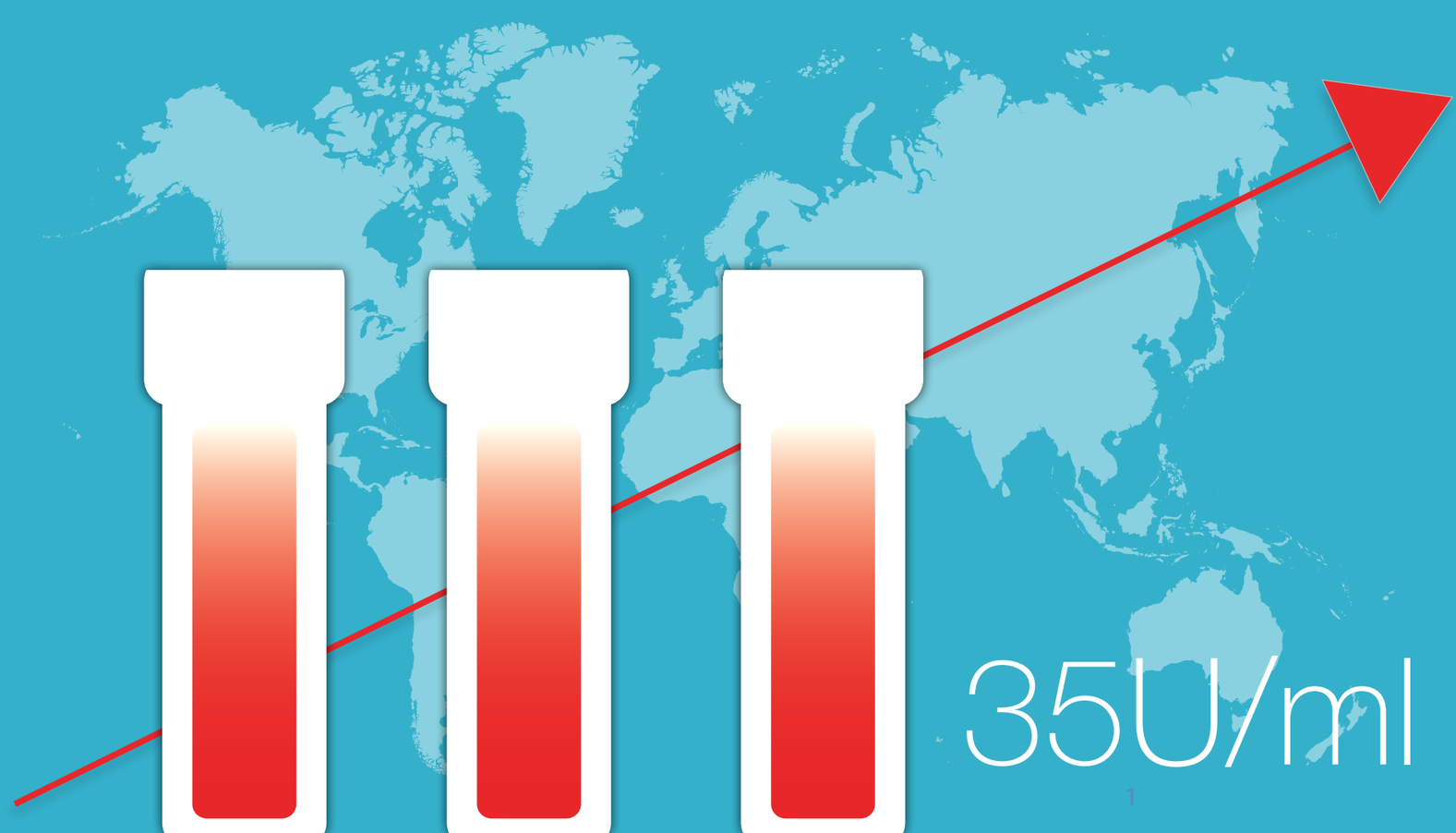
Detecting Cancer Early

A Unique Biobank Presents a Unique Opportunity

By Julie Barnes, PhD, CEO of Abcodia, and Robert Jones, Director of Fisher BioServices-UK



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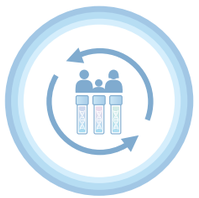

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About the Authors

Julie Barnes, PhD

Robert Jones

Julie Barnes, PhD

Dr. Barnes is Chief Executive Officer of Abcodia, an award winning company focusing on the development of new tests for the early detection of cancer. A neuroscientist by training, Dr. Barnes has spent 25 years in the pharmaceutical industry and biotechnology sector. Between 1996 and 2001, she was Head of Neuroscience for GlaxoWellcome, leading a team of 40 scientists focused on drug discovery for CNS disorders. From there, she joined the healthcare technology company, BioWisdom (now Instem), serving as CSO. In this role, she led the healthcare team, helped to raise several rounds of venture capital investment, and led industry adoption of the award-winning Safety Intelligence Programme. Dr Barnes co-founded Abcodia in 2011 and in 2013 received the Women in Science and Engineering (WISE) Enterprise & Innovation Award in recognition of her leadership and success in a biotech start-up and her contribution to health care.

Robert Jones

Mr. Jones is Director of Fisher BioServices UK, a part of Thermo Fisher Scientific. Mr. Jones joined Fisher BioServices in 1988 and became Director of UK operations in 2004. Prior to Joining Fisher BioServices, he served as Senior Laboratory Scientist for the National Blood Service, specializing in Haematology and Transfusion Science. He is a member of the Institute of Biomedical Sciences and Institute of Clinical Research and is an internationally recognized expert in biorepository science

