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Joint Genome Institute's Automation Approach and History

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(Production Instrumentation Supervisor)

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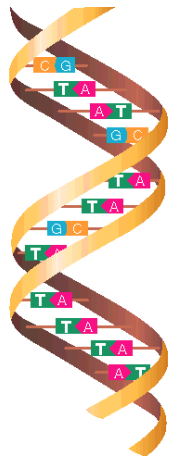
Agenda

- Brief overview of the how the Joint Genome Institute came into existence.
- Overview of DNA sequencing production line at the JGI.
- How our throughput has increased since 1999 to become a high through-put sequencing facility.
- Some instrumentation improvement highlights along the way and how they are used.
- Review our approach to successful selection & implementation of new instruments to meet our needs.



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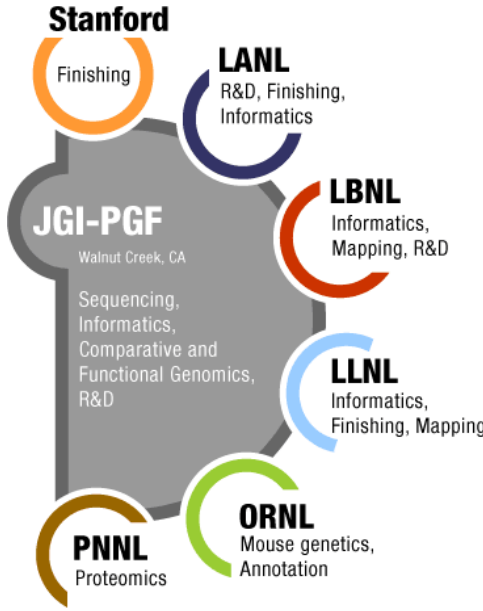
DOE JGI
Production Genomics Facility

Opened in 1999
~240 UC Employees
60,000 sf
~$66M Annual Budget



The DOE Joint Genome Institute (JGI) is a "virtual institute" that integrates the sequencing and analytical activities of six partner institutions:

Mission:

DOE JGI collaborates with DOE national laboratories and community users, to advance genome science in support of the DOE missions of clean bio-energy, carbon cycling, and bioremediation.

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Important Dates in DOE Genomics

- **1986 DOE announces Human Genome Initiative. With $5.3 million, pilot projects begin at DOE national laboratories to develop critical resources and technologies.**
- **1990 DOE & NIH present their joint HGP plan to Congress. The 15-year project formally begins.**
- **1997 DOE creates the JGI uniting activities at DOE human genome centers.**
- **1999 JGI opens the Production Genomics Facility (PGF) in Walnut Creek, staff from LLNL & LBNL.**
- **2000 HGP leaders & President Clinton announce the completion of a "working draft..the first great technological triumph of the 21st century."**
- **2003 HGP completed and published.**

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What IS a Genome???

A GENOME is all of a living thing's genetic material.

The genetic material is DNA (DeoxyriboNucleic Acid)

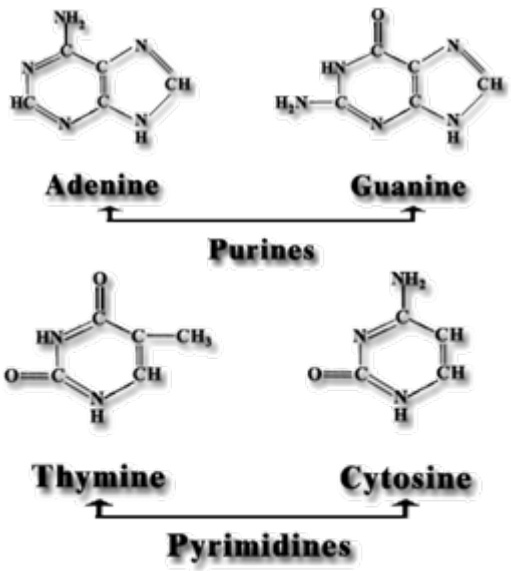
DNA, a double helical molecule, is made up of four nucleotide "letters":

