SAMPLE CERTAINTY:

CURRENT TRENDS IN SCIENCE AND MEDICINE THAT PROMISE TO CHANGE THE WAY YOUR LAB RUNS

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Introduction

The 21st century promises to be the century of biology, with advances in our understanding of the living world leading to dramatic changes in the way we diagnose, treat, and cure disease. Along with those advances come a rising tide of samples. Scientists in all kinds of labs are now facing the possibility and even the likelihood that their existing methods of identifying, tracking, and reporting on those samples may be insufficient to the task ahead.

Granted, scientists and clinicians have more important things to worry about than how their samples are identified and tracked, so it is unsurprising that sample management ranks far down on the list of things to worry about. Yet consider that among 350 scientists surveyed for this paper, nearly 60% reported having occasionally lost samples due to label failure, with almost half of those reporting loss that impacted greater than 2% of their samples. As the number of collective samples increases, the impact of even marginal failure promises to be significant.

As the new world manifests through government regulations, increased collaboration between research and clinical institutions, the rise of robotics, and the need to perform ever-expanding panels of tests, scientists and clinicians face a number of emerging pressures threatening to challenge their current sample-handling practices. This paper explores these and other trends facing laboratories today, and outlines some emerging best practices that promise to alleviate these pressures as well as provide a smoother transition into the century of biology.

The Real Cost of Sample Loss

Loss means different things across various types of labs, from a minor inconvenience to major devastation. In an industrial research setting, loss can mean delays in drug development and production. In a clinical setting, it can mean postponing or undermining patient care. In an academic setting, it can mean damage to findings. The impact of any of these is real to the person in the lab, no matter how rarely it might happen.

In a clinical setting, the cost associated with one lost patient sample became a point of focus beginning as early as 2005 when the average cost of a lost sample was calculated at $712[3].

In the clinical context, the tolerance for loss is understandably lowest. A 2013 study completed in affiliation with the Department of Plastic Surgery at Assaf Harofeh Medical Center in Israel examined the rate of loss of pathology specimens. Their documented loss of 0.07% — which was characterized as “devastating” given the irreplaceability of the samples — was a direct result of failure to place the specimen into correctly labeled containers[1]. Physicians were able to improve their loss only when specimens were placed into appropriate containers immediately — during the surgical procedure as soon as the specimen was removed from the patient.

In patient care, specimen identification errors are widely reported to occur at a rate of 0.1% to 5% or approximately 1 per 1,000 labeled samples[2]. In spite of decades of progress in identification and labeling, the mislabeling rate among blood banks was reported at an astonishing rate of 1.12%. While at a glance these percentages may not seem very significant, the financial consequences of a single unusable sample can have a major impact. In a clinical setting, the cost associated with one lost patient sample became a point of focus beginning as early as 2005 when the average cost of a lost sample was calculated at $7,12[3]. This amount did not include the cost of patient anxiety, delays in diagnosis, or the resulting lawsuits from misdiagnosis or fatalities. Assuming 390 identification errors per million specimens, the overall cost in U.S. clinical labs equaled approximately $280,000 per million samples examined[4]. What’s worse, when one of every 18 identification errors results in an adverse event, we are faced with 160,000 such adverse events per year in the U.S.[4], the true costs of which are unknown. If we also consider that up to 70% of diagnoses are made based on lab results, the importance of accuracy is even more significant. In the College of American Pathologists (CAP) annual survey of automation vendors in 2008, it was estimated that more than 2,000 clinical labs worldwide used some automation. The U.S. Census Bureau counted more than 13,000 diagnostic labs in 2010, leaving more than 85% of labs in the U.S. alone still relying on Excel spreadsheets or Sharpies.

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Outside the clinical context, the impact of loss can still be severe. A series of cancer population studies conducted at the Department of Oncology, University of Cambridge, UK and the Department of Preventive Medicine, UCLA identified sample-tracking errors as an inherent part of the implementation of large experiments[5]. As a solution, they developed a sophisticated quantitative method to identify and detect sample mismatches. The Medizinisches Proteom Center at Ruhr-Universiteat Bochum, Germany identified the organization and storage of proteomics data as an increasingly challenging issue resulting from a rise in the volume of information. They concluded that the need to store results was growing at an exponential rate and required the adoption of a Laboratory Information Management System (LIMS)[6]. In addition, one U.S.-based cancer research institution recently admitted that it took weeks to reconcile labeling mistakes for a lot of 400 samples.

