Next Generation Tools Revolutionizing Medicine

Kevin Hrusovsky
President & CEO

MipTec, September 21, 2010
Agenda

- State of Healthcare
- Technologies for Revolutionizing Medicine
- Innovation: Shining Light on the Future
Life Expectancy: Slowing Progress

- Achieving life extensions has become more difficult to achieve
- **Switzerland** has impressive health progress
- US hasn’t received return on healthcare investment

- **53% decrease** in incidence of infectious disease
- **33% decrease** in infant mortality rate
- **38% decrease** in prevalence of smoking
- **29% decrease** in cardiovascular death rate

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**Life Expectancy at Birth**

- **Female**
- **Male**

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Lyman & Hirsch (2010), *Personalized Medicine*, pp223
## Living to 100 and Beyond: Centenarians and Supercentenarians

<table>
<thead>
<tr>
<th>Country</th>
<th>100 yrs+</th>
<th>Per 100,000</th>
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<tbody>
<tr>
<td>China</td>
<td>17,800</td>
<td>1.3</td>
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<tr>
<td>Canada</td>
<td>3795</td>
<td>11.5</td>
</tr>
<tr>
<td>UK</td>
<td>9330</td>
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<tr>
<td>France</td>
<td>14,994</td>
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<tr>
<td>Japan</td>
<td>36,376</td>
<td>28</td>
</tr>
<tr>
<td>USA</td>
<td>95,548</td>
<td>31</td>
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</table>

"If you live to the age of a hundred you have it made because very few people die past the age of a hundred."
George Burns, 1896-1996

- **Eemeli Vaynyrean**, 100
  Inventor’s gold medal

- **Jaring Timmerman**, 100
  World record for backstroke

- **Ruth Frith**, 100
  Shot-put gold medalist

- **Buster Martin**, 101
  Marathoner, Life Enthusiast
## Scientific Centenarians

<table>
<thead>
<tr>
<th>Name</th>
<th>Lifespan</th>
<th>Age</th>
<th>Notability</th>
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<tbody>
<tr>
<td>Rita Levi-Montalcini</td>
<td>1909 –</td>
<td>101</td>
<td>Nobel laureate: Italian neurologist and senator</td>
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<tr>
<td>Sergey Nikolovsky</td>
<td>1905 –</td>
<td>105</td>
<td>Russian mathematician</td>
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<tr>
<td>Victor Blanchard Scheffer</td>
<td>1906 –</td>
<td>103</td>
<td>American zoologist and author</td>
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<td>Ruth Patrick</td>
<td>1907 –</td>
<td>102</td>
<td>American limnologist</td>
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<tr>
<td>Gerolf Steiner</td>
<td>1908–2009</td>
<td>101</td>
<td>German professor of zoology</td>
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<td>László Tisza</td>
<td>1907–2009</td>
<td>101</td>
<td>Hungarian-American physicist</td>
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<td>Victor Vacquier</td>
<td>1907–2009</td>
<td>101</td>
<td>Russian-American geophysicist</td>
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<tr>
<td>Germaine Tillon</td>
<td>1907–2008</td>
<td>100</td>
<td>French anthropologist</td>
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<tr>
<td>Salome Gluecksohn-Waelsch</td>
<td>1907–2007</td>
<td>100</td>
<td>German-American geneticist</td>
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<tr>
<td>Polly Hill</td>
<td>1907–2007</td>
<td>100</td>
<td>American horticulturist</td>
</tr>
<tr>
<td>Albert Hofmann</td>
<td>1906–2008</td>
<td>102</td>
<td>Swiss discoverer of LSD</td>
</tr>
<tr>
<td>Emma Lehmer</td>
<td>1906–2007</td>
<td>100</td>
<td>Russian-American mathematician</td>
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<tr>
<td>Russell L. Mixter</td>
<td>1906–2007</td>
<td>100</td>
<td>American biologist</td>
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<tr>
<td>Ernst W. Mayr</td>
<td>1904–2005</td>
<td>100</td>
<td>German-American biologist</td>
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<tr>
<td>Morton W. Coutts</td>
<td>1904–2004</td>
<td>100</td>
<td>New Zealand inventor of continuous fermentation</td>
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<td>Ancel Keys</td>
<td>1904–2004</td>
<td>100</td>
<td>American biologist</td>
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<tr>
<td>Bei Shizhang</td>
<td>1903–2009</td>
<td>106</td>
<td>Chinese biologist and educator</td>
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<tr>
<td>Marthe Vogt</td>
<td>1903–2003</td>
<td>100</td>
<td>German-English neuroscientist</td>
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<tr>
<td>Zheng Ji</td>
<td>1900–2010</td>
<td>110</td>
<td>Chinese nutritionist and biochemist</td>
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<td>Ray Crist</td>
<td>1900–2005</td>
<td>105</td>
<td>American chemist</td>
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<tr>
<td>Viktor Hamburger</td>
<td>1900–2001</td>
<td>100</td>
<td>German professor and embryologist</td>
</tr>
<tr>
<td>Waldo Semon</td>
<td>1898–1999</td>
<td>100</td>
<td>American chemist</td>
</tr>
<tr>
<td>Ira Baldwin</td>
<td>1895–1999</td>
<td>104</td>
<td>American bacteriologist and educator</td>
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<tr>
<td>Constance Tipper</td>
<td>1894–1995</td>
<td>101</td>
<td>British metallurgist and crystallographer</td>
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<tr>
<td>Leopold Vietoris</td>
<td>1891–2002</td>
<td>110</td>
<td>Austrian mathematician</td>
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<tr>
<td>Ralph Randles Stewart</td>
<td>1890–1993</td>
<td>103</td>
<td>American botanist</td>
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<td>Horace Alexander</td>
<td>1889–1899</td>
<td>100</td>
<td>British biologist</td>
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<td>Inge Lehmann</td>
<td>1888–1993</td>
<td>104</td>
<td>Danish seismologist</td>
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<tr>
<td>Michael Heidelberger</td>
<td>1888–1991</td>
<td>103</td>
<td>American immunologist</td>
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<tr>
<td>Joel Henry Hildebrand</td>
<td>1881–1983</td>
<td>101</td>
<td>American chemist</td>
</tr>
<tr>
<td>Julia Bell</td>
<td>1879–1979</td>
<td>100</td>
<td>English human geneticist</td>
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<tr>
<td>Harriette Chick</td>
<td>1875–1977</td>
<td>102</td>
<td>British biologist</td>
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<tr>
<td>Mokshagundam Visvesvaraya</td>
<td>1860–1962</td>
<td>101</td>
<td>Indian engineer</td>
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<tr>
<td>Henry Nicholas Ridley</td>
<td>1855–1956</td>
<td>100</td>
<td>British biologist</td>
</tr>
<tr>
<td>Michel Eugène Chevreul</td>
<td>1786–1889</td>
<td>102</td>
<td>French chemist</td>
</tr>
</tbody>
</table>