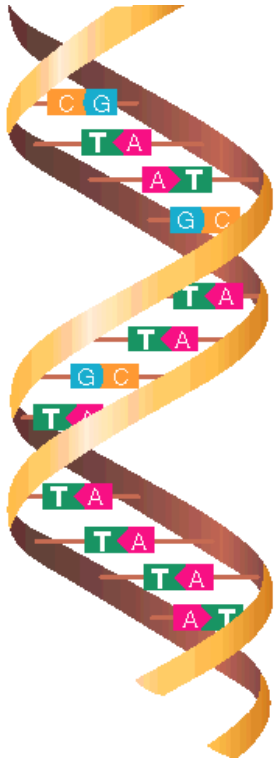
A--

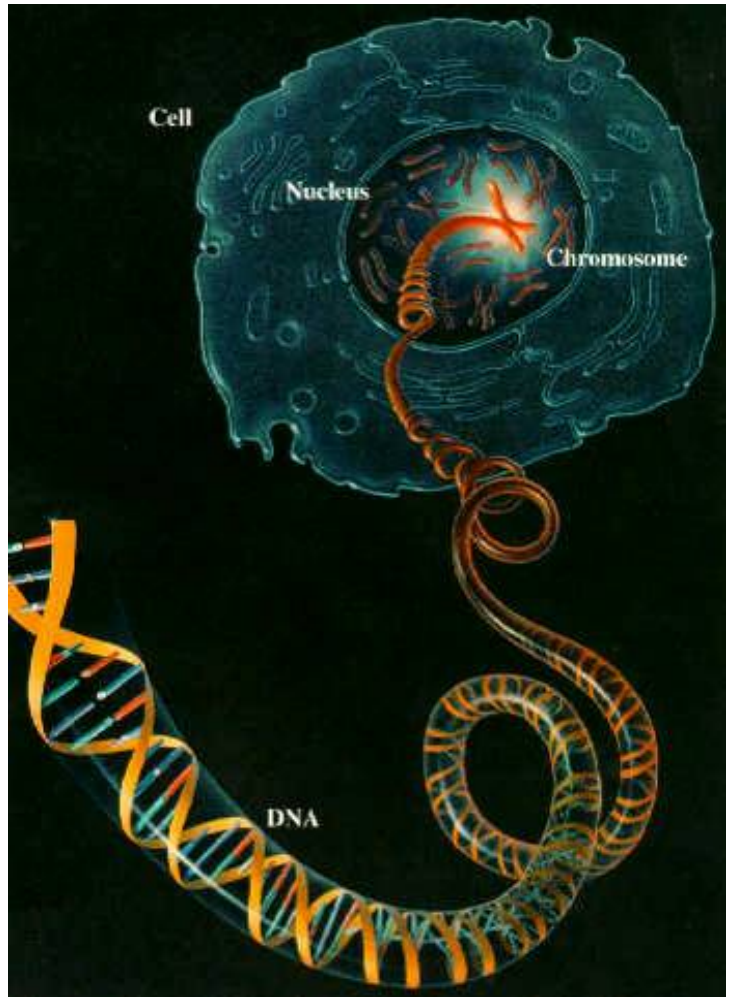
G--

T--

C--







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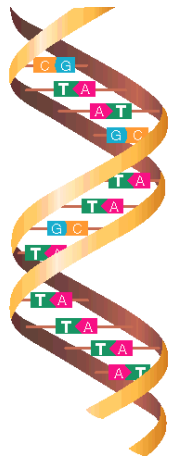
JGI Production Mission

"Produce high quality cost efficient 'assemble-able' sequence in a safe environment."

FY 2006 Goals

- 52 million lanes = 35 billion bases



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How Sequencing is Done

Production Line Overview

- **Library Creation**
  - Shearing the DNA (Genomic Solutions Hydroshear)
  - Insertion of Fragments into Plasmid (Ligation)
  - Transformation (Electroporation)
  - Subcloning the Sheared Fragment (Plating)
  - Colony Picking (Genetix QPix)
- **Production Sequencing**
  - Lysing the Cell (Matrix PlateMate)
  - Rolling Circle Amplification (MultiDrop Micro)
  - Sequencing Chemistry (CyBio Vario)
  - Post Sequencing Reaction Cleanup (BioMek FX)
  - Capillary Sequencing (ABI 3730 & MB 4500)
- **Assembly & QA**
  - Assembly (Phrap, JAZZ)
  - Quality Assessment (Phred Q20)

