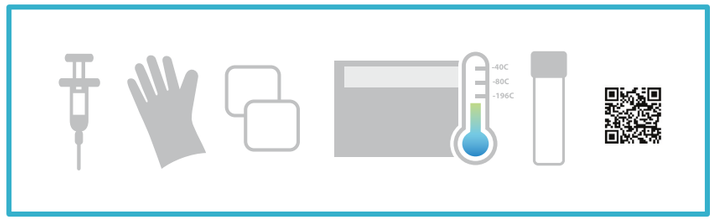


Equipping the Phlebotomists

Equipping the Phlebotomists

By July 2013, the detailed protocol had been tested and refined to the point that collections could begin. Beginning with the completion of the pilot study and continuing through 2016, teams of phlebotomists at each of the three institutions are visiting study participants and drawing the blood samples. At the end of each day, each phlebotomist packages the tubes of blood in a Styrofoam shipper and sends them to Fisher BioServices for processing and storage.

Fisher BioServices provides pre-labeled, barcoded, blood collection kits directly to each of the study sites. The labels are designed and applied to work precisely and accurately with the phlebotomists' Android tablets as well as the automated liquid handling equipment at the company's central laboratory. Fisher BioServices also supplies each site with the latex gloves, containers for the used needles, gauze pads, and other materials needed for blood draws, as well as the Cube® cold box, gel packs and Styrofoam shippers. Consolidating the preparation of the pre-labeled blood collection supplies, laboratory processing, and sample storage with Fisher BioServices enables the collection, lab processing and biobanking to be managed as efficiently as the data.