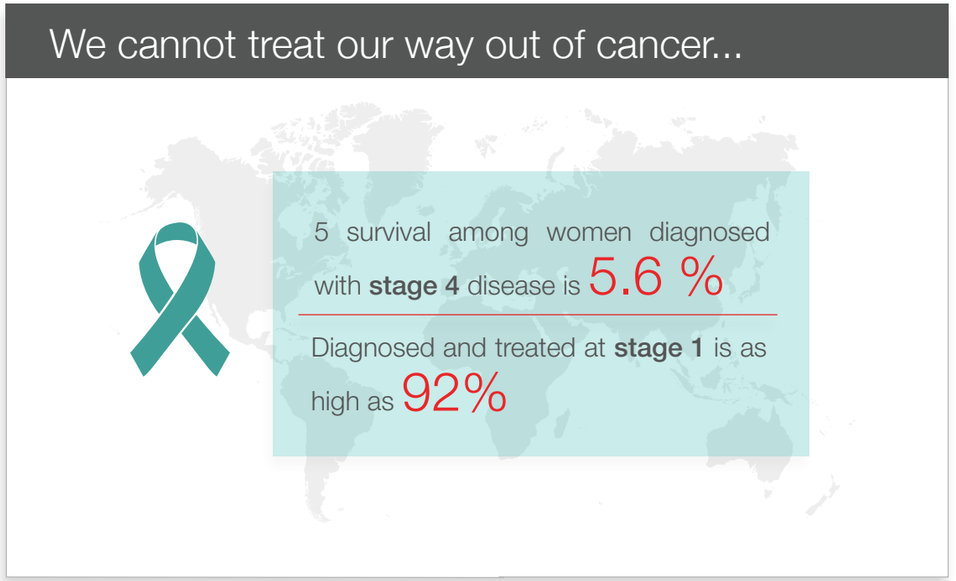
Overview

Introduction

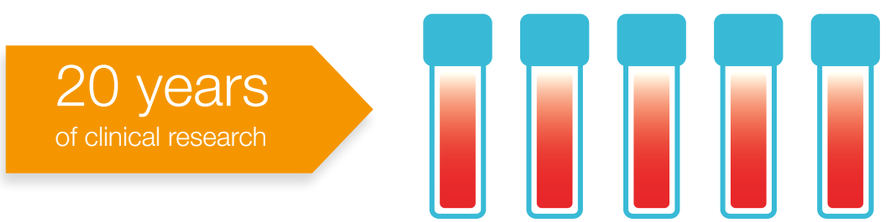
The recently released World Cancer Report 2014, a global analysis by the World Health Organization, noted both the increase in cancer cases worldwide, as well as the burden represented by the spiraling cost of treating late stage disease. The report, as stated in the preface, makes it clear that we cannot "treat our way out of cancer."

The most effective approach to addressing cancer is prevention, and if treatment is necessary, it is best at an early stage, which is associated with much higher survival rates as well as lesser side effects. Ovarian cancer is a case in point: Five-year survival among women diagnosed with stage 4 disease is 5.6 percent, while those diagnosed and treated at stage 1 is as high as 92 percent. However, early treatment depends on early diagnosis, and in spite of major investments of both resources and effort, there are still few biomarkers available for the diagnosis of cancer[2] at a very early stage, when the disease is far more treatable.

This is the story of 20 years of clinical research that has led to the development of a well-validated screening test for ovarian cancer, known as ROCA (the Risk of Ovarian Cancer Algorithm) that successfully identifies early stage disease. Just as significant, this is the story of the establishment of a unique biobank of serum that is now being used to discover and validate additional biomarkers for screening and early diagnosis of other cancers.



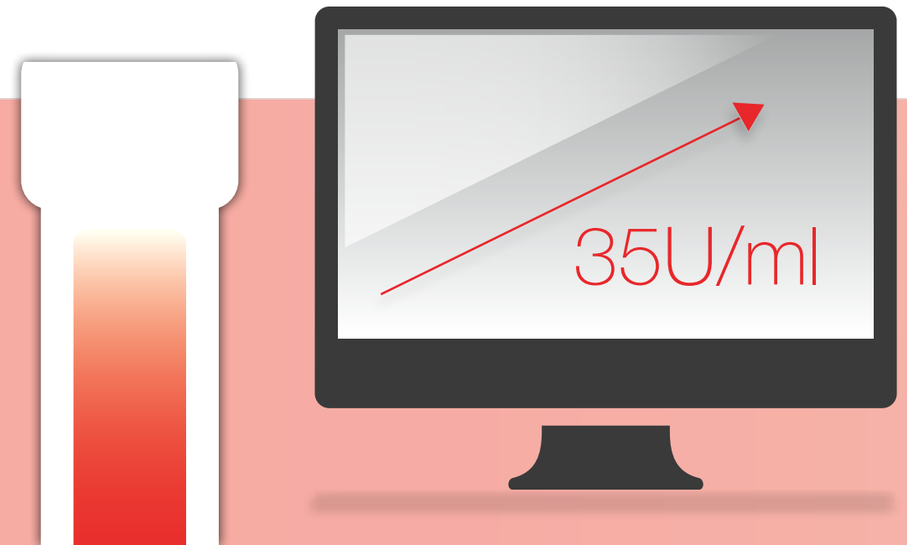
ROCA (the Risk of Ovarian Cancer Algorithm)