**Albert Hofmann, 102** Basel, Switzerland Sandoz (Novartis) Discoverer of LSD

**Rita Levi-Montalcini, 101** Italian Nobel Laureate Growth Factors
Categories of Disease

- A child today: shorter life expectancy than parent, due to increased risk of diabetes

- 50% of deaths are from heart disease or cancer
  - Average age of first heart attack: 66 years
  - Average age of cancer diagnosis: 67 years
  - Earlier detection: chronic vs. acute treatment

- Medical error (adverse drug events and hospital acquired infections) is 3rd leading cause of death

<table>
<thead>
<tr>
<th>Disease</th>
<th># Deaths</th>
<th>%Total</th>
<th>$Spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>632,000</td>
<td>26%</td>
<td>$180B</td>
</tr>
<tr>
<td>Cancer</td>
<td>560,000</td>
<td>23.1%</td>
<td>$125B</td>
</tr>
<tr>
<td>Medical Error</td>
<td>195,000</td>
<td>8.1%</td>
<td>&gt;$100B</td>
</tr>
<tr>
<td>Stroke</td>
<td>137,000</td>
<td>5.7%</td>
<td>$120B</td>
</tr>
<tr>
<td>Respiratory</td>
<td>125,000</td>
<td>5.1%</td>
<td>$75B</td>
</tr>
<tr>
<td>Accidents</td>
<td>122,000</td>
<td>5%</td>
<td>$145B</td>
</tr>
<tr>
<td>Diabetes</td>
<td>72,000</td>
<td>3%</td>
<td>$47B</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>72,000</td>
<td>3%</td>
<td>&lt;$50B</td>
</tr>
<tr>
<td>Pneumonia/Flu</td>
<td>56,000</td>
<td>2.3%</td>
<td>&lt;$50B</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>45,000</td>
<td>1.9%</td>
<td>&lt;$50B</td>
</tr>
<tr>
<td>TOTAL:</td>
<td>2,400,000</td>
<td></td>
<td>$2.1 T</td>
</tr>
<tr>
<td>Top Ten</td>
<td>2,016,000</td>
<td>84%</td>
<td></td>
</tr>
</tbody>
</table>

CDC 2006 Data
Obesity Reduces Life Spans & Natural Resources

- Increase in Obesity and Associated Health Care Cost:
  - **37% increase** from 1998-2006 (2/3 are overweight today)
  - Doubling of costs to **$147B** from 1998-2006 (9.1% of total costs)
  - Expected to grow to **$344B** in 2018
  - Associated diseases: Diabetes; Heart disease, Kidney failure; Cancer