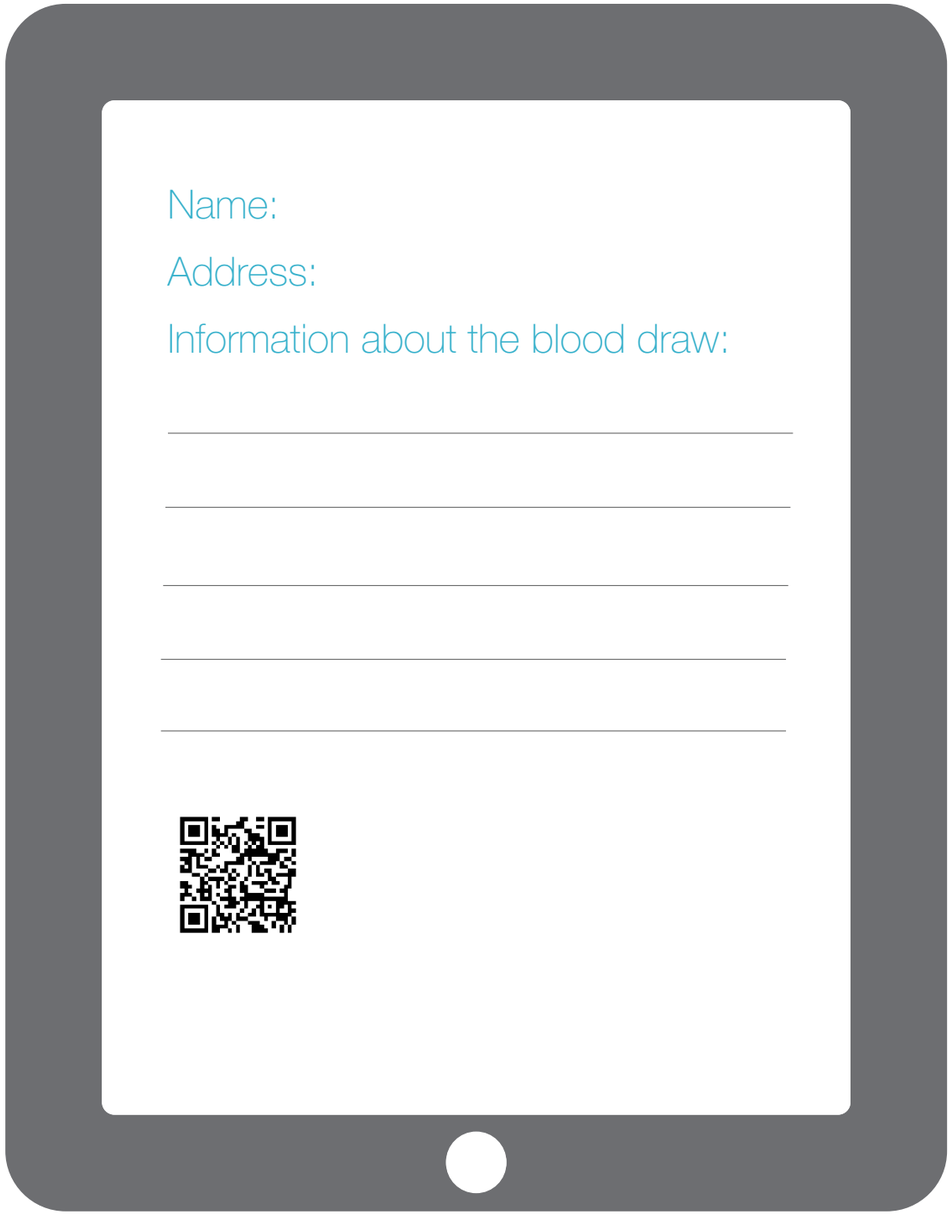


When a participant agrees to donate a blood sample, an appointment is set for a licensed phlebotomist to do the blood draw. The DMS automatically sends all of the relevant details—name, address, notes, and other information—to the Android tablet. Some women cannot give blood and have the option of donating a saliva sample that can be self-collected at home and then mailed back to one of the CTS sites.

Equipping the Phlebotomists

When the phlebotomist arrives for the appointment to collect the blood, the mobile app really shines. The mobile app makes the entire process work and liberates the field phlebotomists to make the most of their interactions with the participants. During the visit, the participant signs the informed consent form and completes a brief smart e-questionnaire on the tablet. Each questionnaire is customized for each participant based on her responses to previous CTS questionnaires. Then the phlebotomist draws the blood. The patient ID, consent, questionnaire responses, and blood samples are all automatically linked to a single unique QR code/barcode by the tablet. The phlebotomist then records some additional details in the tablet, such as the type of needle that was used and other information about the blood draw. The entire appointment, including setup, consent, questionnaire, blood draw, and wrapping up, can be completed in approximately 20 minutes.

At the end of the day, the blood samples are packaged in the Styrofoam shippers provided by Fisher BioServices, and the phlebotomist uses the tablet to scan the FedEx airbill number. As with all of the information collected during the in-person appointment, the airbill number is automatically sent from the tablet back to the main DMS, so that every tube of blood can be tracked during the overnight journey from California to Fisher BioServices' laboratory in Maryland.