In an industrial biotechnology or pharmaceutical setting, the consequences of lost samples include: the requirement to repeat studies for quality control, data integrity, or drug safety; the possible loss of intellectual property; and the potential for delays in approval. Any of these issues places millions of dollars at risk when data or information has to be reproduced. Most large companies have rigorous sample management processes, including a reliance on sophisticated LIMS; but among surveyed lab workers, 26% of clinical labs reported using manual processes to keep their samples and data aligned, while 74% of academic labs are also manual. When the estimated value of each specimen ranges from a few dollars up to $10,000, the scientific and financial value associated with each sample is virtually priceless[7].

The pace of cancer and genomics research has accelerated in the past several years and is accompanied by a huge volume of samples that requires indexing and storage. Biobanks or biorepositories, as the primary collectors of these high quality specimens, could be in control of the links to the next advances in clinical and biological research. In the U.S., there are approximately 180 commercial biobanks, none holding more than 3% global market share. In 2011, it was estimated that nearly 600M biospecimens had been stored in the U.S. with growth expected at an annual rate of 7%or 20M specimens. First years start-up costs for a biorepository wishing to store 50,000 biospecimens can range from $3-5M, not including the costs for an information system. Operating costs may add up to $10M over a tenyear period, making the maintenance of samples a costly proposition itself, beyond the incalculable scientific and medical value they represent[8].

An Increased Scrutiny of Sample Handling

In the face of such stakes, it is little wonder that the regulators, funders and accrediting agencies of the world have taken pains to eliminate or mitigate the sample loss under their purview. In 2004, 1.3% of clinical labs inspected by the College of American Pathologists (CAP) were cited for not having an adequate quality management plan[9] prompting this regulatory body and others to begin the arduous process of documenting and attempting to improve sample management procedures. In 2013, the primary goal of CAP and the Joint Commission's National Patient Safety Goals[10] is a dedicated effort to ensure correct patient and sample identification. Clinical labs have until April 29, 2014 to adopt AUTO 12-A, the standard barcode specimen labeling method developed by the Clinical and Laboratory Standards Institute (CLIA)[11]. (See Figure 1.) Labs that have already complied have noticed a significant improvement in specimen tracking.

Regulatory Agency	Policy	Regulations
The Joint Commission	National Patient Safety Goals (NPSG 01.01.01)	1. Use two identifiers when administering blood or collecting blood or other samples for clinical testing 2. Label containers in the presence of the patient
College of American Pathologists	Quality Management Plan	1. Commit to quality and patient safety 2. Identify risks 3. Implement quality laboratory practices 4. Communicate quality and safety practices 5. Monitor activities 6. Improve continuously
Clinical and Laboratory Standards Institute (CLIA)	AUTO12-A	1. Specifies the standard for barcode specimen labels
Centers for Disease Control (CDC)	Laboratory Medicine Best Practices	1. Use barcode systems 2. Use point-of-care-testing barcode systems 3. Use dedicated phlebotomy teams
National Cancer Institute (NCI)	Best Practices for Biospecimen Resources (Identification B.6.2)	1. Assign a unique identifier or combination of identifiers, such as a number or barcode 2. Comply with HIPAA protocol regarding patient privacy 3. Use an informatics system capable of tracking specimen from collection through processing, storage, and distribution 4. Utilize data elements from a common metadata repository
European Tissue Directive	Directive 2004/23/EC	1. All personnel involved in procuring, processing, or distributing tissues and cells intended for human application should be qualified and adequately trained 2. A system to ensure traceability of tissues and cells should be implemented 3. The identity of donors should remain private 4. Assign a unique code to each donation; identify with a label that references all related information and retain data for 30 years
World Health Organization (WHO)	Sample Management, Module 5, Content Sheet	1. Make available a sample collection and testing handbook 2. Implement a system for tracking sample movement through the lab 3. Establish a policy for sample storage and disposal 4. Maintain sample integrity and comply with all regulations 5. Appoint someone with management oversight responsibilities
Joint Commission International (combined with WHO to establish WHO Collaborating Center for Patient Safety Solutions)	International Patient Safety Goals	1. Identify patients correctly

Figure 1: *A collection of regulatory bodies and their sample-handling policies*

The Centers for Disease Control (CDC) Laboratory Medicine Best Practices Team issued a report evaluating methods for quality improvement. Recommendations included the use of point-of-care-testing barcode systems to reduce patient identification errors in test results[12].