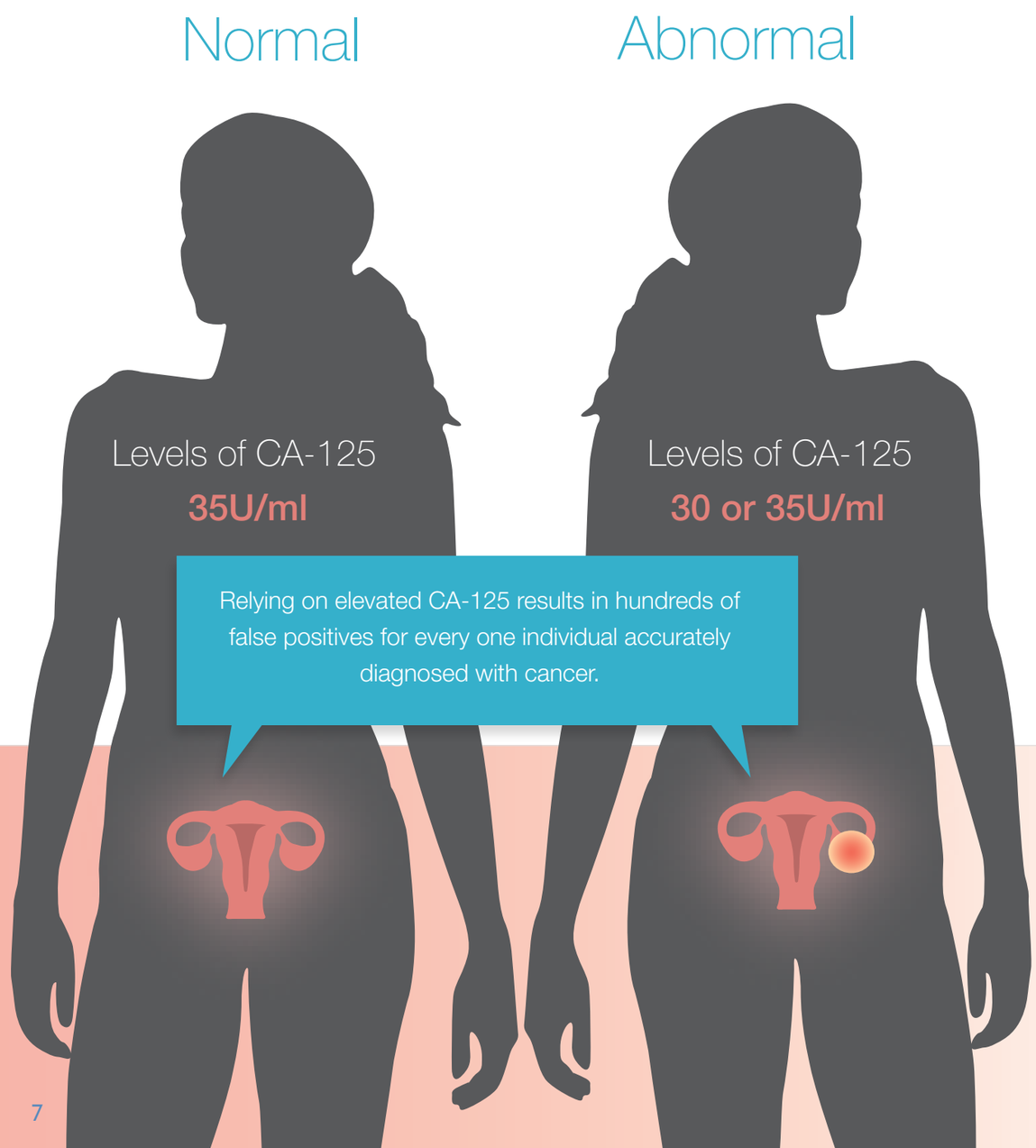


1 The Beginning: Understanding CA-125 in Healthy Women

The Beginning: Understanding CA-125 in Healthy Women

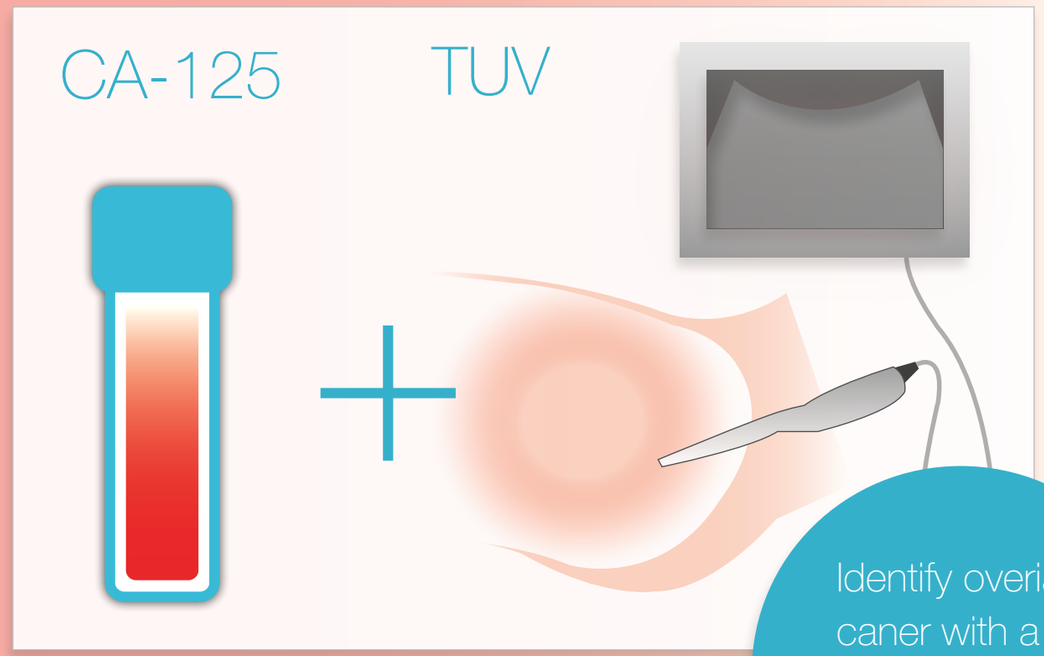
Carbohydrate Antigen 125 (CA-125) is a well-established biomarker traditionally used to aid diagnosis in women presenting to their doctor with symptoms suggestive of ovarian cancer. In such a setting, levels of CA-125 above an accepted threshold of 30 or 35U/ml have been considered abnormal and a flag to a clinician to do further investigations. However, it is now well understood that the use of CA-125 in a simple quantitative way is limited by its low specificity. Elevated CA-125 levels above 35U/ml not only occur in people with cancer, but can also be found in people with no health problems, as well as in patients with relatively benign conditions, such as endometriosis. Thus, relying on elevated CA-125 results in hundreds of false positives for every one individual accurately diagnosed with cancer.