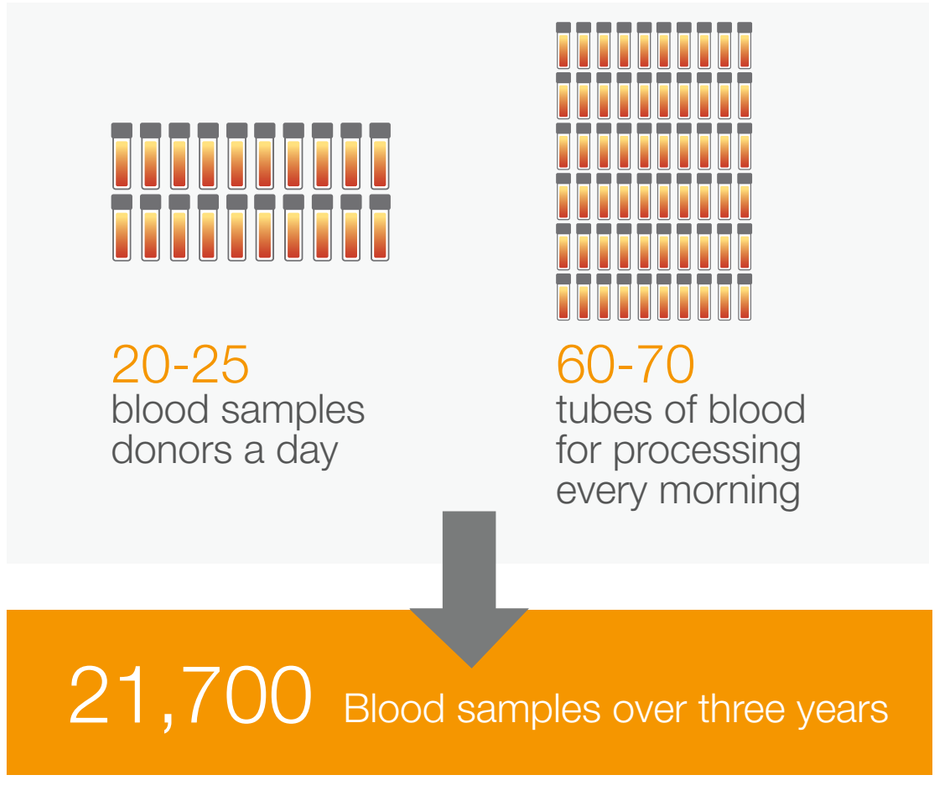
6 Managing and Biobanking the Specimens

Managing and Biobanking the Specimens

The phlebotomists collect three samples of blood from each donor into three different tubes, two of which have an additive that allows the blood to be processed in different ways. The CTS sends blood samples from 20 to 25 donors a day, or an average of 60 to 70 tubes of blood for processing every morning. The project will run through 2016, collecting and biobanking the aliquots of 21,700 blood samples over three years.

Another cost-saving innovation created by City of Hope was in the handling of shipment data. To make the receiving operations as efficient and accurate as possible, Fisher BioServices requests an electronic copy of the shipment manifest in advance, for upload in the inventory management system. This allows Fisher BioServices' receiving team to verify inventory accuracy and rapidly reconcile the received samples with the shipping manifest. Unfortunately, studies that rely on manual processes to send shipment manifests will inevitably encounter snafus, such as a study site forgetting to email the manifest or sending a manifest that is incomplete or contains errors. When that happens, the resulting investigations and fixes are time-consuming and disrupt workflow schedules.

The CTS team created an innovative and cost-saving way to send the shipment manifests to Fisher BioServices. After the phlebotomists have scanned their FedEx airbill numbers, the DMS automatically combines information about every sample that was shipped into a single manifest. Each night at 11 pm West Coast time, the DMS automatically sends that manifest directly to the Fisher BioServices' computers. The delay gives the CTS team time to review the day's work and, if any corrections need to be made, update the manifest before it is sent and uploaded into Fisher BioServices' system. Each of these steps speeds up the process and provides both the CTS and the biorepository staff efficient data management and tracking of the biospecimens.



Managing and Biobanking the Specimens

When the samples are delivered by FedEx—typically arriving at the laboratory by 8:30 am East Coast Time—they are received by Fisher BioServices' technicians according to a standard operating procedure (SOP). This includes scanning the tubes against the uploaded data, completely reconciling the specimens shipped with the data, and inspecting the tubes and samples for damage, evidence of freezing, or other problems.

Fisher BioServices' technicians receive and process the samples within a maximum of two hours, well within the 24-hour window. The blood tubes are centrifuged and the blood separated into the various fractions, each of which is further divided, or aliquoted, into smaller vials for storage in a -80°C freezer. The result is up to 33 samples from each donor. To date, the biobank contains only about 50,000 samples but will eventually include about 314,500 samples for future use in the search for biomarkers.