- Obesity Could Reverse the Progress in Increased Longevity:
  - For the first time in two centuries, the current generation of children in America have shorter life expectancies than their parents.
  - If left unchecked, this could shorten life spans by up to 5 years.

\[\text{Energy consumption per capita 2003}\]

\[\text{Canada}\] 96,521 kWh
\[\text{United States}\] 90,660 kWh
\[\text{Finland}\] 89,934 kWh
\[\text{Sweden}\] 67,033 kWh
\[\text{Australia}\] 66,551 kWh
\[\text{Belgium}\] 66,319 kWh
\[\text{Netherlands}\] 68,282 kWh
\[\text{France}\] 52,780 kWh
\[\text{Germany}\] 48,754 kWh
\[\text{Austria}\] 42,131 kWh
\[\text{Japan}\] 40,632 kWh
\[\text{United Kingdom}\] 45,560 kWh
\[\text{Denmark}\] 44,568 kWh
\[\text{Switzerland}\] 43,240 kWh
\[\text{Spain}\] 37,520 kWh
\[\text{China}\] 13,236 kWh
\[\text{Viet Nam}\] 6,272 kWh
\[\text{India}\] 6,950 kWh
\[\text{Target value}\] 18,000 kWh

\((\text{NEJM, 2005; AHRQ, 2006; CBO, 2008; CDC, 2009})\)
Chocolate Genome Sequenced Irony

- Even chocolate is being sequenced & genetically engineered
  - The team identified gene families linked to cocoa flavour
  - Produce cacao trees that are more resistant to drought
  - Help plants better fight disease
  - Generate higher yields and a better quality end product
The cost of healthcare is increasing for all major industrialized nations
  ▪ 15% of GDP and increasing

Healthcare costs have quadrupled since 1980, but lifespans have only increased by 3-4 years

Extending life further will significantly ramp healthcare costs
  ▪ 65+ year olds spend 4x more per year than under 65
  ▪ 5% of population consume 50% of medical care

Lyman & Hirsch (2010), Personalized Medicine, pp223
Cost of Extending Lifespans with Today’s Medicine

- Extending life further will significantly ramp healthcare costs
  - 65+ year olds spend 4x more per person than under 65
  - 5% of population consume 50% of medical care

*Extending life expectancy from 77 to 84 years would conservatively increase the total cost of medical care by 90%*
Cost Effectiveness is Driving Drug Coverage Decisions

4 of 6 EU countries use cost effectiveness in decision making.
Extending Life Using Today’s Tools is Prohibitive

$400k Total Consumption Yields:
- 77 year average lifespan
- Each additional year costs $25-100k

Colorectal Cancer:
- Today: $250,000 of drugs add 24 months
- 1996: $500 of drugs add 11 months
- Avastin: Expensive, targeted treatment

Accumulated Lifetime Consumption of Medical Care

$950k - $2.7M
A Revolution in Medicine is Needed to Extend Life Economically

Expand lifetime from 77 to 100 years
- Keep lifetime spend at $400k
- Technology & Preventive Approaches

Accumulated Lifetime Consumption of Medical Care

$950k - $2.7M
Transforming “Sick Care” to “Health Care”

**TODAY**
- Reactive
- Blockbuster
- Symptomatic
- Empirical

**TOMORROW**
- Preventative
- Personalized
- Holistic
- Molecular

Next Generation Tools

Today: Reactive, Blockbuster, Symptomatic, Empirical

Tomorrow: Preventative, Personalized, Holistic, Molecular
Revolutionizing Medicine

Fundamental Diagnostics

Genome Sequencing:
Blueprints for predisposition towards disease

Biomarkers:
Molecular sensors for health status

Non Invasive Imaging:
Detailed understanding of environmental impact

Targeted Therapeutics

Vaccines:
Preventative medicine

Biotherapeutics:
Highly selective drugs harness natural defenses to eliminate disease

Stem Cells:
Utilize regenerative medicine to rebuild healthy tissues

Personalized Medicine
Revolutionizing Medicine: Relevant MipTec Sessions in Blue

Fundamental Diagnostics
- Genome Sequencing: Targets & Tools
- Biomarkers: Translational Science
- Non Invasive Imaging: Drug Discovery Technologies

Targeted Therapeutics
- Vaccines: Biotherapeutics
- Biotherapeutics: Biotherapeutics
- Stem Cells: Translational Science & Drug Discovery Tech
Technologies for Revolutionizing Medicine
2003

R&D Startup
- LabChip Technology
$20M Rev / ($45M) EBITDA
CA Headquarters

2003-2006

Acquired Tools & Services
- Robots / Services/ Imagers
$60M Rev / ($22M) EBITDA

2010

Commercial Applications
- Personalized Medicine
$117+M Rev / Positive EBITDA
MA Headquarters