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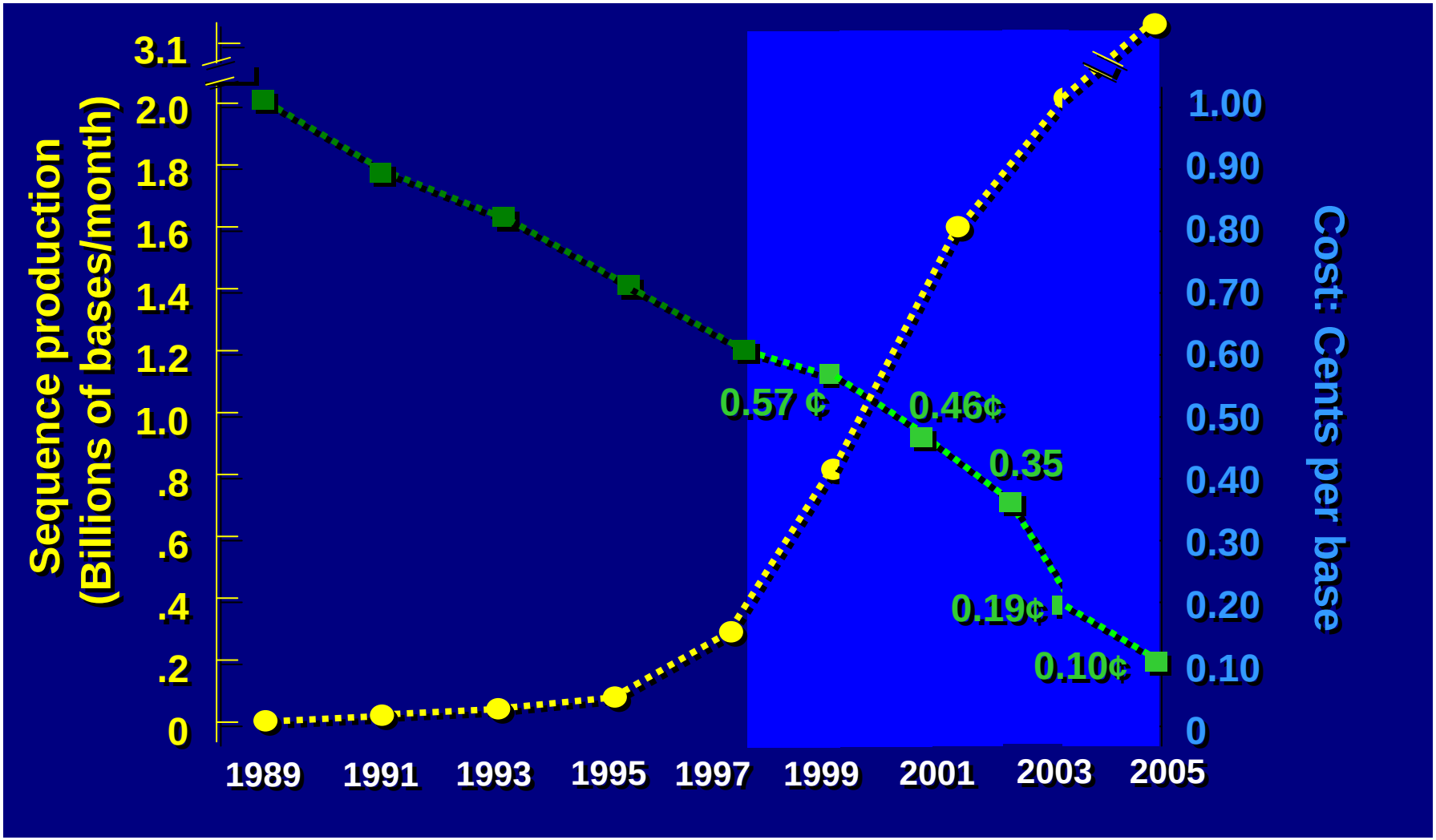
Production Sequencing Efficiencies



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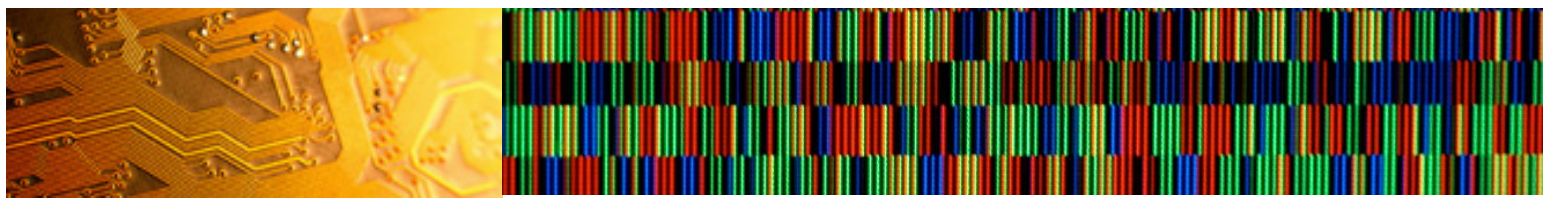
"Moore's Law" of DNA Sequencing

- **April 2002: 1 Gb/month**
- **January 2004: 2 Gb/month**
- **July 2004: 2.5 Gb/month**
- **March 2005: 3.1 Gb/month**