50,000 samples today
314,500 samples for future use

For the Future

For the Future

By combining laboratory research and biochemical data from the blood samples with the survey and outcome data, the CTS is advancing its track record of high-impact cancer research and capitalizing on future cutting-edge work to combat cancer and other diseases among women. The CTS team's innovative use of this new DMS and mobile devices represents a transformation in the way this data is collected and managed, and the CTS is planning to expand this transformation, potentially leading the way to Big Data.

A major factor in the importance of the CTS study is the teams' inclusion of outcome data. In California, researchers have access to state databases and can collect information such as time/cause of death, diagnoses in the State cancer registries, and other endpoints, which greatly expand the types of research possible with the questionnaire data. However, obtaining data from these databases can be time-consuming and expensive. In the future, through Big Data, the CTS and other databases may transfer data as quickly and efficiently as the specimen collection data is uploaded to the City of Hope and shared with Fisher BioServices. For now, however, the CTS is transforming the value of their data with biospecimens, enabling the discovery of biomarkers and beyond.

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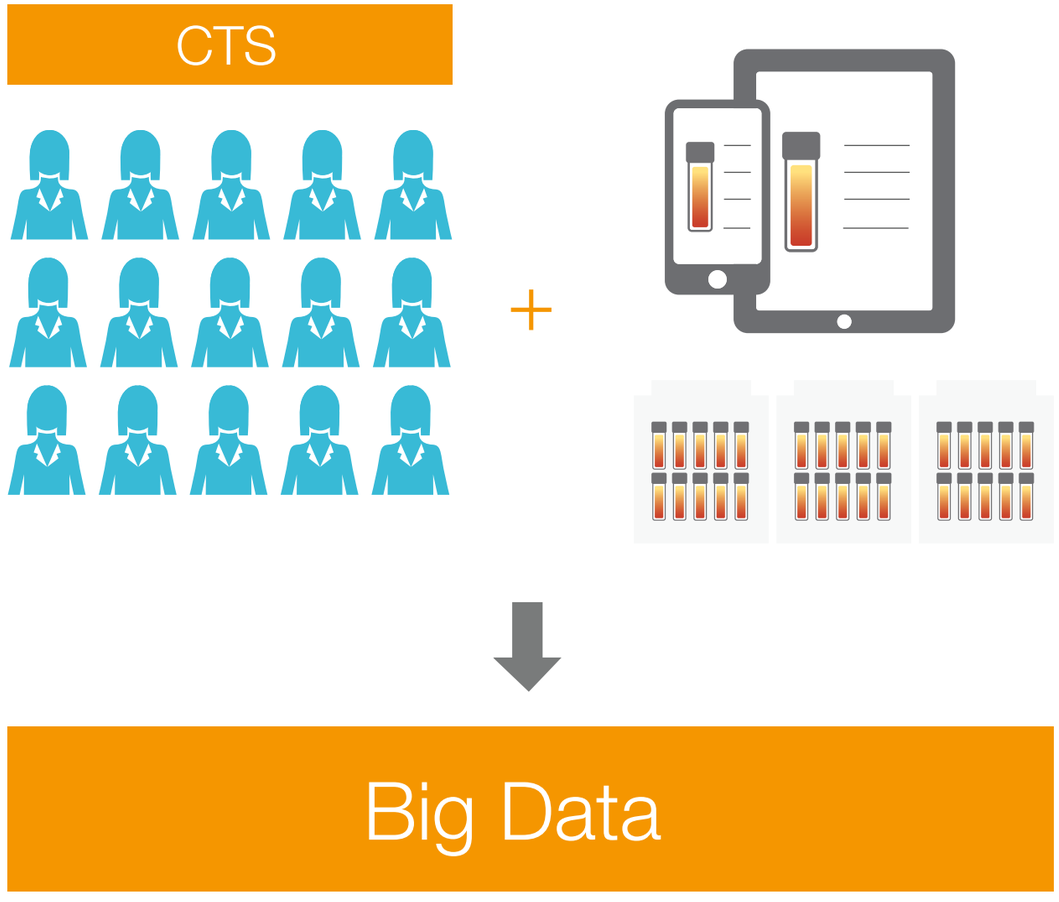


