

Intelligent Systems Application Studies:

# Robotics and Automation for Medical Applications

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## Laboratory Automation Final Report

Study commissioned by:

**precarn**

Intelligent Systems. Thinking Technology.

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## **Laboratory Automation**

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# *Executive Summary*

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This paper examines laboratory automation. It was sponsored by Precarn, a national, industry-led, not-for-profit consortium that supports collaborative research and development in intelligent systems. The results will be used by Precarn to guide their business planning and to inform members of the laboratory automation community.

The information in this paper was obtained from a review of the literature, interviews with representatives from industry, academia, and government in Canada and the United States, and a workshop attended by laboratory automation stakeholders.

Laboratory automation uses mechanical and computer technologies to perform a scheduled series of tasks that increase the throughput, accuracy, and reliability of laboratory tests. While automation has always excelled in situations that are predictive and repetitive, recent advances in the intelligence of laboratory automation technologies have broadened the situations in which they can be applied.

Use of laboratory automation can be segmented in two dimensions. The first dimension is the application area. In diagnostics, tests are conducted on human samples, typically to assess the implications for patient health. In research, tests are conducted on chemical and biological samples, typically to deduce functions and interactions that will lead to new drugs or understandings of biological processes. The second dimension is the volume of testing. Large volume operations can benefit from more complete automation. Small volume operations typically need more flexibility and human intervention.

Just about any laboratory can take advantage of some of the advances in automation – the questions are what to automate and to what extent? The options cover the spectrum from islands of automation, which retain some manual processes, to fully automated integrated systems. The optimal degree of laboratory automation depends on the laboratory setting and considerations of cost, throughput, and flexibility. Other considerations include the time that will be required to complete the installation, the space available, the proportion of the tests that are routine, the availability of skilled technicians, safety, and reliability.

Components of an automated laboratory include the control and information system, and mechanisms for sample storage, preparation, transport, and analysis. Laboratory automation trends include:

- **Intelligence** – In diagnostic laboratories, the goals of automation are intelligent sorting, transportation, routing, and analysis. Such intelligence contributes to patient safety and laboratory cost efficiency. In research laboratories, progress in automating the screening and

synthesis of compounds has shifted the bottleneck in drug discovery to data analysis. Intelligent systems could help automate the analysis of this data.

- **Quality Assurance** – In parallel with expectations about increasing laboratory productivity and cost effectiveness, there are increasing pressures for laboratories to ensure higher levels of quality. In research laboratories, quality is a necessary condition for excellent research; in diagnostic laboratories, it is necessary for patient health.
- **Standards** – Ideally, a laboratory automation system would combine the best components from a variety of equipment vendors. However, this is complicated by a lack of standards in component operation and communication. There is a trend towards open standards in programming languages and communications protocols.
- **Higher Densities** – Originally, micorplates had 96 wells; in an effort to increase throughput while maintaining compatibility with existing automation equipment, the number of wells has increased to 1,536 or more on the same sized plate. Working with smaller volumes requires more precise, and expensive, equipment, and there is a greater risk that environmental factors will interfere with results.
- **Miniaturization** – Emerging technologies, such as microarrays, microfluidics, and lab-on-a-chip, may enable laboratory automation to be condensed down to fewer pieces of equipment, and therefore there will be less need for transport and robotics to move samples between workstations.
- **Modular Automation** – Fully integrated total laboratory automation (TLA) systems include sample sorting, routing, centrifugation, aliquot preparation, analysis, and sometimes, post-analytical storage and retrieval. Modular systems of laboratory automation have been developed in recent years as an alternative to TLA. Many remain uncertain as to whether maximum centralization (TLA) is to be preferred over maximum decentralization ( point-of-care testing).
- **Laboratory Design** – Laboratory system design and architecture are closely linked. For large-scale systems, facility layout is critical to their design and success. As a result, there has been a trend to consolidated core laboratories serving multiple disciplines. But, in reaction, there has also been a counter-trend towards point-of-care testing in clinical situations that places fewer demands space.

The original motivation for laboratory automation was primarily cost. While this is still a driving requirement, there are many other reasons to automate, including error reduction, productivity, safety, and labour satisfaction. In fact, the reasons for automation have become so compelling that it is no longer simply a competitive advantage for laboratories, but rather is now a competitive necessity.

Given the trends in laboratory automation, and Canada's strengths, the areas suggested for future focus include: system intelligence, imaging, and standards. This will require cooperation among industry, academics, hospitals, and government. Precarn has a role to play in monitoring research trends, facilitating the involvement of the other stakeholders, and organizing demonstration projects.

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# *1. Introduction*

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Precarn is a national, industry-led, not-for-profit consortium that supports collaborative research and development in intelligent systems. Precarn's mission is to make Canadian firms more globally competitive by promoting the development and use of intelligent system technologies and expertise.

Intelligent systems emulate the human ability to perceive, reason, make decisions, and act. They enable machines and devices to anticipate requirements and deal with environments that are complex, unknown, and unpredictable. The broad range of intelligent technologies includes robotics, sensors, knowledge-based software, and human-machine interfaces [Precarn 2004].

Precarn has commissioned studies of the application of intelligent systems in six priority application areas. The objective of the studies is to determine future market and technology trends in order to identify directions for further research, development, and commercialization of technologies.

One of these application areas is Robotics and Automation for Medical Applications. Hickling Arthurs Low (HAL) Corporation and Canadian Surgical Technologies and Robotics (CSTAR) have been invited to undertake the investigation of this area. The results will be used by Precarn to guide their business planning, and to inform members of the medical robotics and automation community.

There are many ways in which robotics and automation can be used in medical applications. We are concentrating our efforts in two sub-areas: robotics intervention (covering areas such as robotic assisted surgery, tele-surgery, robotic tools in diagnosis, and robotic delivery systems) and laboratory automation (covering areas such as genomics, proteomics, drug discovery, and diagnostics). The focus of this paper is on laboratory automation.

Information in this paper was obtained from three sources. The foundation for the paper is a review of the literature on laboratory automation. This was augmented by interviews with representatives from industry, academia, and government in Canada and the United States. Finally, the literature review and interview results were used as the basis for a workshop attended by laboratory automation stakeholders. Four questions were considered at the workshop:

- What are the major issues in laboratory automation today?
- What are the most important technology trends and how will they impact the use of laboratory automation?

- What are Canada's strengths and opportunities in these areas?
- What should be the role of stakeholders (industry, academics, hospitals, government, and Precarn)?