Caliper Total Solutions Enable…

Fundamental Diagnostics

Targeted Therapeutics

Genome Sequencing:

Vaccines:

Biomarkers:

Biotherapeutics:

Non Invasive Imaging:

Stem Cells:

in vitro

in vivo
Molecular Imaging: Bioluminescence, FL, X-Ray, uCT
Sequencing: *Revolutionary Impact*

- Fundamental understanding of disease mechanisms
- Assessment of environmental impact on health
- Optimizing diet & habits based on genetics

**Bottleneck:** Sample preparation of next gen sequencing libraries
Small molecule discovery transitioned to plates 15-20 years ago, but genomics & biotherapeutics are only now making the transition.

Key Learnings from Small Molecule Microplate Adoption
- Major productivity improvements are possible
- High fidelity/predictive assays are essential
- High quality analytical platforms are critical
Zephyr Genomics Workstation
Sample extraction and library purification

Software
• SPRI purification protocol
• Normalization protocol
• Press and go

Hardware
• Magnet
• Integrated shaker w/ temp control
• Integrated barcode reader

Zephyr NGS Workstation
Sample extraction and complete library production

Methods
• SOLiD library construction
• Illumina library construction
• Nextera methods
• Target enrichment
  • Agilent’s SureSelect
  • Nimblegen’s SeqCap EZ

Integration and Capacity
• Twister II
  • Tips, reagents, consumables
• Integration
  • GX
  • Thermocycler
  • Covaris
  • qPCR

QC
PCR
Shearing
Quant. PCR

Sequencing: Automated Library Preparation
Sequencing: **Automated Library Purification & QC**

- **LabChip XT**
  - Fractionation of sheared DNA
  - Size from 50 to 500 bp +/- 5%
  - 4 samples per chip in 20 minutes

- **LabChip GX**
  - HT quantification and sizing
  - Advanced smear analysis
  - 96 samples in 2 hours
  - Automation capable
  - LIMS compatible
  - Integrated sample tracking

*Use after shearing and/or after library construction!!!*
<table>
<thead>
<tr>
<th>Top 15 Core Genome Centers</th>
<th>Genome Analyzer</th>
<th>HiSeq 2000</th>
<th>SOLID</th>
<th>454 GS-FLX</th>
<th>HeliScope</th>
<th>Pac Bio</th>
<th>Total</th>
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<tbody>
<tr>
<td>Beijing Genomics Institute (privately funded)</td>
<td>29</td>
<td>128</td>
<td>2</td>
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<td>Broad Institute of MIT and Harvard</td>
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<td>University of Queensland's IMB</td>
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<td>78</td>
<td>37</td>
<td>6</td>
<td>8</td>
<td>554</td>
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Sequencing: *Future Enabling Caliper Technologies*

LabChip XT: Follow-on assays
- 100 to 1000 bp
- 0.5 to 5 kbp
- 0.5 to 10 kbp
- microRNA
- Cells
- Proteins
- Chromosomes

Technologies that could be integrated on chip:

Extracted from Coupland, LabChip, 2010, 10:544
Biotherapeutics & Vaccines: Revolutionary Impact

- Revolutionary investments underway
- Harness our natural immune system to fight disease
- Use native substrates and inherent selectivity of antibodies for better toxicity profiles
- Novel developments of antivirals and cancer vaccines
- Estimated to be $130B market in 2010, growing at double digit rates
- Increasing to $180B in 2014 and projected to represent 30% of big pharma revenue
- Pfizer-Wyeth, BMS-Medarex, Lilly-Imclone; Biologics are key to M&A activity
Vaccines – Preventative Medicine

- Children will be treated with specific vaccines based on genetic profile
- Smallpox is eradicated!
- Polio reduced from 400,000 cases in 1980 to 1600 in 2009
- Guinea Worm disease reduced from 890,000 in 1989 to 3,200 in 2000
  - Is cancer the next disease to be eradicated? Merck – cervical cancer; Dendrion – prostate cancer;
Biotherapeutics & Vaccines: Key Manufacturability Bottleneck

**Bottleneck:** Availability of process analytical technologies to optimize manufacturing practices, implement quality-by-design approaches, and demonstrate bioequivalency

Key Manufacturability Issues
- Genzyme scale up required new BLA submission to FDA
- Complexity yields regulatory & manufacturing challenges
- Biosimilars require proof of equivalency
- Requires higher throughput analytical platforms for process development optimization
Biotherapeutics & Vaccines: Caliper Enabling Technology Today

- 21 CFR compliant assessment of proteins and glycans
- Size, titer, & purity from 96- and 384-well plates
- “70 times faster than CE” Amgen, Pfizer
- “LabChip enables QbD studies” Biogen
- “Enabling platform for biosimilars / vaccines” Novartis, FDA
- 21 CFR Part 11 compliant software
- New: high throughput Glycan analysis
Microplate Approaches Requires Automation