The Beginning: Understanding CA-125 in Healthy Women

22,000 healthy women



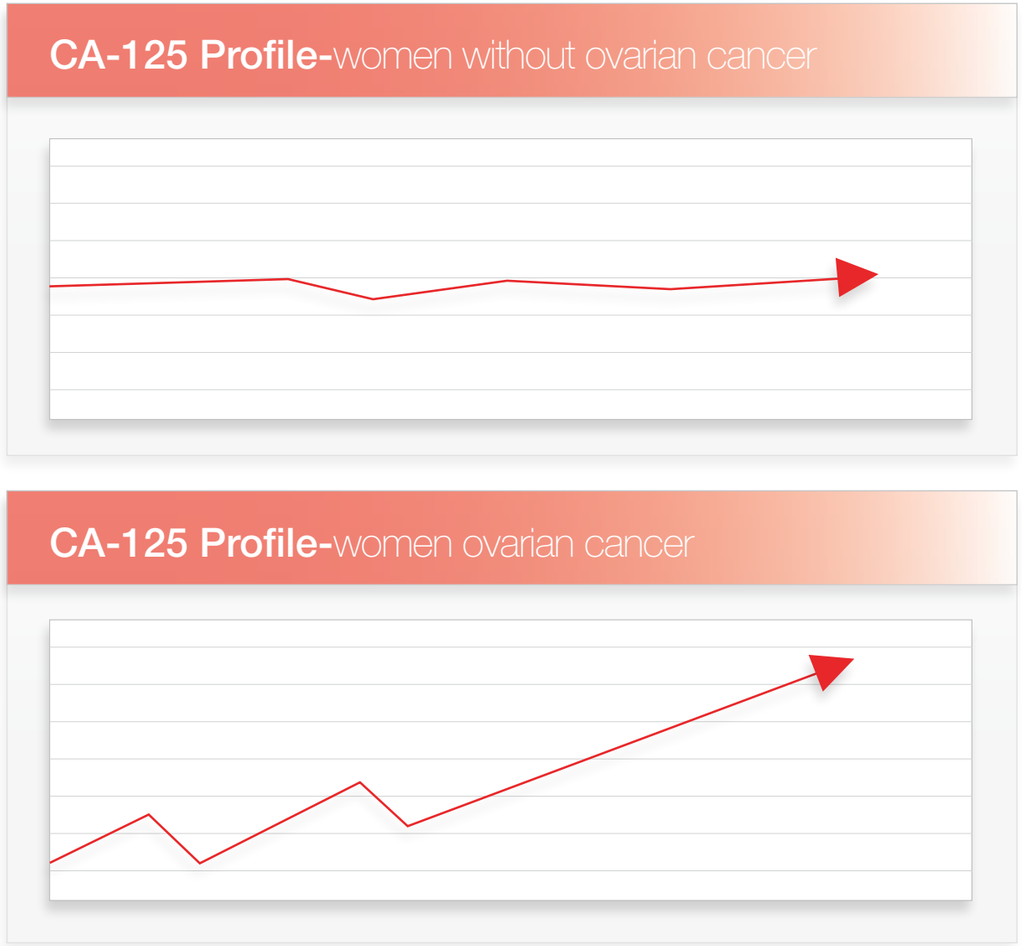
For many years, groups around the world have investigated the possibility that CA-125 could be used for screening healthy women for early detection. One of these investigators, Professor Ian Jacobs, then a Research Fellow at the Department of Obstetrics and Gynecology at Cambridge University, set out in the early 1990s to determine whether or not regular testing for CA-125 could be used more specifically in early diagnosis, by assessing change over time and also by combining it with other potential tests. In his first UK study, he recruited a cohort of 22,000 healthy women and assessed the ability of CA-125 when combined with trans-vaginal ultrasound (TVU) as an annual multi-modal approach to detecting early ovarian cancer. This study revealed that such combination screening could identify ovarian cancer with a high specificity of 99.8 percent, thus reducing the number of false-positive surgical procedures performed to only five[3]. A second study of 5,550 women in Sweden yielded similar results, reducing the number of false-positive surgeries to two. Most significantly, later analyses of the data showed that the survival rate among women diagnosed earlier using both CA-125 and TVU increased from 41.8 months to 72.9 months.

2 The Meeting of Minds: Clinical Insight and Statistical Power

The Meeting of Minds: Clinical Insight and Statistical Power

In working with this clinical data set to consider how to improve sensitivity, another perhaps more fortuitous result revealed itself. Jacobs was working with a biostatistician affiliated with Harvard Medical School and Massachusetts General Hospital (MGH) in Boston, Steven J. Skates. Dr. Skates noticed patterns in the data, often referred to as "subject-specific temporal behavior." That is, women without ovarian cancer had a flat CA-125 profile, consisting of a baseline level individual to each woman around which her CA-125 levels fluctuated to a minor extent. This baseline level could be well above or well below 35U/ml—the critical issue was that this baseline did not change significantly over time.

In contrast, women who later developed ovarian cancer showed a sharp increase in CA-125 values from her original baseline (regardless of whether the initial baseline value was high or low) that significantly exceeded normal background fluctuations. That is, all the 22,000 women studied had very individual CA-125 levels, both above and below 35U/ml. However, women who eventually developed ovarian cancer showed changes in CA-125 level that rose rapidly from the baseline value. This leap in CA-125 is called a change-point CA-125 profile. More significantly, this characteristic pattern of change in CA-125 levels occurred early in the course of the disease.

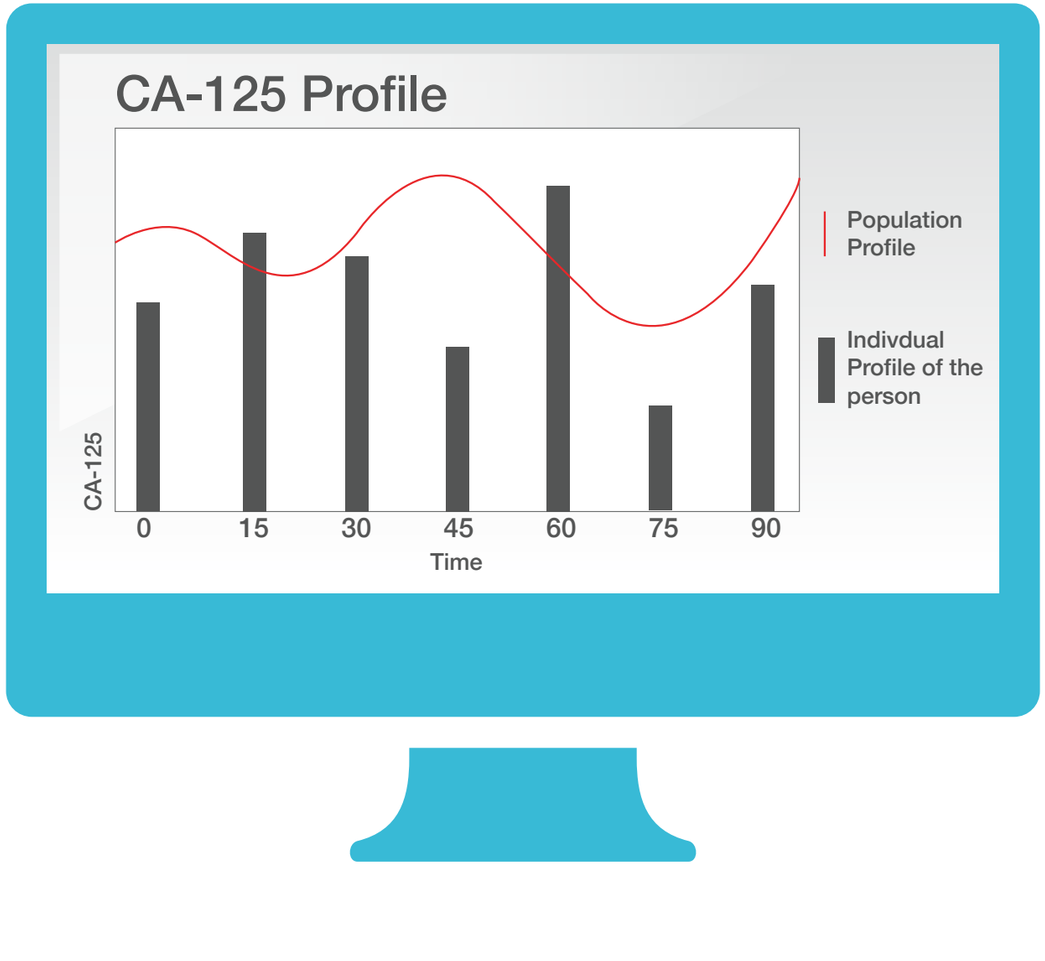


3 The Invention of the Risk of Ovarian Cancer Algorithm (ROCA)

The Invention of the Risk of Ovarian Cancer Algorithm (ROCA)