The following chapters use the information obtained from the literature review, interviews, and workshop to discuss laboratory automation applications, technologies, trends, benefits, Canadian strengths and opportunities, and future directions.

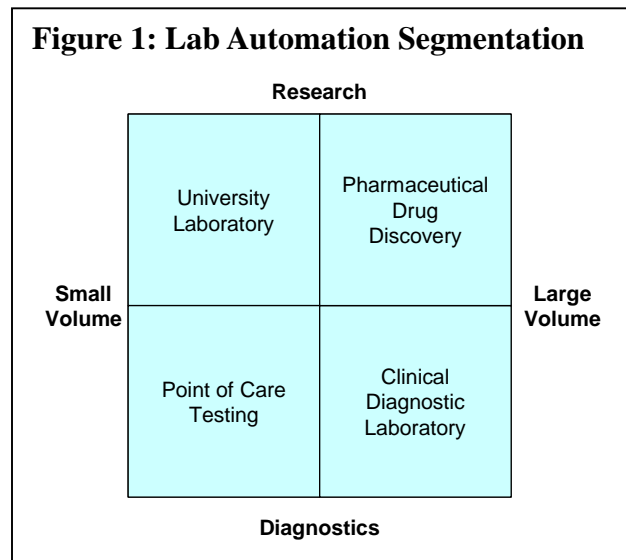
# 2. *Laboratory Automation Applications*

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## 2.1 *Overview*

Laboratory automation uses mechanical and computer technologies to perform a scheduled series of tasks that increase the throughput, accuracy, and reliability of laboratory tests [Hynd 2000]. While automation has always excelled in situations that are predictive and repetitive, recent advances in the intelligence of laboratory automation technologies have broadened the situations in which they can be applied.

In most cases, these systems will not necessarily process tests more quickly than is possible by a focused human [Hudson]. However, the systems can work consistently for extend periods with minimal human intervention. The resulting benefits include higher total throughput, reduce potential for human errors, limited human exposure to hazardous material, improved record keeping, reduced labour costs, consistent performance, and less need to find and train skilled technicians [Hudson].



Use of laboratory automation can be segmented in two dimensions (see Figure 1). The first dimension is the application area. In diagnostics, tests are conducted on human samples, typically to assess the implications for patient health. In research, tests are conducted on chemical and biological samples, typically to deduce functions and interactions that will lead to new drugs or understandings of biological processes.

The second dimension is the volume of testing. Large volume operations can benefit from more complete automation. Small volume operations typically need more flexibility and human intervention.

Major users of laboratory automation can be found in each quadrant. For example, pharmaceutical drug discovery is a research application undertaking very large test volumes, while university laboratories may employ similar tests, but at much smaller volumes. Similarly, central clinical diagnostic laboratories in large hospitals must process large test volumes, while point of care testing focuses on rapid response to targeted needs in small quantities.

Laboratory automation has been developing for the last twenty years. During that time, major advances have been made in the technology in parallel with changes in the need for automation and the philosophy about how it should be employed. Initially, the focus was on large, high-volume installations. Progress in these applications has enabled the development of automation technologies that are now cost-effective and flexible enough for the academic and small biotech sectors [Cechetto 2004].

## 2.2 *Diagnostics*

Clinical diagnostic activity typically involves the qualitative or quantitative determination of an analyte or a cell in a patient sample [Truchaud 1997]. Instrumentation may include tests for chemistry, immunoassay, hematology, coagulation, drug screening, and others [Orsulak 2000, Truchaud 1997].

Like the health care industry in general, the diagnostic laboratories are being challenged by many factors – rising costs, shrinking budgets, shortages of skilled personnel, and pressures to ensure patient safety. Among the many variables that can affect the efficacy of the health care environment, three in particular are prompting dramatic changes to diagnostic laboratory processes, and greater demand for automation [Browning 2004]:

1. **Labour Shortages:** Staff vacancies are at a 12- year high, and job shortage rates range from 7 to 20%. An estimated 8,000 vacant positions are generated annually. The average lab technician is in his, or her, late forties, so the labour pool is both dwindling and aging. Laboratories must take steps to adopt new processes and systems to offset the labour shortage.
2. **Medical errors and patient safety:** According to the Institute of Medicine (IOM), medical errors lead to as many as 98,000 deaths and 1 million injuries per year in the United States. Laboratory test results are an important determinant of a doctor's clinical decision in treating a patient, so quick turnaround time and accurate diagnostic results are vitally important. In fact, the laboratory provides as much as 80% of the information used by physicians to make important medical decisions. Laboratories are obligated to provide the right test for the right patient at the right time.
3. **Length of stay:** A hospital's economic well-being is contingent on positive patient outcomes and low length of stay. The sooner a laboratory provides physicians with valuable patient test results, the sooner physicians can diagnose and treat their patients. That, in turn, can mean a shorter patient length of stay and have an immense impact on a hospital budget. Laboratories must provide physicians with fast, accurate test results and decrease variability in test turnaround time to help lower patient length of stay.

In reaction to these pressures, there is a trend to seek solutions through laboratory automation. The hope is that automation will decrease turnaround time, improve test reliability, reduce unit costs, increase productivity, provide a safer working environment, and free technicians to perform other duties. To a great extent, these hopes are being realized – analytical equipment has been successfully automated, yielding dramatic improvements in throughput, precision, convenience, and data handling [Orsulak 2000].

Most of the developments have been aimed at core clinical laboratory operations, and have primarily addressed routine pre-analytical and analytical processing of traditional specimens arriving in blood collection or similar aliquot tubes. Much less attention has been given to specialized applications such as processing specimens for urine toxicology, and only recently have vendors attacked the problems associated with sorting and maintaining the laboratory's inventory of specimens [Orsulak 2000]. With automation, it is now feasible to combine the stat and routine tests in the same system [Young 2000].

The original objective was for 'Total Laboratory Automation' (TLA) that would maximize the degree of automation in large clinical laboratories. The concept was conceived in Japan about 20 years ago and has been widely accepted there. However, in the United States, only a very small proportion of even the largest hospital and reference laboratories have installed such systems [Young 2000]. Today, there are estimated to be 170 laboratories in Japan, 35/50 in North America, and several in Europe with total automation systems [Hawker 2000].