**Example Applications**

- LabChip GX sample preparation
- Glycan kit automation
- Protein purification (tips, plates or columns)
- Design of experiment optimizations
- Tube-to-plate reformatting and processing
- Enzymatic steps (e.g. proteolytic cleavage)

**Automation**

Sample Collection

Sample Preparation

- 25 minutes per plate

Complete preparation:
- Isolation of protein from cell culture
- Protein prepared for GX analysis

**Microfluidics**

Analysis

- 41 seconds per sample
  - (70 minutes per plate)

Complete analysis:
- Electropherogram with annotation
- Tabular data with advanced filtering
- LIMS compatible
Biotherapeutics: Caliper Collaborates with FDA

Caliper invited by FDA to educate its reviewers about enabling Quality by Design (QbD) to improve safety and efficacy of biologics

- “Better and more rapid characterization of biologics is critical for “QbD”
- “We are encouraged with companies submitting biological applications under the QbD Pilot Program using the LabChip”
- “The LabChip GX creates opportunities for improving the speed and quality of characterization of protein products”
- Recent adoption in QA, QC at Lilly, Covance, Dow/Phenex, and major implementation at Biogen IDEC
Biomarkers

- Early detection using molecules in the blood stream
- Track treatment effectiveness using sensor proteins
- Monitor residual disease
- One company is offering sequencing for all employees with cancer and will pay for off label drugs if the right genotype/biomarkers are present
Cancer Needs Biomarkers and a Personalized Approach

*Drug Discovery Today, 2009*

Top 15 Selling Oncology Drugs
- Generated $26.4B in sales in 2006
- Produced avg Response Rate of 35%

→ **FAILED:** 65% Non-Responders

High Failure Rate
- Results in toxicity with no benefit
- Wastes precious time before trying potentially effective treatment
- Wastes precious health dollars
  
  \[65\% \times \$26.4B = \$17B \text{ WASTED}\]

Biomarkers
- Identify which patients may benefit
- Particularly well-suited for matching targeted therapies to the ‘right’ patients

→ **HER2 test for Herceptin**

→ **KRAS test for Erbitux**
## Companion Dx Invigorates Small Molecule Discovery Programs

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Drug(s)</th>
<th>Technology Platform</th>
<th>Purpose</th>
<th>PIII Prospective Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcr-Abl</td>
<td>Gleevec</td>
<td>Genetic</td>
<td>Efficacy</td>
<td>Yes</td>
</tr>
<tr>
<td>C-kit</td>
<td>Gleevec</td>
<td>IHC</td>
<td>Efficacy</td>
<td>Yes</td>
</tr>
<tr>
<td>CCR5</td>
<td>Selzentry</td>
<td>Viral tropism</td>
<td>Efficacy</td>
<td>Yes</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Plavix, Effient</td>
<td>Genetic</td>
<td>Safety</td>
<td>No</td>
</tr>
<tr>
<td>EGFR</td>
<td>Erbitux, Vectibix</td>
<td>IHC</td>
<td>Efficacy</td>
<td>Yes</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Herceptin</td>
<td>IHC/FISH</td>
<td>Safety</td>
<td>Yes</td>
</tr>
<tr>
<td>HLA-B*1502</td>
<td>Tegretol</td>
<td>Genetic</td>
<td>Safety</td>
<td>No</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>Ziagen</td>
<td>Genetic</td>
<td>Efficacy</td>
<td>No</td>
</tr>
<tr>
<td>KRAS</td>
<td>Erbitux, Vectibix</td>
<td>Genetic</td>
<td>Safety</td>
<td>No</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Camptosar</td>
<td>Genetic</td>
<td>Safety</td>
<td>No</td>
</tr>
<tr>
<td>VKOR1</td>
<td>Coumadin (warfarin)</td>
<td>Genetic</td>
<td>Safety</td>
<td>No</td>
</tr>
</tbody>
</table>
# Strong pipeline of companion diagnostics