Based on the patterns observed over time, Skates proposed using CA-125 levels in a different way. Rather than looking at a single threshold level, he proposed calculating a patient's risk of cancer based on a series of CA-125 measurements and their fluctuations. Skates applied statistical modeling to the data, creating separate profiles of CA-125 levels among the women who developed ovarian cancer and those who did not. The analyses resulted in a hierarchical change-point model that became known as ROCA, the Risk of Ovarian Cancer Algorithm.

ROCA compares a woman's individual blood profile of CA-125 over time with the longitudinal CA-125 profiles of thousands of other women who developed ovarian cancer[4]. The probability of ovarian cancer increases the closer a woman's profile is to the change-point profiles seen in women with ovarian cancer, compared with the flat profiles for healthy women. After every additional CA-125 measurement, a woman's ROCA score is recalculated, and clinical recommendations provided (i.e., no action needed, screening at shorter intervals, or referral for TVU). This systematic method has proven both more accurate and more efficient than using a single cut-off level of CA-125 because it maximizes sensitivity for any level of specificity. ROCA both "distributes" screening in a stepwise fashion according to probability of disease and also identifies women who may have developed ovarian cancer at a very early stage of the disease.



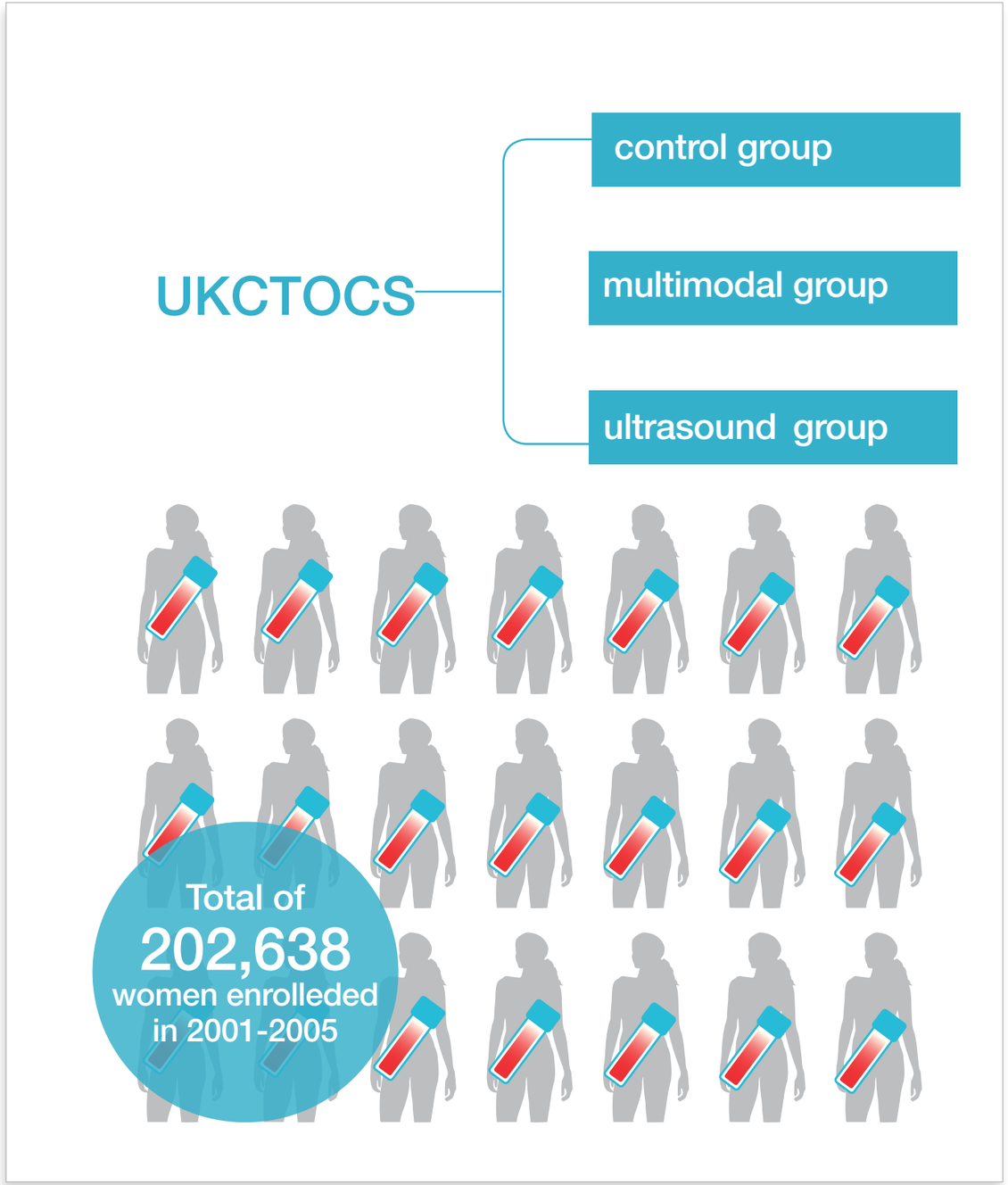
Proof is in the Prospective Validation

Proof is in the Prospective Validation

To test this statistical strategy, Jacobs and colleagues formed the UK Collaborative Trial of Ovarian Cancer Screening, or UKCTOCS, based at the University College London [Professor Jacobs joined the University College London (UCL) in 2004, to establish the UCL Institute of Women's Health]. Professor Usha Menon is serving as Co-Principal Investigator and Trial Coordinator.