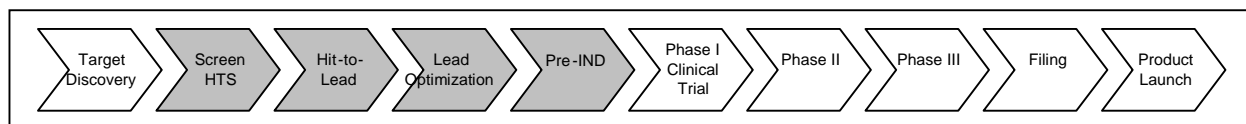
While in the beginning the impetus for automation may have been a quest for a monolithic system, there is now a realization that the optimum balance of functionality, capacity and throughput can vary with the situation and demand a more modular approach. Accordingly, there is now considerable choice in flexible systems that support distributed testing (point-of-care and remote automated laboratories) as well as core laboratory automation (work cells and, most recently, integrated modular automation).

## 2.3 *Research*

Research activity involves the analysis of the reaction of compounds under different situations, typically in the search for new drugs. Research is conducted by organizations such as established pharmaceutical companies, biotech start-ups, and academic research centers.

The art and science of drug discovery and development exist on a continuum that often requires an average of about 8 to 12 years to complete (Figure 2). More sophisticated science, more complex disease targets, a more intensive regulatory process, and a growing need for more elaborate data have increased the length, complexity and cost of the pharmaceutical research and development process [Hallock 2004].

In drug discovery, the demand for new drugs has outpaced the ability of companies to generate and characterize leads using conventional assay techniques. As a result, automated solutions are now playing a mission-critical role in filling the development pipeline for pharmaceutical companies and contract research organizations [Zymark].

**Figure 2: The Drug Discovery Process**

Laboratory automation applies primarily to the shaded steps

But, even small research labs are benefiting from automation. For example, university laboratories provide small molecule screening to researchers across Canada who would otherwise not have access to such facilities, and provide students with training and experience equivalent to that found in industry [Cechetto 2004].

Most laboratory automation efforts have focused on the early stages of the process: target identification and validation, screening, and lead optimization. Target identification begins with drug candidates that may be molecules derived from natural sources, such as plants, or through combinatorial chemistry [Hudson]. Drug candidates are often stored in libraries of 10,000 to 10,000,000 different compounds. These libraries are significant intellectual property assets of drug companies.

High Throughput Screening (HTS) is the use of laboratory automation to enable the rapid processing of large numbers of drug tests, commonly defined as 10,000 samples per day [Hudson]. It is used to search a large number of potential drug candidates for activity against a specific disease. The trend is to screen ever-higher numbers of samples, leading to the term UHTS, or Ultra High Throughput Screening, referring to the analysis of more than 100,000 samples per day.

HTS was enabled by the development of the microplate, which provided a platform that enabled hundreds of experiments to be conducted simultaneously in parallel, while using less consumables and equipment compared to the previous test-tube approach [Hudson], and requiring less tedious and repetitive work by lab technicians.

## 2.4 Issues

The interviewees and the workshop of sector representatives were asked to identify major issues in laboratory automation today. They created the following list:

1. **Standardization and interoperability:** the proliferation of many specialized vendors of laboratory equipment, proprietary control systems, and the lack of standards for interoperability makes it difficult to create integrated systems. This is especially a problem when third-party vendors change their firmware.
2. **Cost:** both up-front capital cost and ongoing operating costs. Perversely, in public organizations it is often easier to obtain capital funds than operating funds, resulting in equipment that is underutilized.

3. **Intelligent data analysis:** the bottleneck in laboratory automation is shifting to data analysis – how to manage, access, and manipulate the large amounts of data generated by automated systems. Can intelligence be added here?
4. **Data integration:** integration of laboratory data with a patient's records and automated record keeping.
5. **Remaining automation gaps:** the remaining 'gaps' in laboratory processes impact the overall efficiency of the system and create bottle-necks, but the cost of automating them is very high.
6. **Laboratory design:** fully automated systems tend to be large and require considerable floor space. They also require specialized services (electricity, plumbing, communications, ventilation) that can be problematic when retrofitting older buildings.
7. **Human Resources:** as automation systems change and evolve, people with a variety of competencies need to be recruited and trained. Training must be on-going.
8. **Throughput:** plates, samples, and data.
9. **Industry consolidation:** suppliers are being absorbed into larger companies. This may mean less competition and therefore less innovation.
10. **Government regulation:** new technology regulations are becoming stricter. There are increasing regulatory requirements for software and software components will be sold as part of regulatory compliance.

These and other issues will be discussed in the following chapters.

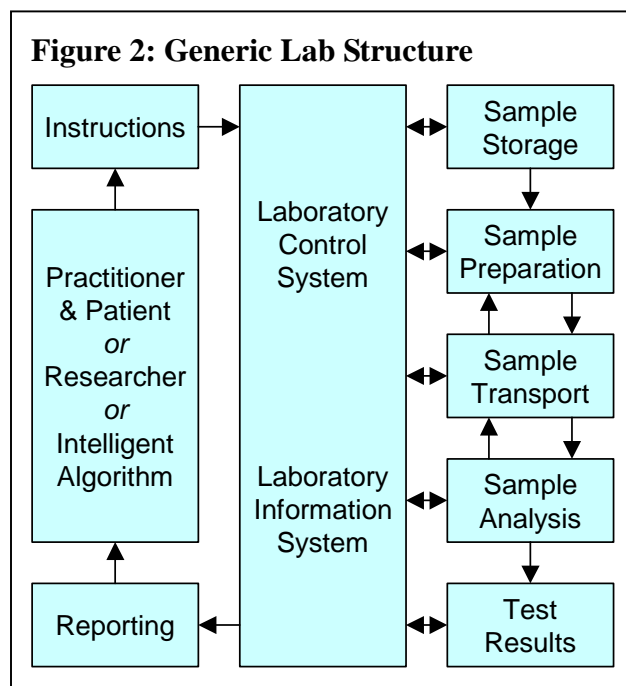
# 3. *Laboratory Automation Technologies*

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## 3.1 *Overview*

Just about any laboratory can take advantage of some of the advances in automation – the questions are what to automate and to what extent? The options cover the spectrum from islands of automation, which retain some manual processes, to fully automated integrated systems [Gurevitch 2004].

The optimal degree of laboratory automation depends on the laboratory setting and considerations of cost, throughput, and flexibility. Cost and throughput are typically proportional, while throughput and flexibility are inversely proportional. In general, the more human interaction that is involved, the more time a test takes and the more opportunity there is for variability and human error. Flexibility is usually the priority in small academic labs, and throughput in large industrial settings.