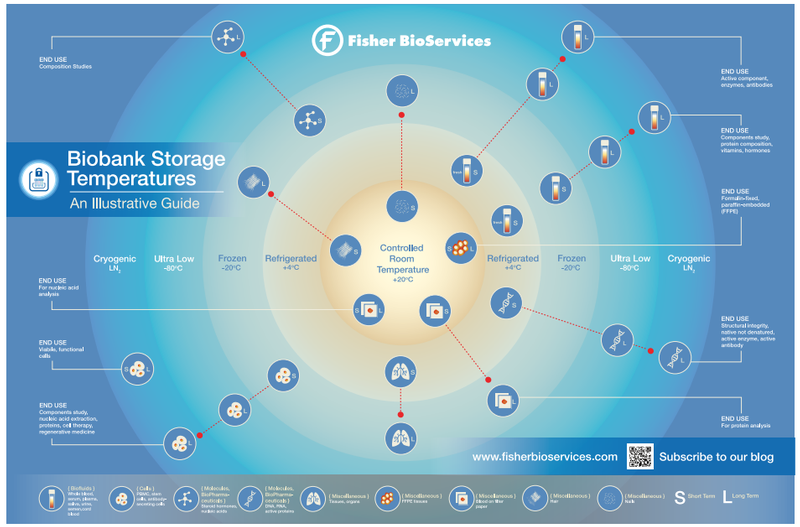
Additional Resources

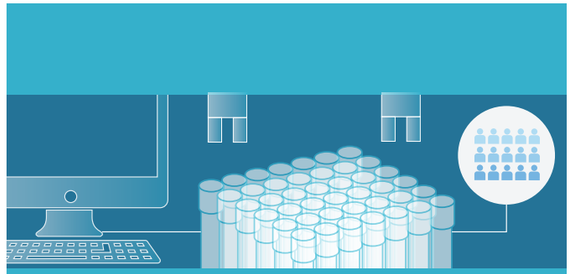
As a worldwide provider of biobanking and clinical trial sample management, Fisher BioServices can assist companies looking to store critical biological materials, biotherapeutics, manufacture sample collection kits, and process samples.

- Simple to complex sample collection kit design and production
- Sample processing, global biobanking, and data management
- Online access to inventory for data searching, requesting samples, and exporting reports

Explore Your Solutions

Additional Resources





Automating Your Sample Collection for Biobanking: 10 Things to Consider

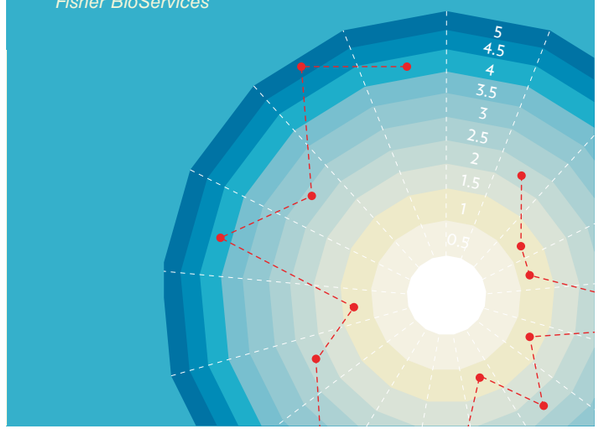
By Kathleen Groover, Ph.D., Project Director;
Karon Drew, Manager of Project Planning;
Skip Lewandowski, IT Manager

Fisher BioServices

Defense in Depth:

Off-Site Storage of Biological Specimens and Biopharmaceuticals for Risk Mitigation

By Bruce C. Simpson, Director of Commercial Operations, Fisher BioServices



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