The primary aim of UKCTOCS is to determine whether ROCA can reduce ovarian cancer mortality, which is being tested in a randomized controlled trial with three arms: a control group (no screening), a multimodal group (annual screening of CA-125 levels followed by a TVU as a secondary test) and an ultrasound group (annual ultrasound screening with additional ultrasound screening in six to eight weeks as the secondary test).

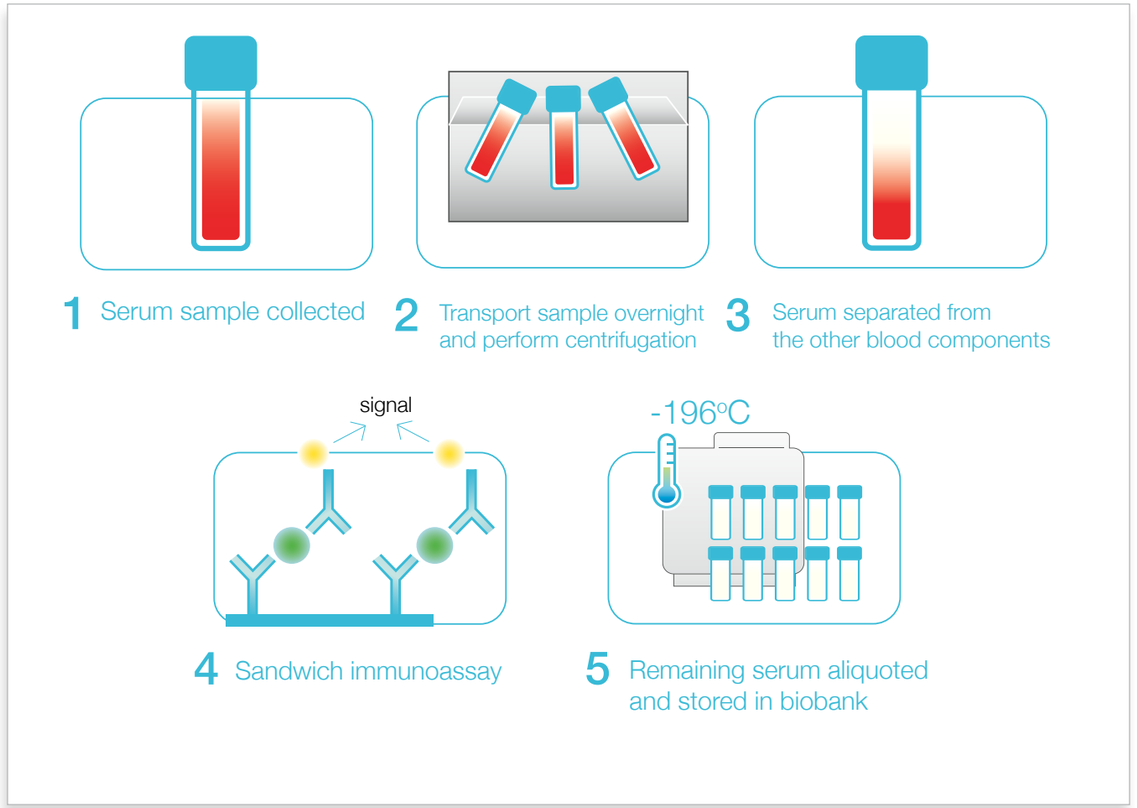
More than 1,200,000 women throughout the UK, including 13 National Health Service areas in England, Ireland, and Wales, were invited to participate. The eligibility criteria included being between 50 to 74 years of age at enrollment, postmenopausal, and free of active cancer. Among those who initially responded, 23 percent were determined to be eligible. Of those who were sent appointments, 205,090 (73.6 percent) attended the appointment, donated a serum sample, and completed the questionnaire. A pilot was run in 1998, and the full study ran between 2001 and 2005. A total of 202,638 women were enrolled in only slightly more than four years!



Proof is in the Prospective Validation

For each volunteer, extensive health-related information is being collected via questionnaire, including the educational level, alcohol consumption, tobacco use, body size change from age 20 to present (as indicated by clothing size), health conditions such as diabetes or rheumatoid arthritis, and other questions. Where applicable, additional data is gathered and matched to the volunteers from national sources, including the UK Office of National Statistics and the UK annual report of Hospital Episode Statistics.

In the active arm, serum samples were collected annually until 2005 for the measurement of CA-125. Blood was drawn into 8ml gel separation tubes at the clinical trial center and transported overnight to the UKCTOCS central laboratory, centrifuged at 1500g for 10 min and the serum separated from the other blood components. Serum CA-125 concentrations were determined by electrochemiluminescence sandwich immunoassay using two monoclonal antibodies (OC-125 and M-11). The remaining serum was aliquoted into barcoded straws and frozen in a large liquid nitrogen (LN_2) tank at -196°C.



Proof is in the Prospective Validation

The UKCTOCS is scheduled to run through 2015, and is not yet complete. A second follow-up questionnaire was mailed to participants in April 2014, and data analysis with regard to the primary mortality outcome will proceed during late 2014 and 2015.

Over the same time period, a smaller ROCA validation study has been conducted in the US, at MD Anderson[5]. In this study of 4051 women, 117 were referred for TVU on the basis of an elevated ROCA score and 10 ultimately underwent surgery. Four of these 10 women had ovarian cancer, and of the remaining six, two had ovarian tumors of low malignant potential (both stage IA), one had endometrial cancer (stage I), and three had benign ovarian tumors. This US study confirmed ROCA's 99.9 percent specificity as reported in the interim UKCTOCS report, and the positive predictive value of 40 percent for specifically predicting ovarian cancer compared to other gynecologic conditions.