(equivalent to 1 human genome/month)

Total (3/99-4/06) 114 Gb

(equivalent of sequencing 38 human genomes)



Main Production Metrics; Read Length & Pass Rate

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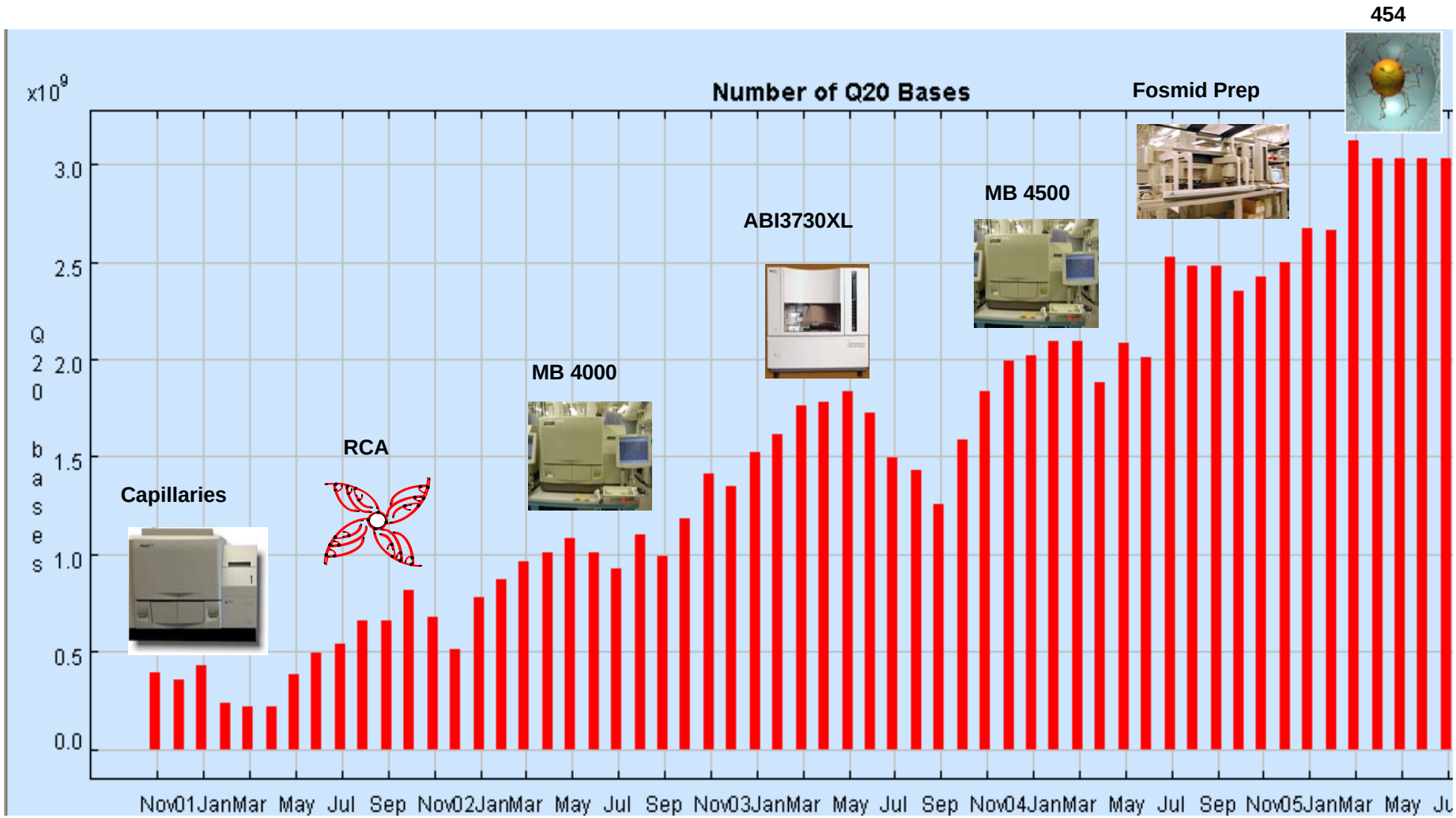
New Technologies Fuel Growth in Capacity and Reduce Costs