The National Cancer Institute (NCI) in their Best Practices for Biospecimen Resources reiterated many industrywide regulations including the use of unique identifiers and barcodes. Also included were HIPAA regulations for the handling of human specimens once they leave a diagnostic setting. In this case, all patient identifiers must remain confidential, requiring the research laboratory to maintain a secure database and create their own identification system[13]. The European Tissue Directive set standards for the donation and distribution of human tissues and cells. They also required complete documentation, control, and tracking of specimens using established standard operating procedures[14]. The World Health Organization (WHO) combined efforts with the Joint Commission International to establish international patient safety standards which are followed by many countries including those in the Asia Pacific region[15].

The near universal embrace of barcoded labels reflects both the increased need for machine readability in the sample handling workflow, along with the need for maintaining patient privacy. These two issues together might be enough to push all labs toward barcode identification systems in the near future.

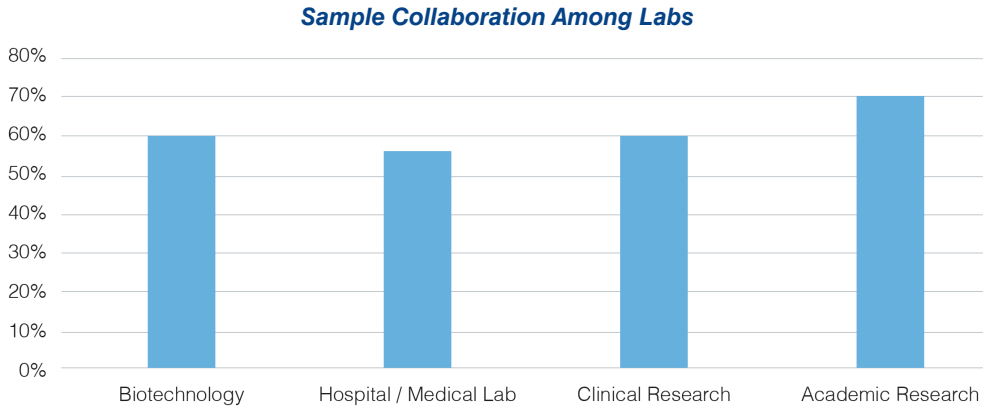

Figure 2: *Rate of collaboration among types of labs*

Interestingly, the majority of labs report using semi-automated or non-automated processes that include handwritten labels. And not surprisingly, these handwritten labels were reported to cause the biggest problems, with 60% of those surveyed reporting label failure. Handwritten specimen labels have been repeatedly shown to have the highest failure rates[16]. However, only hospital/medical labs had widely adopted an automated LIMS system, with more than half of clinical labs surveyed currently without LIMS but planning to implement one within the next five years. As collaboration and cross-lab sample sharing become the established norm, sample-handling practices are poised to mature along with it. (See Figure 3.)

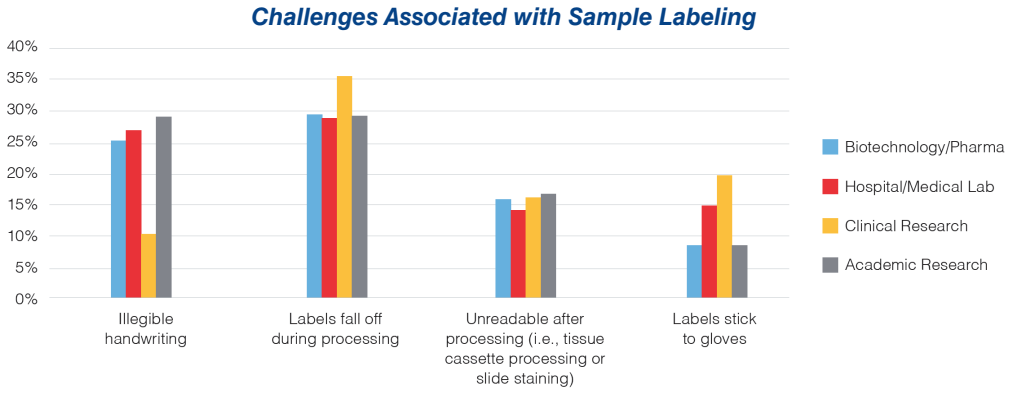

Figure 3: *Specific problems reported with labels*

Isolating the Weak Spots in the Sample Handling Workflow

As the scientific community collectively arrives at new best practices for sample management, many are scrutinizing the workflow process to identify weak points that could be strengthened. In many cases, the weak point occurs during the pre-analysis phase, when a sample is initially identified and labeled. (See Figure 4.)