Other considerations include the time that will be required to complete the installation, the space available, the proportion of the tests that are routine, the availability of skilled technicians, safety, and reliability.

The specifics of a laboratory automation system will differ depending on the application and size, but the generic structure will resemble Figure 2. On the left side of the figure is the source of the instructions for the tests to be done. For a diagnostic laboratory, this is the Practitioner/Patient that orders a test and provides a sample. For a research laboratory, this is the researcher who designs an experiment. In either case, the instruction for a test may be guided by the results reported from previous tests. Increasingly in the future, an intelligent system may act in this

capacity by designing new tests based on data mined from previous tests.

In the centre of the figure is the software that controls the operation of the automated equipment and maintains the information flows and storage. Given the increasing sophistication of the automation equipment and the increasing volume of information that is created, this software is becoming particularly important to the success of the system.

On the right of the figure are the classes of components that make up a laboratory automation system – some means to store samples, prepare them for analysis, analyze them, record the results, and transport them between the stages. The phases of a lab process are commonly termed pre-analytical, analytical, and post-analytical. The degree of automation is often described in terms of ‘walk away time’ – the amount of time the system can operate without human intervention.

The following sections look at each of these components of a laboratory automation system.

## ***3.2 Control and Information Systems***

Control of a laboratory automation system begins with a physician, who requests a clinical test, or a researcher, who designs a test suite. In the case of a diagnostic test, a specimen must be taken from a patient, identified (often through the use of bar codes), and transported to the laboratory along with the details of what is to be tested. In some hospitals, the test request may be entered into a Hospital Information System (HIS) that interfaces with the Laboratory Information System (LIS).

The LIS keeps track of what tests are to be done and the results of the tests that have been done. In the case of research, this can represent a significant amount of information. In the case of a diagnostic laboratory, the confidentiality, security, and traceability of this information can have serious legal implications.

Control information follows each sample through the system to the various computers running the laboratory equipment. At each analytical station, the control system replaces the intelligent operator (the medical technologist) with embedded rules that allow a predefined level of uninterrupted or controlled operation before human intervention [Markin 2000]. Communications between equipment from different vendors is a perennial problem that is now being addressed through the development of standards.

An automated system must have the ‘intelligence’ to:

- Schedule workload;
- Implement test instructions;
- Control and monitor instruments;
- Facilitate quality control;
- Verify results;
- Repeat or cancel tests as needed; and
- Report and store results.

### 3.3 *Storage*

In diagnostic laboratories, specimens may be contained in plates, flasks, bottles, or dishes, and may be closed or capped. The specimens must be sorted, stored until need, and then retrieved. This process consumes an appreciable amount of time and effort, and accounts for a large portion of errors in diagnostic laboratories [Felder 2003].

Proper specimen storage can reduce sample degradation from long-term exposure to incorrect temperatures, decrease the chance of specimen mix-ups, and reduce the time necessary to find the specimen and put it back in the analytical queue [Felder 2003].

In research laboratories, tests are conducted on compounds stored in libraries and retrieved as needed. Sample libraries include discrete compounds, defined compound mixtures, and natural product extracts. Sample libraries can exceed one million compounds today and these are being screened against an expanding range of targets.

As compound libraries continue to grow in size, assay systems become increasingly complex, and high throughput screening (HTS) technology becomes ultra-HTS, the need to store more samples and more discrete compound collections in labware of varied dimension, shape, and function, represents a significant problem for drug discovery laboratories. Containers include conventional 96-well microtiter plates, thinner high-density plates, deep-well plates used for cell-based assays and for storage of larger sample volumes, and 1.5-mL microtubes [Gedrych 2000].

Storage issues include:

- **Sample Collection:** Sample acquisition, structural diversity, physical storage, physical manipulation, sample purity and stability.
- **Materials Management:** Logistics, information technology, quality control, and systems integration.
- **Instrumentation and Laboratory Automation:** Sample preparation, sample retrieval, and screening set creation.

### 3.4 *Preparation*

The preparation stage is typically the most heavily automated. General robotic tasks include steps such as sample transportation, identification, sorting, LIS data recording, centrifugation, cap removal, aliquotting, and loading samples into diagnostic devices [Hallock 2004]. Preparation issues include:

- **Traceability** – recording of tasks, times, and environmental conditions.
- **Safety** – isolation of hazardous materials, protection against breakage.
- **Materials handling** – volume detection, ability to use different sizes of secondary tubes, no carryover by tips or fluidic device, compatibility with sample storage.

## 3.5 *Transport*

The core of laboratory automation is the transportation, and the loading and unloading, of samples among the storage, preparation, and analysis components of the system. This can be accomplished using linear tracks, stackers, and cylindrical robotic arms. The choice of transport mechanism is typically a trade-off between throughput and flexibility in adapting to changes in the system configuration.

Systems can be fully integrated or consist of several connected workcells. A workcell can be thought of as a small, automated solution that addresses a single task such as reading plates, or some portion of an assay. A workcell may consist of a single automated device, or several. An advanced workcell may be capable of performing most or even all steps for an assay [Hudson].

## 3.6 *Analysis*

After sample sorting and preparation, investigations are performed either by automated systems, which are often closed or dedicated to a group of assays (biochemistry, hematology, immunoassays, coagulation, urinalysis, cell counting, etc.), or by methods with a lower level of automation (bacteriology, virology, parasitology, cytology, histology). The equipment may include [Hudson]:

- Pipetting workstation (also known as a liquid handling workstation or a liquid handler)
- Result detection (absorbance, fluorescence, chemiluminescence, bioluminescence, and radioactivity)
- Washers – rapidly rinse the plate with the needed buffers or reagents.
- Dispensers – Perform bulk pipetting.
- Sealers – Automate the sealing of microplates with a protective layer.
- Bar code labellers and readers – Apply bar code labels to microplates.
- Incubators – Provide the temperature and humidity environment required by many assays.
- Autosamplers – inject samples from microplates into analytical instruments.

Cell culture is used for many purposes, including toxicity studies, monoclonal antibody production, human viral vaccine production, artificial tissue engineering, and cell and gene therapy. The cell culture process includes cell growth, harvesting, reseeding, and analysis. The cell culture incubator includes atmospheric control, evaluation of pH, nutrient and waste concentration, and an information system that is able to manage operations, especially vessel handling [Triaud 2003].

# ***4. Laboratory Automation Trends***

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The following sections discuss trends in laboratory automation relating to intelligence, quality assurance, standards, microplates, miniaturization, modular automation, and laboratory design.