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Capillary Sequencing

MegaBace

1000

Qty 10; 2000 to
Qty 84; 2002

4000

Qty 21; 2002 to Qty 36, 2003

4500

Qty 36, upgraded 2004

7 days a week operation 400 plates/day

ABI

377

Qty 28; 1997

Qty 5; 2001
Qty 35; 2002
Qty 55; 2003

3730s

Qty 70; 2004

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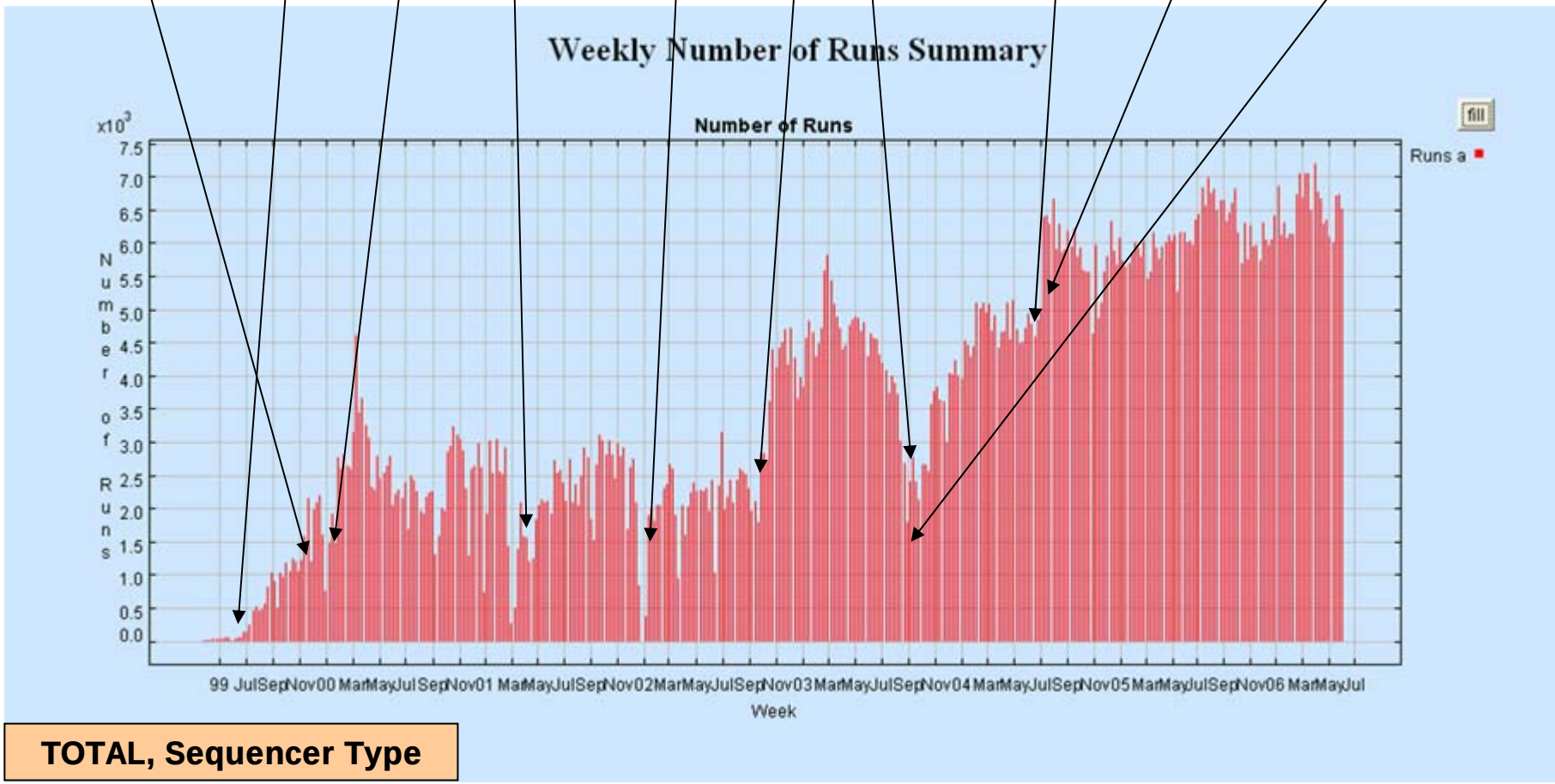
7yr Throughput Increases Correlated with # Sequencers

ABI

MB

28, ABI377s | 5, ABI3730s | 35, ABI3730s | 55, ABI3730s | 70, ABI3730s

20, MB1000s | 84, MB1000s | 21, MB4000s | 36, MB4000s | 35, MB4500s



TOTAL, Sequencer Type

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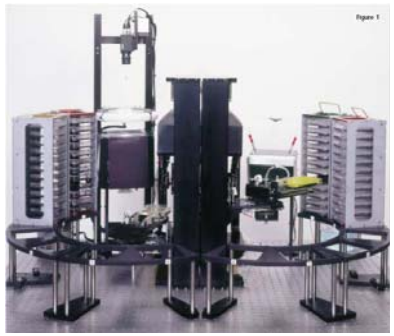
Colony Picking