For example, researchers at the University of California at Los Angeles (UCLA) Medical Center categorized sample identification errors into three generalized groups:

1) Specimen/requisition mismatch
2) Unlabeled specimens
3) Mislabeled specimens[17]

Workflow Step	Phase	Risk
■ Determine Tests and Samples Required ■ Sample Preparation and Labeling ■ Transportation of Samples to the Lab	Pre-analysis	Identification Labeling Error
■ Tests and/or Experiments ■ Obtain and Analyze Results	Analysis	Data/Sample Alignment
■ Generate Reports ■ Sample Storage or Disposal	Post-analysis	Label Failure

Figure 4: *Risks in the sample handling workflow*

In this particular review of 120 institutions and more than 16,000 potential specimen errors, over 50% of the errors were due to mislabeled specimens. Specific error-prone steps include patient identification and specimen handling, which occur primarily in a patient setting often outside the walls of the laboratory. In a 2008 review of more than 3.3M specimen labels by 147 clinical laboratories, 10 of 17 errors were related to patient identification. More specifically, the greatest number of errors resulted from mislabeled specimens followed closely by those that were either unlabeled or improperly labeled[2]. (See Figure 5.) According to established policies at UCLA, samples missing identification will automatically be discarded if they are replaceable (e.g., a blood sample). If the sample is irreplaceable (e.g., tissue from a biopsy), laboratory personnel are required to notify the original provider in an attempt to identify the specimen. This process requires that the original provider of the specimen go to the laboratory, correctly label the sample, and confirm this re-identification by signing a form. If the sample cannot be identified and must be rejected, the physician who ordered the test will be notified to decide what further action to take[18]. This process consumes lots of time and has associated costs, not the least of which are the inconvenience to the patient.

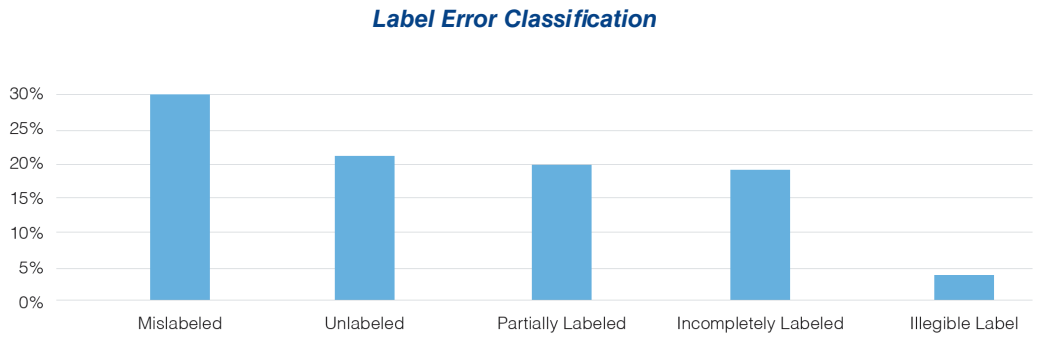

Figure 5: *Frequency of labeling error types, showing is labeling as the leading cause of label failure*

At Central Maine Medical Center, the risk of sample mis-identification is mitigated by regulations stating that all samples must be labeled in the presence of the patient and include their full legal name, two unique identification numbers such as date of birth and a medical record number, and the sample source or site. A sample will be rejected if it is not labeled, has exceeded its preservation time limits, has been collected in an inappropriate manner or container, or the sample container is broken or leaking[18]. Other hospitals add mislabeled and inadequate volume to the list of rejection criteria.

Beyond the pre-analysis phase, nearly a quarter of the respondents to our survey indicated reported experiences of having a label fall off of a sample container during processing. Selecting label materials with special adhesives that are designed for the containers and the research environment are simple ways to solve these problems.

In Pursuit of a Better Workflow

Faced with the common points of failure, labs could eliminate most errors through two key improvements in their own sample identification and handling workflow:

- **Reduce labeling errors** through the establishment of a standardized barcoding system at the point of sample acquisition. This might be part of a larger LIMS system, but might also be a stand-alone barcoding system. The elimination of handwriting represents a dramatic improvement in itself.
- **Reduce label failure** with durable labels designed to endure the temperature extremes to which samples are subjected, such as liquid nitrogen freezing, autoclaving, staining procedures, or long term storage. All processes have the potential to corrupt, smudge, or otherwise render the label unreadable or simply separated from the specimen container.