## ***4.1 Intelligence***

While the hardware and software portions of a laboratory automation system are interdependent, the trend has been away from a focus on the physical movement of samples among devices towards a focus on the control and interpretation of the vast amounts of data that are involved.

In diagnostic laboratories, the goals of automation systems are intelligent sorting, transportation, routing, and analysis. Intelligent systems can provide solutions to the complex process of sample dilution, repeat and reflex analysis, and queuing for medical urgency. Once specimens have been analyzed, storing and retrieving them efficiently will permit automated re-analysis and other forms of intelligent retesting [Felder 2003].

Such intelligence contributes to both patient safety and laboratory cost efficiency by allowing the laboratory to provide data for patient diagnosis more rapidly. In the future, autonomous system software should be able to make effective management decisions through adjustable autonomy (changing their level of independent decision making based on the circumstances) and by prioritizing new goals, learning from past experience, and providing user-friendly output [Felder 2003].

In research laboratories, progress in automating the screening and synthesis of compounds has shifted the bottleneck in drug discovery to data analysis. As a consequence the overall throughput increase of the drug discovery process is not nearly as much as expected and has not yet resulted in an increased number of drugs discovered [Nicolaou 2001].

HTS has created huge databases that are reservoirs of potentially valuable information ready for mining [Cechetto 2004]. Intelligent systems could help automate the analysis of this data by emulating the data analysis process of human experts by inspecting results, evaluating the quality and promise of active data points, and identifying leads [Nicolaou 2001].

## 4.2 *Quality Assurance*

In parallel with expectations about increasing laboratory productivity and cost effectiveness, there are increasing pressures for laboratories to ensure higher levels of quality. In research laboratories, quality is a necessary condition for excellent research; in diagnostic laboratories, it is necessary for patient health. According to the Institute of Medicine, diagnostic mistakes are identified as a key source of medical errors. Automating pre- and post-analytical tasks – which is where most errors in the lab occur – can play a significant role in the reduction of medical errors and in the improvement of patient safety [Browning 2004]. Quality has numerous aspects:

- Equipment must be properly adjusted,
- Samples must be protected from contamination (for example, from other samples and outside pollutants) and degradation (for example, from oxidation and temperature)
- Samples must be properly identified and tracked.
- Results must be properly recorded and safeguarded.

Several major commercial laboratories have implemented six sigma quality management systems. Six sigma dictates that laboratories should achieve an error rate of no more than 3.4 errors per million laboratory operations. Achieving a six sigma quality level will require widespread use of automation technology since it has proven difficult to avoid errors when manually performing the complex tasks found in diagnostic laboratories. For example, 60 percent of the labour in a diagnostic laboratory is focused on the pre-analytical phase of laboratory testing, and this phase accounts for a significant proportion of errors. Examples of pre-analytical errors include failure to place stat specimens in stat queues, excessive waiting time for specimens following centrifugation, improper aliquotting, and lost and mislabelled specimens. Automated pre-analytical processors have already demonstrated their utility in reducing labour and errors, but they will also improve the documentation of errors, for which each laboratory will become accountable in the future [Felder 2003].

## 4.3 *Standards*

Ideally, a laboratory automation system would combine the best components from a variety of equipment vendors. In fact, this is almost a necessity as most vendors are small and specialize in certain aspects of automation and analysis equipment, and with the rapid progress in equipment capabilities, changing components is a frequent occurrence. However, this is complicated by a lack of standards in component operation and communication.

The laboratory automation community has recognized the need for standards and as a result, there is a trend towards open standards in programming languages and communications protocols to improve the interoperability of devices and software within a system. Standards cover aspects of automation ranging from bar code labels, specimen containers (tubes), and carriers to the electromechanical and computer interfaces between devices, automation systems, and information systems and various operational considerations [Hawker 2000]. Initiatives for laboratory automation standards include:

- The Clinical and Laboratory Standards Institute (CLSI) (formally National Committee for Clinical Laboratory Standards) works on standards in the following areas:
  - Automation and Informatics
  - Clinical Chemistry and Toxicology
  - Evaluation Protocols
  - General Laboratory Practices
  - Healthcare Services
  - Hematology
  - Immunology and Ligand Assay
  - Microbiology
  - Molecular Methods
  - Point-of-Care Testing
  
- Health Level Seven (HL7) is an American National Standards Institute (ANSI) accredited Standards Developing Organizations with a mission to provide standards for the exchange, management and integration of data that support clinical patient care and the management, delivery and evaluation of healthcare services. Specifically, to create flexible, cost effective approaches, standards, guidelines, methodologies, and related services for interoperability between healthcare information systems.
  
- The Standards in Automation special interest group of the Society for Biomolecular Screening works on liquid handling standards, evaluation of readers, and instrument automation. The Microplate Standards Development Committee of the Society for Biomolecular Screening recommends, develops, and maintains standards to facilitate automated processing of microplates on behalf of and for acceptance by the American National Standards Institute (ANSI).

## 4.4 *Higher Density Microplates*

Originally, microplates had 96 wells arranged in 8 rows and 12 columns [Hudson]. In an effort to increase throughput while maintaining compatibility with existing automation equipment, the number of wells has increased to 384, 1,536, or more on the same size of plate. The resulting smaller wells have both advantages and disadvantages.

In addition to increasing throughput, the smaller wells require lower reagent volumes, a potential cost saving in some situations. However, working with smaller volumes requires more precise, and expensive, liquid handling equipment. Also, the smaller the volume, the more environmental factors will interfere with the ability to determine results [Truchaud 1997]. For example, 1,536 well plates are less frequently used due to the associated evaporation problems [Hallock 2004].

In many cases, more accurate positioning of the plate is required on the target device because of the smaller wells and higher density of wells. The 1,536-well plate produces a density that already stretches the ability of liquid handlers and other devices, and even higher densities are being developed [Hudson].

With the requirement for more precision, standards become more important. The Microplate Standard initiative is being led by the Society for Biomolecular Screening on behalf of, and for acceptance by, the American National Standards Institute (ANSI). The mission of the Microplate Standards Development Committee is to recommend, develop, and maintain standards to facilitate automated processing of microplates.

## 4.5 *Miniaturization*

The trend toward increasing miniaturization and higher throughput screening will no doubt continue. Cutting-edge developments not only include 1,536 and denser microplate formats, but also emerging technologies such as microarrays, microfluidics, and lab-on-a-chip:

**Microarrays** – Oligonucleotides, cDNAs, proteins, peptides, or other small molecules organized in a grid on a glass or plastic slide, silicon chip, fibre optic array, or filter membrane.