The Creation of a Unique Serum Biobank

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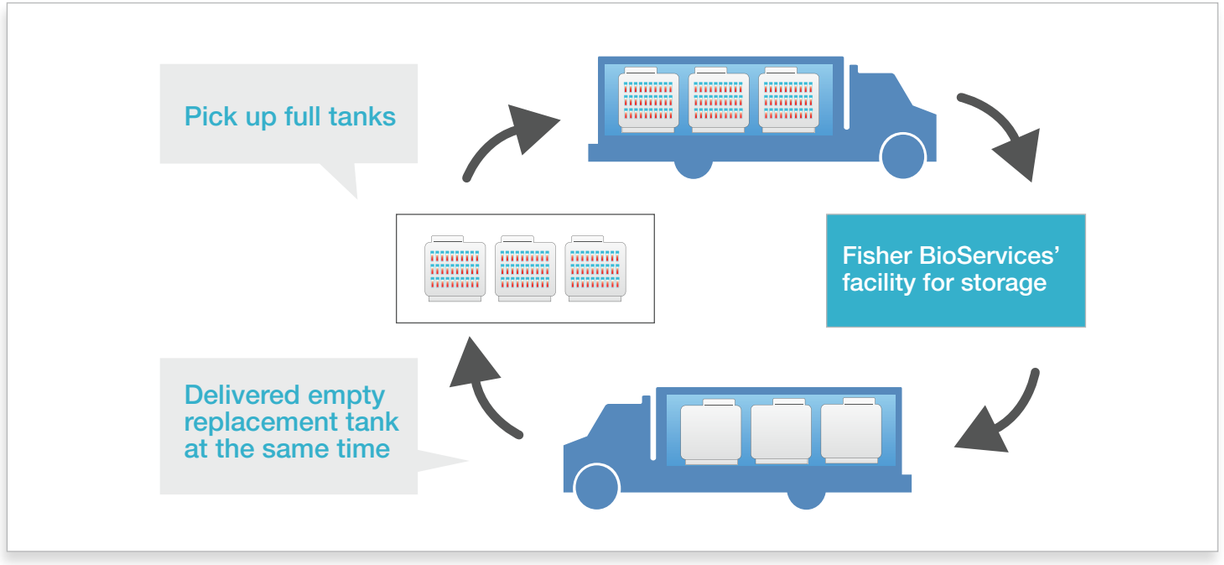
The creation of a serum biobank as part of the UKCTOCS was envisioned from the beginning. Without biological samples, there is no way to identify additional biomarkers for the early detection of cancer, and a clinical trial of the size of UKCTOCS presented a great opportunity to preserve the spare serum for future studies. By linking participants' serum samples to their clinical outcomes, both the samples and the data were transformed into a powerful research tool. As part of the strategic plan for the serum biobank, the team also ensured that best practices were used in the collection, handling, and storage of the samples. High priority was also given to ensuring that the proper patient consent was in place.

When serum collection began, the UCL study laboratory had two LN_2 tanks, and as enrollment proceeded very quickly, the tanks soon filled to capacity. To resolve this issue, the study leaders contracted with Fisher BioServices UK, a biorepository company and part of Thermo Fisher Scientific, for sample management for the duration of the study and downstream as well. Fisher BioServices created a unique and simple solution; when one of the two tanks at the laboratory was full, they sent a truck to pick it up and transport it to Fisher BioServices' facility for storage. At the same time, they delivered an empty replacement tank, installed and validated it on site at the laboratory, ready to receive samples. When the second tank filled, the process was repeated.



The Creation of a Unique Serum Biobank

The serum biobank now contains pre-diagnostic serum samples from more than 500,000 volunteers that are available for biomarker research. The aliquots of these samples fill 25 of these large tanks, each of which holds about 250,000 straws in a very dense, space-efficient arrangement. The tanks are all housed at Fisher BioServices' facility in Bishops Stortford, about 35 miles (or about 56 kilometers) northeast of central London. Besides solving the space issue, Fisher BioServices has extensive risk mitigation infrastructure in place to protect the tanks and their contents from disaster, and also has a laboratory onsite.

The biobank is a cost-effective collection as well as scientifically significant; the serum samples are preserved in liquid nitrogen, at a temperature below -130°C, while DNA and other blood components are generally 'biobanked' at -80°C in mechanical freezers. The LN_2 tanks are far more energy-efficient than the mechanical freezers and the useful life of a LN_2 tank is also much longer (mechanical freezers must be replaced every eight to 15 years). In addition, by storing the serum samples in specialized straws, the research team could fit a quarter of a million samples in each tank. Sending the samples to researchers for study is also easy: Fisher BioServices' technicians retrieve the straws, divide the serum sample into 0.5 ml aliquots and ship the requested aliquots to the investigating laboratory as directed. The remainder is returned to storage in the tank.

When distribution of the serum for research began, the aliquoting of the samples presented two challenges, for which Fisher BioServices created a solution. The first was removing the sample from the 10ml straw without losing even a micro-drop of the irreplaceable serum. To do this, the laboratory technicians use a plunger to clear the straw and aliquot the sample into .5 ml vials for high-throughput analysis. The requested aliquots are shipped and the remaining serum is dispensed into a 96-well 2D barcoded plate (to reduce subsequent freeze-thaw cycles) that is linked to the original sample in the inventory tracking system.

6 The Creation of Abcodia

The Creation of Abcodia

UCL intends to fully harness the value of the vast collection of serum samples derived from UKCTOCS, and formed a separate independent entity, Abcodia, in February of 2011. Abcodia's mission is to advance tests for cancer screening, and the company has exclusive commercial rights to the serum biobank. Based on the unique case study exemplified by ROCA, the company is particularly interested in the longitudinal profiling of interesting biomarkers with the potential for detecting cancer before symptoms present. UCL remains the key shareholder and custodian of the biobank, and also retains access to use the biobank for academic research with any IP derived from that research flowing to Abcodia under an agreed value share. In addition, Abcodia can itself develop its own IP from the biobank, for onward commercialization.

In 2013, the company formed a strategic alliance with Cancer Research UK, the world's leading charity dedicated to cancer research. This alliance, known as the Early Diagnosis Consortium (EDC), aims to discover and validate biomarkers for use in cancer screening. Announced on the 6th June 2013, the EDC combines Cancer Research UK's extensive clinical oncology and scientific network with Abcodia's expertise in the longitudinal profiling of biomarkers, including Abcodia's collection of serum samples. The consortium includes Cancer Research Technology (CRT), a wholly owned subsidiary of Cancer Research UK, who together with Abcodia will commercialize any IP developed under the partnership.

abcodia

Develop its own IP from the biobank,for onward commercialization.

Alliance Cancer Research UK

Make **ROCA** available to eligible women around the world

Abcodia has also in-licensed ROCA from MGH and is working with the co-inventors, Jacobs and Skates, to bring ROCA to the market. Currently, the company is taking the important steps required to secure a CE mark on the product and will be seeking other necessary regulatory approvals required to make ROCA available to eligible women around the world. The licensing of ROCA by Abcodia highlights the real value of industry/academic partnerships such as the one between Abcodia, UCL and MGH. It is the hope that other such partnerships will be formed across a range of disease areas, not just cancer, to take advantage of this unique prospective biobank. The company encourages all entities to "get in touch."