*Examples of joint Roche Pharma and Diagnostics programs*

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Compound</th>
<th>Potential companion diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>Tarceva</td>
<td>EGFR mutations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER1/2/3 expression, HER2 gene amplification</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab (RG1273)</td>
<td>HER2 expression/gene amplification</td>
</tr>
<tr>
<td></td>
<td>T-DM1 (RG3502)</td>
<td>BRAF V600E mutation</td>
</tr>
<tr>
<td></td>
<td>BRAF Inh/PLX4032 (RG7204)</td>
<td>BRAF V600E mutation</td>
</tr>
<tr>
<td></td>
<td>MEK Inh/CIF (RG7167)</td>
<td>BRAF V600E mutation, KRAS mutation</td>
</tr>
<tr>
<td></td>
<td>MEK Inh/CKI27 (RG7304)</td>
<td>BRAF V600E mutation, KRAS mutation</td>
</tr>
<tr>
<td></td>
<td>MDM2 Antagonist (RG7112)</td>
<td>P53 mutation, MDM2 gene amplification</td>
</tr>
<tr>
<td></td>
<td>PI3K Inh (RG7321)</td>
<td>PI3KCA mutations</td>
</tr>
<tr>
<td></td>
<td>PI3K/mTOR Inh (RG7422)</td>
<td>PI3KCA mutations</td>
</tr>
<tr>
<td>Inflammation</td>
<td>MabThera (RA)</td>
<td>RF, anti-CCP antibodies</td>
</tr>
<tr>
<td></td>
<td>Lebrikizumab (Asthma)</td>
<td>Serum periostin, CEA &amp; IgE levels</td>
</tr>
<tr>
<td></td>
<td>Rontalizumab (SLE)</td>
<td>IFN-induced genes</td>
</tr>
<tr>
<td>Virology</td>
<td>Pegasys (HBV)</td>
<td>Quantitative HBs Ag</td>
</tr>
<tr>
<td></td>
<td>R3484 (HPV)</td>
<td>HPV genotyping</td>
</tr>
</tbody>
</table>

*List not exhaustive*

Not all products available in all countries; some products in development
Roche and Plexxikon collaborate on kinase inhibitor
Anticipate launching diagnostic test & drug at same time
81% of metastatic melanoma patients with a BRAF (V600E) activating mutation responded to treatment with PLX4032

“These results represent a major breakthrough and provide proof that the treatment of metastatic melanoma can be individualized for a substantial percentage of patients.”
NEJM Editorial, August 26, 2010

“We have never seen an 80% response rate in melanoma, or in any other solid tumor, for that matter, so this is remarkable.”
Paul Chapman, M.D., Memorial Sloan-Kettering Cancer Center

Source: Flaherty et al., NEJM, v. 363, pp. 809-819
GE & CardioDx Partner to Improve Health Care Costs

- **STEP 1**: Use Corus CAD test ($1195) to test for 23 biomarkers to predict disease and reduce costly tests.
- **STEP 2**: For potential CAD patients, follow up with angiography ($300 0 to $5000) &/or stress test ($600)
- **STEP 3**: If patient still potentially has CAD, follow up with invasive cardiac catheterization ($3000)

Improving Diagnostics with Biomarkers & Imaging

Heart attacks are leading cause of death; no single diagnostic test

- ~400,000 patient study on elective catheterization, a costly and invasive procedure
- ~2/3 of patients did not have obstructive coronary artery disease (CAD);
- 1.5 M cardiac catheterizations / year ($4.5B cost) with 2/3 or $3 Billion wasted
Molecular Imaging: *Revolutionary Impact*

Provides rapid and cost effective approaches to monitor disease progression, and predict drug efficacy using tools that can translate into clinical applicability

- In depth understanding of disease *in vivo*
- Observe functional biology in real time
- Earlier detection: single molecule imaging
- Accelerated pre-clinical discovery
  - 70% reduction in time to results
- Translational and clinically practical
Clinical Translatability from Multimodality & Single Cell Imaging

**Multimodality Co-Registration**
IVIS 3D and Quantum FX low dose µCT

**Single Cell Imaging**
500x more sensitive than MRI, orders of magnitude more than PET

Optical

uCT Co-Registration

Atlas Co-Registration

IVIS Detection limit
1-2 cells

PET Detection limit
$10^7$ to $10^6$ cells

500x more sensitive than MRI, orders of magnitude more than PET
Regenerative medical application of stem cells: Optical imaging models to accelerate development

Limb ischemia model
Model resulted in positive clinical trials

Stem cell neural and spinal cord repair model

**IVIS can sensitively detect neural SC in the brain and spinal cord through intact skull and bone**

Long-term viability and proliferation studies of neural stem cells in the brain (top) and spinal cord (bottom)
IVIS Imaging *A Picture is Worth a Thousand Assays*

- **License**
- **Service**
- **Product**

### Units Sold/Year Installed Base
- 2005: 97
- 2006: 120
- 2007: 132
- 2008: 143
- 2009: 149
- 2010F: 160+ est.

**Addressable Market:** 8,000+ units in 2010

### Disease Areas
- **Oncology**: 44%
- **Infectious Diseases**: 11%
- **Stem Cell Biology**: 8%
- **Neuroscience**: 6%
- **Cardiovascular**: 3%
- **Metabolic Diseases**: 3%
- **Gene Therapy**: 8%
- **Immunology**: 11%
- **Inflammation Research**: 6%