**Microfluidics** – Lab-on-a-chip technology based on the transport of nanoliter or picoliter volumes of fluids through microchannels within a glass or plastic chip. Microfluidics systems evolved from MEMS research.

With the development of these technologies, laboratory automation will be condensed down to fewer pieces of equipment and there will therefore be less need for transport and robotics to move samples between workstations.

## 4.6 *Modular Automation*

Fully integrated total laboratory automation (TLA) systems include sample sorting, routing, centrifugation, aliquot preparation, analysis, and sometimes, post-analytical storage and retrieval [Orsulak 2000].

Modular systems of laboratory automation have been developed in recent years as an alternative to TLA. They allow more flexible use of space or positioning of functions in existing facilities. The trend in automation has moved from total laboratory automation to a modular approach for a number of reasons [Hudson]:

- Long implementation timeframes: A TLA system may take 6-12 months between the time of the initial order of the system and the time it becomes fully operational. Workcells can be more rapidly configured, installed, and brought into operation.
- Inflexibility: The large-scale systems can be installed to be highly effective in the execution of a specified assay, but it is often difficult as well as prohibitively expensive to reconfigure them for a different assay. Workcells can be more easily reconfigured when the need arises.

- Large investment: TLA systems can be very expensive to implement, costing from \$150,000 to over \$1,000,000. Workcells make fewer demands on laboratory design, can be scaled more easily, and have lower maintenance requirements.

Many remain uncertain as to whether maximum centralization, as represented by total laboratory automation, is to be preferred over maximum decentralization, as represented by point-of-care testing [Young 2000].

If assays change relatively frequently, or if a company wishes to have lab technicians run equipment, then it is likely that a modular approach will be more cost effective because it is easier to train technicians and to modify equipment operation. If time is the most critical issue, then full automation is usually the preferred solution [Gurevitch 2004].

Generally, the largest laboratories are interested in completely integrated automation platforms, or total laboratory automation systems. The majority of medium-sized to small labs are interested in consolidating their analytical workstations with task-targeted automation to create a less expensive alternative to TLA. These labs typically seek integrated workstations. It is also possible for the smaller laboratory to use workstations that target specific tasks [Felder 2003].

## 4.7 *Laboratory Design*

Laboratory system design and architecture are closely linked. For large-scale systems, facility layout is critical to their design and success, with each part of a laboratory designed and built to fit its ultimate function. As a result, there has been a trend away from discipline-specific, bench-intensive laboratories to consolidated core laboratories serving multiple disciplines [Wing 2000]. Interestingly, in these cases the implementation of automation has often been used as a mechanism to force or expedite laboratory redesign [Markin 2000].

But, in reaction, there has also been a counter-trend towards point-of-care testing in clinical situations that places fewer demands space [Wing 2000].

## 4.8 *Trends*

The interviewees and the workshop of sector representatives were asked to identify the most important technology trends in laboratory automation. They created the following list:

**Imaging:** increasingly important, especially high-resolution images. The rapid growth of image sizes will require new technologies in storage, compression, and presentation. Image analysis will become more important and intelligent systems will be required as images become larger and more complex. Systems are advancing to handle bacteria. Pharmaceutical companies are screening 3456-point plates; HTS facilities in universities are working with 384 moving to 1536. HTS takes digital pictures, more than one per well, and stores thousands of pictures. Algorithms provide information about the cell; in the future, intelligence will be built into the algorithms to guide image acquisition.

**Miniaturization:** reductions in assay volumes; micro and nano-fluidics; plate density, size, and handling. Nanotechnology dispersing is important, using piezoelectric sensors and acoustic waves for detection. “Micro-fluidics is having a big impact in R&D” in the pharmaceutical industry according to an industry researcher.

**Data Analysis:** – Software development has not kept up with hardware advances. Spreadsheets are currently used, but now the number of data points exceeds the capacity of the software. Commercially available relational databases are used for examining results, but commercial solutions are not necessarily tuned to individual user needs.

**Liquid Handling:** Volumes will get smaller, with microlitre plates moving down to nanolitres. The issue will be accurately dispensing small volumes. Software for scheduling of liquid handler plates could be intelligent and optimize the run, order, and timing sequence in the laboratory.

**Automated Detection:** Micro-fluorescence absorption radioactivity is important. New ideas include cantilever systems to assist protein identification, single cell use (not tissues), and label free detection (ways other than fluorescence to detect protein interaction). In the future, mass spectrometry and liquid chromatography will be on-line (multimodal detection on a single sample). A researcher commented that we would see in the future, “the integration of multiple technologies into a fully integrated experiment. The information from other tools such as mass spectrometers will be integrated to determine cell shape. The techniques will be used eventually to look at human biopsy. This scenario is still many years away. Right now, experiments are conducted separately, doing the integration at the end point.”

**Complexity:** the number and complexity of tests done at one time will increase. High content screening to enable more than one variable to be measured at a time will be introduced. “Screening in the context of the biological system would be a powerful tool”. Measuring ADMET in one assay (absorption, distribution, metabolism, excretion, and toxicity).

**System design:** automation to: (i) move plates or specimens faster, with higher reliability (motors designed for distributed motion, a new plate motion technology), (ii) servers that accommodate third party equipment, (iii) shrinking of systems in modular form (small systems that can do more), (iv) scalable automation of assays, (v) more use of vertical space (robots moving vertically) because of a premium on laboratory space, and (vi) more modular, standardized equipment. There is a trend from, do it all systems to smaller, focussed systems.

**Disruptive technologies:** for example, lab-on-a-chip and in-silico (simulation) techniques may reduce the need for laboratory equipment.

# 5. *Benefits*

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The original motivation for laboratory automation was primarily cost. While this is still a driving requirement, there are many other reasons to automate – many of which cannot be quantified in economic terms. In fact, the reasons for automation have become so compelling that it is no longer simply a competitive advantage for laboratories, but rather is now a competitive necessity. The following sections examine cost and other benefits that are expected from laboratory automation.