UCLA spent several years studying exactly where their blood specimen errors were occurring. Researchers initially identified three specific areas that were causing most problems (in review: mislabeled specimens, specimen/requisition mismatch, and unlabeled specimens). They followed these trends using statistical analysis over three safety cycles and further identified the following possible interventions: a reorganization of phlebotomy services, implementation of a customizable electronic event reporting system, and installation of an automated specimen processing system. After handling more than three million blood specimens, they reported their critical error rate at less than 1 in 1,000 specimens received[2].

The Louisiana Cancer Research Consortium (LCRC) — a cancer research center that includes three university health centers — processes approximately 40 new participants every month and houses over 30,000 samples (a number that continues to grow every day). Having suffered major losses during Hurricane Katrina in 2005, they decided to implement a standardized data platform as they rebuilt their program and elevated their status for NCI funding. NCI's caBIG® guidelines aim to create a collaborative information network to easily share approaches to detection, diagnosis, treatment, and prevention of cancer and ultimately to improve patient outcomes. Their goals are to provide an infrastructure for collecting specimen information and develop standard practices for sharing that information in the cancer community. LCRC adopted an integrated system with customized data entry, automated label design and printing, and electronic tracking, and further selected durable synthetic labels and a standardizable form. The result was a significant improvement in workflow and accuracy. Data entry time was reduced from an average of 40 minutesto five minutes. Printed orders were automatically sent to technicians which reduced time wasted searching through batches to match labels for aliquots. Redundancy was also reduced, allowing technicians to crosscheck information about participants.

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Other labs have chosen to tackle workflow inefficiencies by leveraging the Lean improvement methods developed in Japanese industrial manufacturing environments to optimize processes. Lean improvement methods begin by dividing work into individual components or tasks, and continues by examining flow to establish baseline levels of quality andpossible locations in the process where errors can be reduced[19].

A 2012 study at The Department of Pathology, University of Colorado, found that culture change and specific work process changes could improve pathology patient safety. First they identified and classified their errors based on clinical impact, i.e., no harm or near-miss events. Most near-miss events in this situation were attributable to incorrect labeling of specimen containers. To reduce errors, they implemented a lean-based quality improvement (LQIP).

LQIP components included coursework in patient care followed by a cultural change event designed to establish improvement goals. Work activities were observed by impartial observers to identify errors in real time. Documented errors, their associated root cause, and an action plan were recorded using the Lean A3 method. Participant observers were also consulted for their familiarity in the current process. To lower the frequency of operator failure, breakdown points in workflow were targeted. Action plans included workflow redesign, education, or training.

Workflow redesign dramatically reduced the number of process-driven errors by 40%[20].

Conclusion

The 21st century laboratory is faced with an expanded set of opportunities for medical care and research, with new technologies changing our ability to leverage biological understanding for improved patient care. But with these opportunities come several challenges in the way samples are identified and handled in the lab, especially as older manual methods are rapidly becoming insufficient given rising sample volumes and cross-lab collaboration. While reducing inefficiency will become a priority for labs struggling with outdated methods, oversight bodies will help to ensure that all labs embrace new methods for tracking data and samples effectively.

Preserving samples is critical issue for the livelihood of labs, to ensure that sample identification endures as long as the sample needs to last. If the need is to store samples for years, lab personnel should be confident that the label information remains clear and relevant.

Moreover, preserving samples is a critical issue for the livelihood of labs, to ensure that sample identification endures as long as the sample needs to last. If the need is to store samples for years, lab personnel should be confident that the label information remains clear and relevant. To ensure that samples are labeled with permanent identification, best practices indicate the following considerations:

- Use machine-printed labels. Removing the variable of handwriting can eliminate one of the biggest known risks in sample identification.
- Use labels tested for the environment. With many samples going into extreme environments during processing and storage, it is key to use a label material that has been shown to withstand these environments.
- Test all labels before use. Even with performance data from the label manufacturer, good practice calls for testing new materials through the entire sample-handling workflow.
- Move to automated tracking. Best practice calls for applying a sample identificaiton code before the sample is processed, which can be easily achieved with a simple automated system.

Minimizing errors in the process has always been the goal of the clinician and the scientist. Scrutiny of weak spots in the existing sample identification and handling process points to several potential improvements, including the adoption of standardized labeling methods, barcoding, and the use of labels designed to withstand extremes in the lab environment. With minor changes, many labs can dramatically reduce the risk of failure in their sample workflow, protecting not just their samples, but also the potential value that each sample represents for future studies and discovery.

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