### Total High Impact Journal Publications: 64
- **Nature Journals**: 11%
- **Science**: 47%
- **PNAS**: 41%
- **Cell**: 9%

### Total Publications

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>200</td>
</tr>
<tr>
<td>1996</td>
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<td>1997</td>
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<td>2008</td>
<td>2,800</td>
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<tr>
<td>2009</td>
<td>3,000</td>
</tr>
<tr>
<td>2010</td>
<td>3,200</td>
</tr>
</tbody>
</table>
Impact: Stem Cells in medicine

Enabling treatment of Alzheimer's, Parkinson’s, spinal cord injury, stroke, burns, heart disease, diabetes, osteo and rheumatoid arthritis, Duchenne’s muscular dystrophy, vision and hearing loss

- Human embryonic and adult stem cells
- Induced pluripotent stem cells
- More compete understanding of genetic and molecular control
- Study cell proliferation and differentiation
- Used to develop and test new drugs
Stem Cell Therapy to Regenerate Healthy Tissue

- Stem cells will be used to rebuild healthy tissues and repair damage from:
  - Environmental factors
  - Disease
  - Lumpectomy
  - Accidents
Stem cells to reverse heart disease & neural and spinal cord repair

Investigative development, tracking, and monitoring using IVIS optical imaging

IVIS can sensitively detect neural SC in the brain and spinal cord through intact skull and bone

Long-term viability and proliferation studies of neural stem cells in the brain (top) and spinal cord (bottom)
Upfront Investment in Vaccines & Diagnostics Extends Life

Better Therapeutics:
1. Vaccines
2. Biotherapeutics
3. Stem Cells

Better Diagnostics:
A. Sequencing
B. Biomarkers
C. Imaging

Accumulated Lifetime Consumption of Medical Care

$950k - $2.7M

"Sick" Care 2010 vs "Healthy" Care 2015
Newborn Child in 2015 …

Children being born this decade will experience the revolution in medicine

Every newborn will have their genome sequenced:
- Genetic profile securely stored, making analyses available:
  - Predisposition to disease
  - Need for certain vaccines
  - Drug efficacy/safety indicators
Improving iHealth one app at a time

<table>
<thead>
<tr>
<th>Find a Specialist</th>
<th>How Many Calories?</th>
<th>Drug-Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Online ratings and locations for doctors and specialists</td>
<td>Take picture of plate of food, send for analysis; track daily fat/calorie intake</td>
<td>I'm taking Vicodin &amp; Claritin at the same time, is that a problem?</td>
</tr>
</tbody>
</table>

**Symptom Analysis**
Questionnaire walks through symptoms and identifies issue.

**What’s this?**
Take a picture of a rash and send to MD online. Should I go to hospital?

**Too Drunk To Drive?**
Built in breathalyzer function eliminates DUIs

**Drug Dosages**
How much ibuprofen should I take based on my age, weight, sex

**Which Drug is Right?**
Based on my genome sequence, should I take Claritin or Singulair?

**Is he a good match?**
Based on our sequences, will we have cute kids?

**Finger Prick Analysis**
Blood sugar, cholesterol, and other biomarkers

**Exercise Meter**
How many steps did you take, how much activity
Innovation:
Shining Light on the Future
Open our Minds and Learn from Others
Steal Shamelessly Best Practices
• Invictus
• Coach Carter
• Remember the Titans
• Apollo 13
• Rudy

Long Life Resources
• http://www.livingto100.com/
• http://www.realage.com
• http://www.healthstatus.com/
• http://www.personalgenomes.org/
• http://www.webmd.com/
• http://familyhealth.com/
Technologies to Efficiently Predict Human Outcomes