Agar Colonies on BioAssay Plates into 384 Destination Plates



1999 Genomic Solutions & Hybaid Colony Pickers

OLD

Throughput ~Trays/day

96 pin picking head

Throughput (2 shifts = 16hrs)

~115 Bioassay Trays to produce 300 (384 well) destination plates/day based on ~1000 colonies/tray

QPix2 (Qty 1; 2000, Qty 3; 2001, Qty4; 2002)

QPix2 XT

(Qty 1; 2004)

2nd Due 7/06

NEW

2 BioAssays & Stacked Dest Plates

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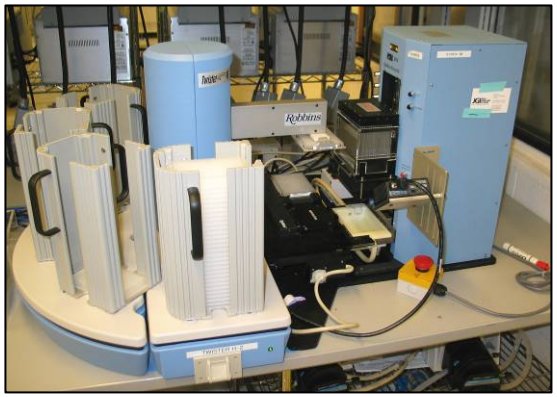
Sequence Chemistry

Aliquot RCA Product to Daughter Plates & Dispense FWD & REV Chemistry

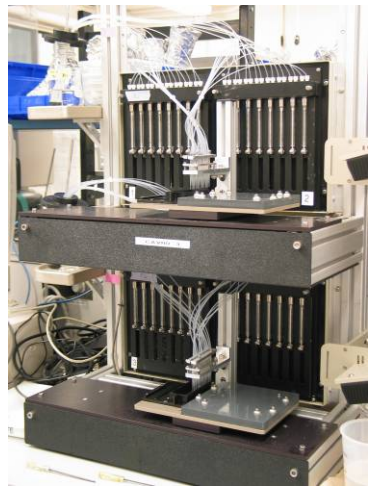
Hydra-Twister System

Qty 2; 2001



21 source to 42 destination ~1hr/batch

OLD



Cavro Syringe Pump Dispenser System

42 plates ~40min/batch

Typical Aliquot 1.5uL RCA Product into two destination plates followed by 3.5uL Sequencing Chemistry Cocktail Dispense

Throughput (2 shifts = 16hrs)

6 batches, 42 source plates = 84 destination plates

500+ plates/day

NEW

CyBi-Well Vario Integrated System

Qty 2; 2006

2.5hr/batch

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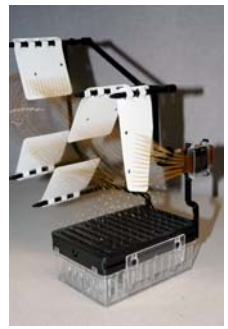
Why Automate?

- In high throughput environment;
  - automation does not necessarily increase productivity of workers,
  - does increase repeatability
  - increase equipment reliability
  - frees up operator to perform other tasks
  - reduce risk to operator of ergonomic issues



- "Islands of Automation"
  - modular instruments with stacks of micro-titer plates transported & loaded by operators
- Semi-Automated Approach
  - minimizes cost and maximizes flexibility
  - compared to fully robotic systems
  - presents a unique set of challenging issues when moving large volumes of plates

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Why Automate?

- **Need to automate driven by;**
  - **Lowering Reagent Volumes of expensive reagents <1uL & increments of 0.1uL**
  - **Dilutions only go so far**
  - **Wet & dry dispense**
- **1536 not going to work in the near term**
  - **sequencers in 384 format**
  - **no thermal cycling**
- **Physical constraints of laboratory space, big issue currently (next slide)**