## 5.1 *Cost*

A number of laboratories have examined in some detail the costs associated with the automation of the their laboratories. The following are some example results:

- Overall, laboratory process automation resulted in a 7% reduction in total cost per reportable result [Browning 2004].
- In 1990, the fully burdened cost per test was approximately \$24.00. In 1995, the cost per test was reduced to approximately \$16.00 and is estimated to fall below \$10.00 by 2005 [Markin 2000].
- The unit costs of producing a clinical laboratory result in chemistry decreased from \$2.25 per requisition in 1996 to \$1.45 per requisition in 1998 [Markin 2000]
- The payback (accumulated cost savings equalling the cost of the reorganization and automation implementation) was 2.5 years [Markin 2000]
- Comparison of the costs of manual and robotic methods: Manual 22.5 hrs, L£1350, Automated 7.5 hrs, L£450 [North 2000]
- Automation of the pre-analytical phase produced savings of 40% [De Capitani 2002]
- The \$4.02 million cost of the project will be paid off in ~4.9 years subsequent to placing the system into daily use [Hawker 2002]

Major influences on cost are labour, equipment and consumables, and these are examined next.

## Labour

Typically, studies find that the most significant cost savings of automation implementation are from the reduction in personnel (and therefore their salaries, benefits, and taxes) [Gurevitch 2004]. In one study, more than 40% of savings were from personnel [De Capitani 2002].

One case found that automation had the following reductions in labour [Markin 2000]:

- Consolidation of like processes
  - STAT Lab consolidation: 6 technologists
  - Similar processes: 8 technologists
- Delay of specimen transportation
  - Pneumatic tube system: 3 entry-level positions
- Robotic process: 8 technologists
- Implementation of outreach testing process: 3 entry-level positions
- Management efficiencies: 4 managers

Another study found the cost of personnel for the pre-analytical phase to be 596 euro/day after automation, compared to 993.8 euro/day before automation [De Capitani 2002].

A comparison of pre and post-implementation hiring rates of employees estimated a savings of 33.6 employees, whereas a similar comparison of ratios of billed units per employee estimated a savings of 49.1 employees [Hawker 2002].

## Consumables

Consumables, such as reagents, can be an expensive part of laboratory testing. Not only is there the purchase cost, but also the costs involved in properly disposing of these consumables after they are used. One of the oft-stated goals of automating a laboratory process is to reduce the cost of consumables, usually by reducing the size of reactions [Gurevitch 2004].

## Equipment

While automation tends to produce savings for labour and consumables, this is offset against the capital and maintenance costs of the automation equipment. Not only is the equipment expensive, but also instruments need to be frequently upgraded - not because equipment is worn out, but because instrument technology is advancing so rapidly (one case reported replacement at the rate of one instrument every six months on each HTS system) [Harding 2002].

Equipment also incurs support costs for calibration, regulation compliance, utilities, maintenance (including service contracts), computer interfacing, and inventory control, among others [Van Lente 2000].

## 5.2 *Error Reduction*

One of the main advantages of laboratory automation is reducing experimental error. Manual operations typically have high error rates due to boredom or fatigue [Gurevitch 2004]. With workstations, mistakes happen less often, but affect more samples when they happen. With fully automated systems, mistakes happen very rarely but affect a large number of samples very quickly.

In one example, the experimental error rate for a process was 50%, leading to 100% re-runs of the experiments. Automating the processes cut this to 10%. Improving the quality and quality control of the reagents cut this to 3%. In reducing this error, costs also were reduced and throughput was increased, finally rerunning 3% of experiments. In another case, lost specimens decreased by 58% [Gurevitch 2004].

The following error rates have been reported for genomic and chemical discovery processes [Gurevitch 2004]:

- Manual: 10%–30%.
- Workstations: 1–10%.
- Full Automation: 1%–5%.

## 5.3 *Productivity*

Not surprisingly, automation increases laboratory productivity. This has obvious cost benefits, but also benefits patients in terms of faster turn-around time for clinical tests, and benefits drug companies in terms of shorter time to market for new drugs.

A diagnostic laboratory found that automation dropped turnaround time on five of their most frequent tests from 49.2 to 18.9 min, an improvement of more than 60%. More importantly, at the 90th percentile, the test turnaround times on the same test mix were reduced from 72.2 to 33 min, a 55% improvement. In another case, median turnaround time decreased by an estimated 7 h, and turnaround time at the 95th percentile decreased by 12 h [Browning 2004].

For research laboratories it is estimated that if more productive discovery programs or better preclinical screens could boost clinical success rates from one in five to one in three, the capitalized total cost per approved drug would be reduced by as much as \$221 million to \$242 million. In addition, shifting just five percent of all clinical failures in phase III/regulatory review to phase I would reduce out-of-pocket clinical costs by up to \$20 million [Hallock 2004].

## 5.4 *Safety*

Laboratories are potentially dangerous places – containing perhaps HIV, hepatitis, and other pathogens. Therefore, the issue of safety is of particular concern to laboratories and their personnel. Automation means that tubes are handled less frequently and therefore technologists

have less chance of a sharps injury or splash from opening a sample tube. In one laboratory, exposure to biohazards such as splashed or spilled samples or broken test tubes was reduced by 25% through automation [Browning 2004].

Another concern is repetitive stress injuries, which are also reduced by automation [Hudson].

## ***5.5 Labour Satisfaction***

Given its impact on employment numbers, it is perhaps surprising that laboratory automation is often seen as an attraction by laboratory technicians. Skilled laboratory personnel are in short supply, and they see a modern automated laboratory as their preferred work environment; there is less dull, repetitive work, the work is safer, and they are exposed to new learning experiences on the latest equipment. Employers report that an automated laboratory has proven to be a key advantage in attracting and retaining highly qualified staff [Cechetto 2004].

# 6. *Canadian Strengths and Opportunities*

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The interviewees and the workshop of sector representatives were asked to identify Canadian strengths and opportunities in laboratory automation. They created the following lists:

## 6.1 *Strengths*

**Biotechnology:** Canada is seen as having a robust biotechnology structure (industry, universities, and government) as well as strengths in production automation that can be combined to develop rapid biological methods so processes can be turned into production. This will be important in the future, as screening will require biological material not short molecules. In the view of an industry interviewee, “Precarn has a role in bringing the science and production capabilities together to achieve the breakthroughs; NRC can also be involved and new commercial entities spun-off.” NRC’s strength is its combination of research capabilities, particularly pathogens and facilities.

**Proteomics:** Canada is at the forefront in proteomics research using robotics; science and production can come together to further this strength (“the issue is the cost of integrating systems and getting them to work”, according to a researcher).

**Imaging:** Algorithms for image analysis, enabling the definition of the cell edge, have been a strength in industry, supported by research in universities; an interviewee from university saw an opportunity for assisting this research further.