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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.

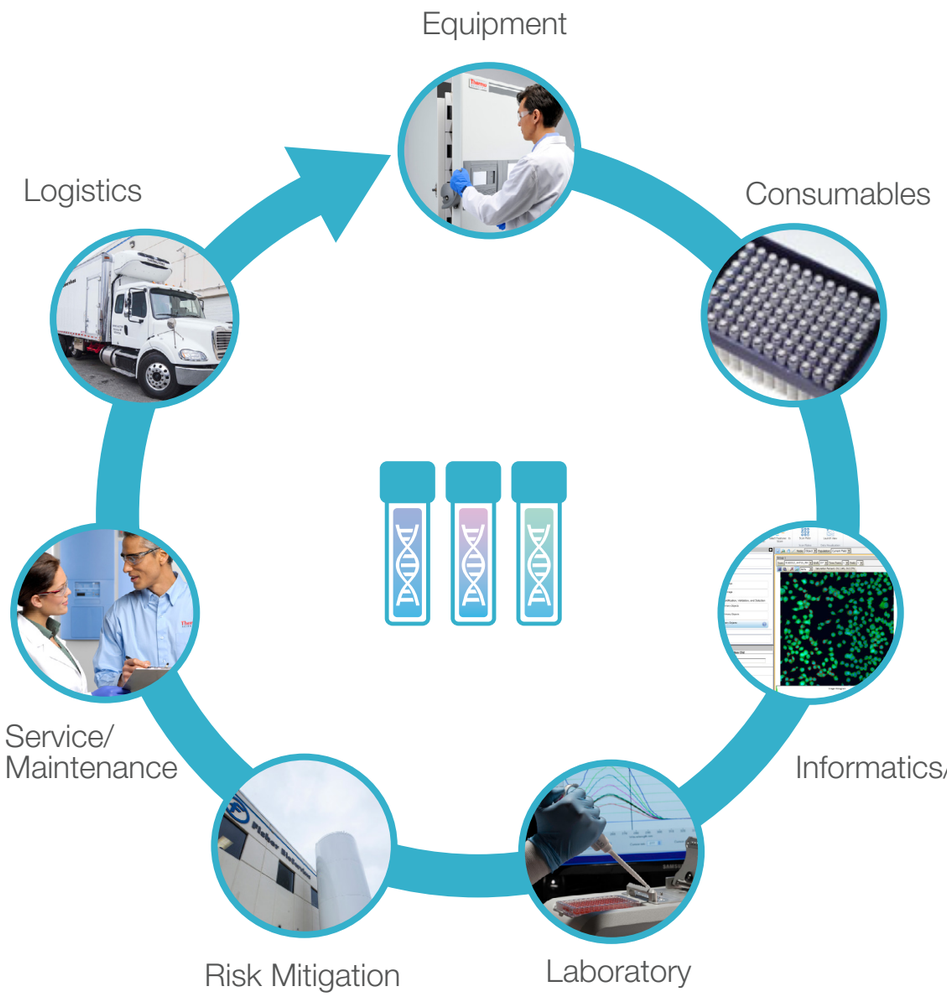
- Simple to complex sample collection kit design and production
- Sample processing, global biobanking, and data management
- Online access to inventory for data searching, requesting samples, and exporting reports

Explore Your Solutions

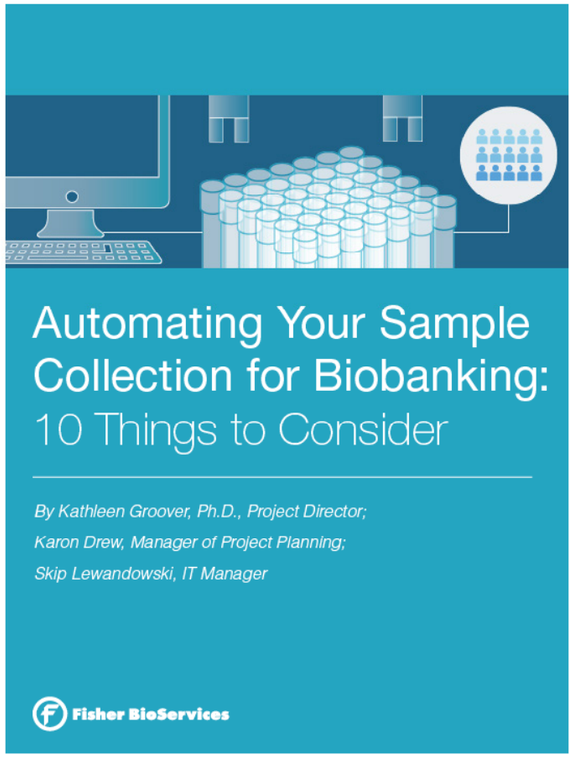
Additional Resources

Every phase of your sample lifecycle is critical to your risk mitigation strategy. Explore additional resources to learn how you can support every step of your biobanking workflow.

- Comprehensive Biobank Resources



Additional Resources



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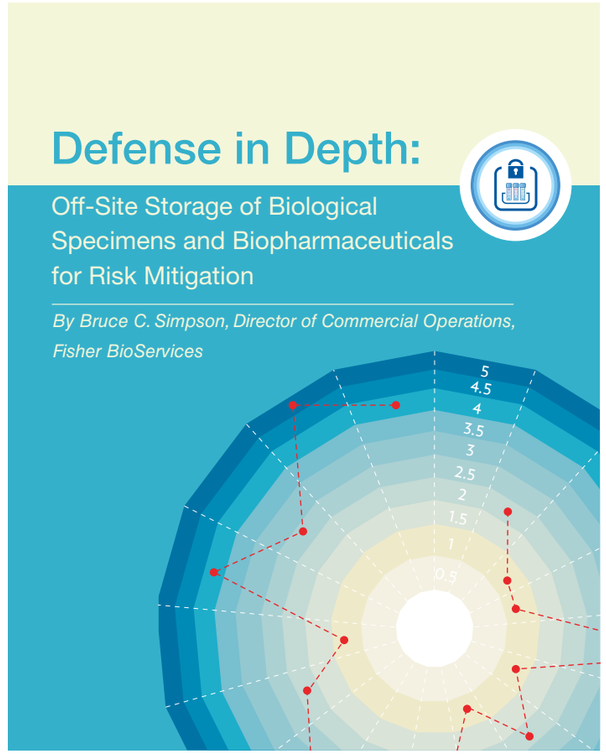

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