2006 Community Sequencing Program

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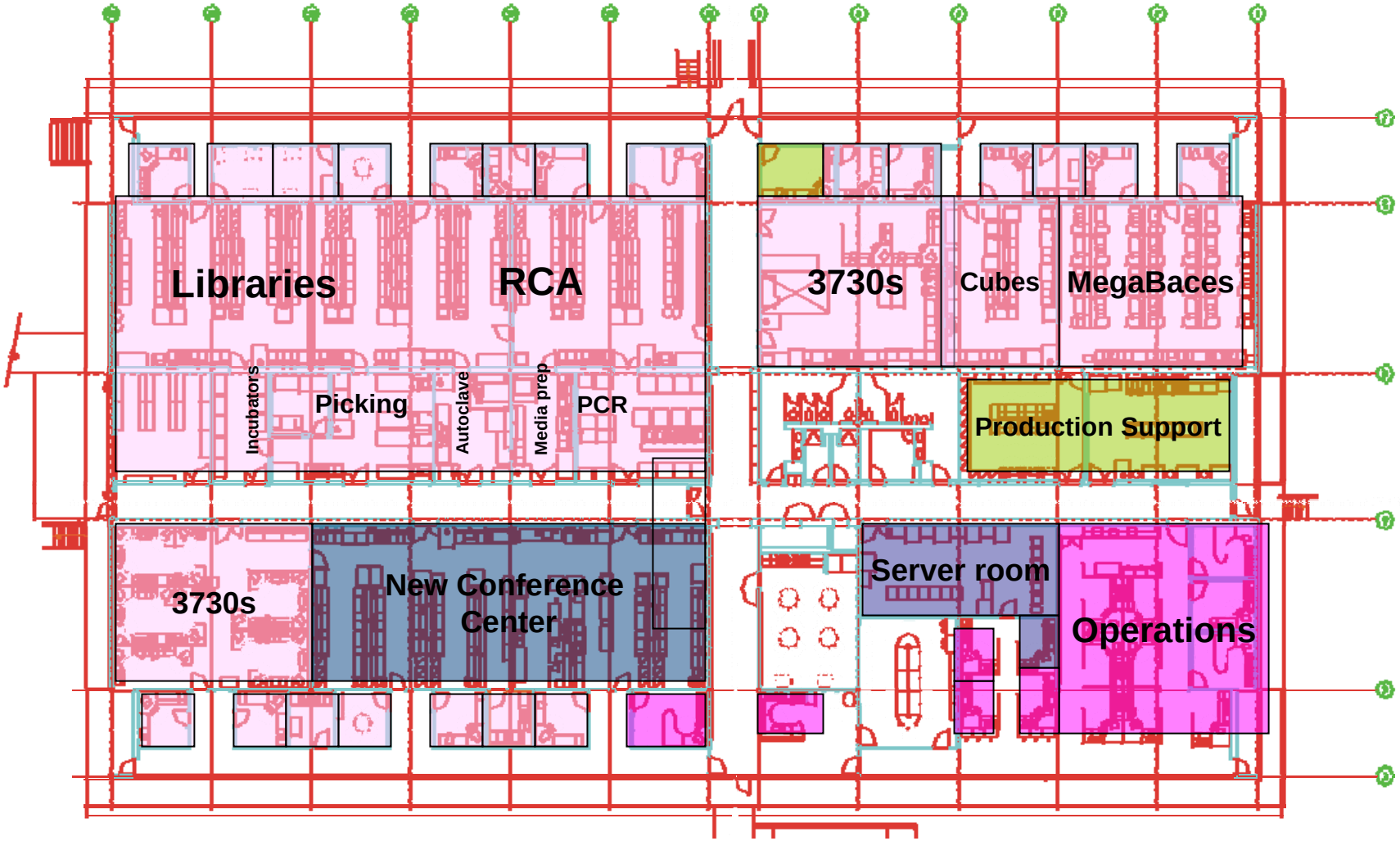
JGI Facility Layout



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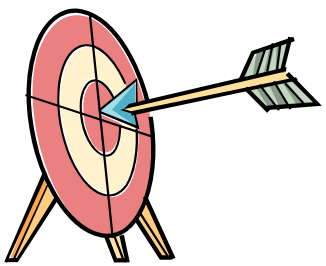
Approach to Automation Selection

- **Performance**
  - Configuration, plate types (source & destination, conditioned (thermal cycled & incubated)), reagent types, throughput, software compatibility, GUI ease of use, barcode scanning, ancillary services
  - Error Rate (defining major & minor), how going to test stacker, pipettor, dispenser, barcode reader, tip wash.
  - Measurement device, volumes, wet or dry dispense
  - Safety – seismic restraint, ergonomics, hazards, “E” stop
  - Integrated system test – method outline
  - Operational testing
  - Precision %CV, accuracy, reliability, ergonomic design



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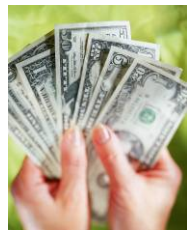
Approach to Automation Selection



- **Cost**
  - Expense warranted, efficient use of tax payer money
- **Delivery**
  - time, how, installation, training

- **Service**
  - field support, location of service engineers, response time, loaner parts, consumables supply