**People:** The talent pool in Canada was noted as an asset. A workshop participant commented that “Canada is the land of opportunity for high-quality researchers, especially non-US citizens.” It was however pointed out by both users and producers that it is difficult to attract and retain individuals with the right skills. One producer said sales and marketing people with international experience (needed because there are “no opportunities for big sales in Canada”) are particularly hard to find. At the same time, the automating of processes in the laboratory is removing many of the routine tasks and making laboratory positions more attractive.

**Institutional infrastructure:** Funding from Genome Canada, CFI, and others. As a result, there is increased funding for research. However, in the words of a workshop participant, “laboratory automation is the last to receive money”. Strong institutional receptor base: especially in health care (hospitals). Strong university research base. National Internet backbone (CANARIE).

**Contract Research Organizations (CROs):** Canada has some of the world’s largest.

## 6.2 *Opportunities*

**Health care:** for example, automated tissue imaging can be used as the input engine for telepathology. Hospitals in the north (and many in southern Ontario) have a shortage of pathologists.

**Intelligent systems:** these could include LIMS, PAT, clinical data (pathology, etc), and biomarker data. Data could be tied-in from automated labs involved in HTS, pathology, and clinical trials. Imaging, bioinformatics, in-silico drug design, screening.

**Computer-assisted diagnosis:** can be helped by Canada’s large Internet backbone and expertise in computer analysis.

**Universities:** research - good funding produces good results. To get basic research out of academic labs, and into the marketplace, requires venture capital support.

**Standards:** develop a Canadian hardware/control interface standard and a data collection standard. Fund small companies to develop interface platforms to existing equipment. Fund development of supervisory control and data collection software.

**Collaboration:** use the smaller size of our ‘scientific market’ as an advantage to increase exchanges between scientific fields.

# 7. *Future Directions*

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## 7.1 *General*

During the 1990's HTS automation and related technologies evolved rapidly and now, in the opinion of some, has reached a first plateau of maturity. However, there are still opinions about recommended directions for the future evolution of laboratory automation.

A survey of directors of screening organizations was conducted in 2001 to evaluate their perceptions of the current vs. desired state of high-throughput screening (HTS) automation [Hamilton 2002]. The survey encompassed attributes such as automation flexibility, throughput and operation. Questions were posed related to three aspects of screening automation: flexibility, throughput, and process complexity. Additionally the survey sought ranking of various automation attributes from two standpoints: 1) The technical importance of those attributes, and 2) The limitations those attributes place on the screening organization. Seventeen directors of US-based HTS organizations participated in the survey. The results included the following desires:

- Reduce the time required to complete a target screen. Respondents averaged 25.6 days and would like to reduce that to 11.6 days.
- Increase the duration of walkaway time. Respondents averaged 9.6 hours and would like to increase that to 15.4 hours.
- Simplify assays. Respondents averaged 7.3 unit operations per protocol and would like to decrease that to 5.3 unit operations per protocol.
- Improve system reliability. Respondents averaged 9.9% system downtime due to system failure and would like to decrease that to 2.1% system downtime.

Of note was the finding that no group was working at ultra-HTS levels. Up and downstream infrastructure realities proved to be a hindrance to pushing toward ultra throughput.

Other opinions in the literature on future directions for laboratory automation include:

- The need for very accurate, fast and realistically priced detection units. The sensitivity required by detection systems has forced detection technology towards CCD cameras [Hynd 2000].

- Development in the training and education of laboratory personnel [Hynd 2000].
- Reducing the number of instruments required in the clinical laboratory. The future clinical laboratory may well exist within one box [Van Lente 2000].
- Faster, less costly, automation systems that accommodate all tube sizes, including paediatric tubes [Felder 2003].
- User interfaces to the system [Markin 2000].
- The interfaces among hospital information system, the laboratory information system, the automation control system, and the hardware components [Markin 2000].

## 7.2 *Canada*

The interviewees and the workshop of sector representatives were asked to identify directions and roles for stakeholders in Canadian laboratory automation. They provided the following feedback:

- *Where should research and development in laboratory automation be focused?*

Given the trends discussed previously, areas identified for attention in developing new approaches include: (i) maintaining quality, which can suffer with low volumes - artifacts can be a problem; (ii) imaging using microscopes to look at cells - if proteins can be labelled, e.g. fluorescent labelling (see above), their movement in cells can be tracked through confocal microscopes with highly focused CCD cameras (the informatics is complicated), (iii) improved sensitivity and speed for plate readers, (iv) more rapid processing of biological material for screening, (v) high content screening focusing on karyotic cells and RNA interference, and (vi) designing/building more flexible, but standardized robotics, that allow for the integration of instruments.

- *What are the current and future roles of intelligent systems in laboratory automation?*

Components of laboratory automation where intelligent systems would have an important role include: (i) data analysis, performed live in automated fashion, in order to determine, for example, whether the data fails a quality control test, and to influence inputs to the system (some pilot tests are underway in pharmaceutical companies on this), (ii) intelligence in software, to automate decisions based on results, e.g. rerouting a plate (happening now, will be “big” in the future), and (iii) intelligence in hardware (a producer said this is part of the development in making equipment smaller).

- *What should be the roles of the various stakeholders?*

### **Industry**

- Be willing to take risks

**Academics**

- Basic research discoveries.
- Openness to partnerships with industry.
- Market/showcase research findings/technologies to industry.
- Provide return on public investment.

**Hospitals**

- Facilitate access of researchers to large numbers of clinical samples that will form the basis of large studies.
- Facilitate communication between the various ethics boards so that good ideas are not lost (many researchers are 'afraid' of using human tissue samples simply because of the administrative obstacles involved).

**Government**

- Ensure the financial security of technology clusters ("It is extremely hard to spend three years training a team and to retain the best elements when their jobs are not secure").
- Intellectual Property management: "IP is important but should be used in moderation. Often it is viewed as an obstacle to collaboration, especially when it necessitates extensive negotiations even for high risk projects that may not even produced 'marketable' IP. Maybe the philosophy should be, let's see if this will work first?"
- Maintain funding for academic research at competitive levels
- Sponsor/support exciting trends to market/industry
- Support small companies with an SBIR-like program.

**Precarn**

- Getting alignment of the key stakeholders involved, given the disparate groups involved.
- Raising the profile of laboratory automation.
- Monitoring research trends, niches, gaps; giving research workshops; identifying market opportunities.
- Tech-transfer champion.
- Organizing demonstration projects.

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