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Approach to Automation Implementation

- **Technology Transfer**
  - New or upgrading instrument technology
  - Internal process improvements
  - New processes introduced to production from R&D
- **Performance**
  - Acceptance criteria
  - Operational testing
    - Duplicate partial batch
    - Single production batch
    - Statistical Analysis of Results
- **Training**
  - SOP written during development phase, working draft
  - Operator needs to know what to expect

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Summary

- Brief history of the Joint Genome Institute
- DNA sequencing production line
- Increased throughput since 1999
- Instrumentation improvement highlights
- Our approach to successful selection & implementation

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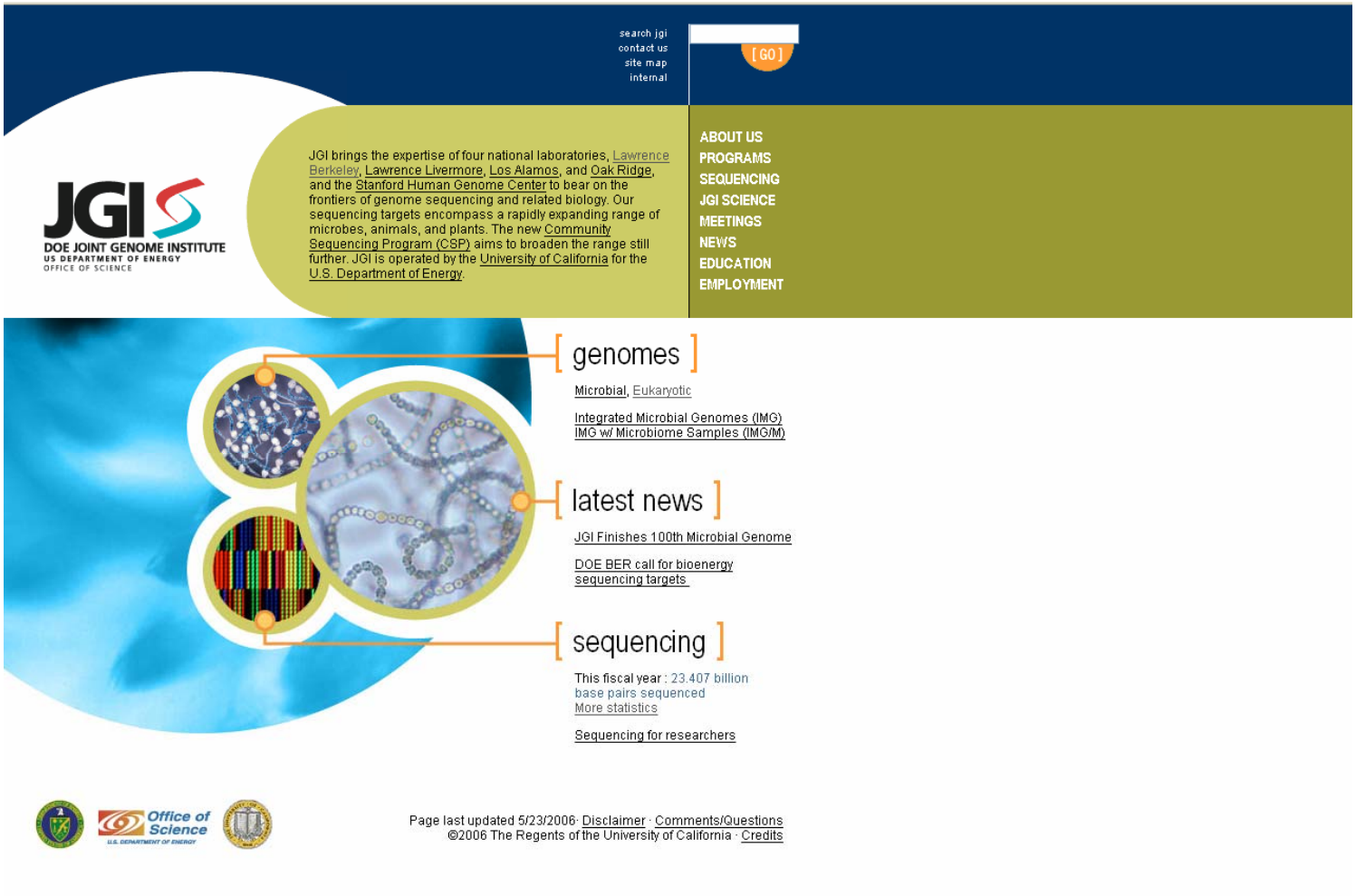
More Information?



More Information www.jgi.doe.gov

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