Strategic Goal

PATIENT

Human Outcome

MOLECULE

Cost

Low

High

DNA, RNA, Protein

Microfluidics

Imaging

Sequencing

Mice

Tissue

Human

Cells
## Caliper’s LabChip Evolution

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Application</th>
<th>Product</th>
<th>Company</th>
<th>Investment</th>
<th>Date</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partner</td>
<td>HTS</td>
<td>None</td>
<td>Roche</td>
<td>$17M</td>
<td>1998</td>
<td>Immature technology, little economic benefit</td>
</tr>
<tr>
<td>OEM Dev’t</td>
<td>Low Throughput</td>
<td>Chips</td>
<td>Agilent &amp; Bio-Rad</td>
<td>$50M</td>
<td>1998</td>
<td>$80M revenue; <strong>$6M annual</strong>, single digit growth, Over 7,000 units and 6 million chips; Bioanalyzer &amp; Experion.</td>
</tr>
<tr>
<td>Technology Access Partners</td>
<td>Drug Screening</td>
<td>EZ Reader</td>
<td>Amgen, Lilly, Millenium, Pfizer</td>
<td>$25M</td>
<td>Late '90s-Today</td>
<td>$50M+ sales; <strong>$7M annual</strong>, single digit growth; 250 instruments, 10,000 chips; Millions of compounds screened, drugs in clinic.</td>
</tr>
<tr>
<td>Internal Dev’t</td>
<td>High Throughput</td>
<td>GX/GXII</td>
<td>Biogen, Pfizer, FDA, Amgen</td>
<td>$10M</td>
<td>2005-Today</td>
<td>$40M+ sales; <strong>$12M annual</strong>, 25% growth; 500 instruments, 15,000 chips; Improved manufacturability and accelerated R&amp;D for biotherapeutics, biosimilars, &amp; vaccines.</td>
</tr>
<tr>
<td>Healthy mix of all 4 models</td>
<td>Genomics &amp; MDx Sample Prep</td>
<td>GX, XT, Licenses</td>
<td>Wako, BD, Agilent, Others</td>
<td>Undisclosed</td>
<td>Today</td>
<td><strong>$5M today</strong>, Molecular diagnostics &amp; next generation sequencing sample prep; strong licensing pipeline of additional MDx &amp; NGS deals.</td>
</tr>
</tbody>
</table>
Revitalizing Small Molecule Discovery: Better Decision Making

- **IVIS in vivo imaging**
  - Rapid, high fidelity, economical safety and efficacy studies
  - Accelerated Speed to Clinical Trials
  - Savings in time, FTE, animal usage, histology work

- **LabChip EZ reader**
  - High fidelity data w/ rapid chemistry cycles (24 hours)
  - “Perform rapid off rate analysis to support lead optimization efforts to improve safety margins.” Pfizer
  - “LabChip eliminated the use of radiochemicals.” AZ
  - “LabChip provides excellent data quality.” Novartis

“EZ Reader & ProfilerPro enable us to reduce chemistry optimization time by 6 months”
- Merck
Life science tools can be deployed to create more efficient and productive innovation cycles.

Early cumulative data can be leveraged through a “continuous improvement feedback loop”

This allows the drug developer to reiterate and to reach a “Go/No Go” more quickly, cost-effectively, and with a higher level of confidence.

Innovation Cycle for Small Molecule Drug Development

- Faster phenotyping
- Higher quality hits
- Profiling attributes
- Mechanism of action
- Go/No Go

- Target ID
- Targets
- HTS
- Hits
- Improve Lead
- Identify Lead
- In vivo imaging
- Preclinical biomarkers
- Continuous Improvement Feedback Loop
- Cellular biomarkers

= data generated
Strategy: Deliver the Promise of IIH

- **LabChip & Robots**
  - Biotherapeutics & Genomics

- **Imaging**
  - Expand Modalities / Diseases

- **Molecular Dx**
  - Add Channel and Content

- **Dx & Surgical Support**
  - Expand Translational Modalities

-Molecular Apps-
Caliper Innovations

**Genome Sequencing**
- Revolutionize sample prep by integrating complete workflows on chip
- Chromosome sorting; enzymatic processing; jumping library prep
- GX assay expansion to increase relevance to NGS workflows
- Expand automation using Zephyr Genomics Workstation

**Biotherapeutics & Vaccines**
- GXII assay expansion to expand protein sizing, add glycan families
- Imaging models for PK/efficacy of large molecules
- Models to improve tracking and treatment of bacterial and viral infection

**Non Invasive Imaging**
- Expand modalities and disease relevance
- Develop additional probes and reagents
- Development of translational imaging approaches and probes

**Biomarkers**
- Expand modalities and disease relevance
- Develop additional probes and reagents
- GX diagnostic assays for detection, prediction and drug response monitoring

**Stem Cells**
- Imaging approaches to monitor stem cell differentiation
- Regenerative medicine approaches using tracked stem cell
- LabChip approaches to purification of specific stem cell populations
Caliper technology was instrumental in these discoveries

### FDA Approved

<table>
<thead>
<tr>
<th>Company</th>
<th>Product/Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer, Sutent</td>
<td>Sunitinib (sunitinib)</td>
<td>Kidney and stomach cancer</td>
</tr>
<tr>
<td>Novartis, Tasigna</td>
<td>Nilotinib (nilotinib)</td>
<td>CML, chronic myeloid leukemia, Gleevec resistance</td>
</tr>
<tr>
<td>Novartis, Zometa</td>
<td>Zoledronic acid</td>
<td>Metastasis of breast, lung, prostate and multiple myeloma</td>
</tr>
<tr>
<td>BMS, Sprycel</td>
<td>Dasatinib (dasatinib)</td>
<td>CML, chronic myeloid leukemia, Gleevec resistance</td>
</tr>
<tr>
<td>Cubist Pharma, Cubicin</td>
<td>Daptomycin</td>
<td>S. aureus infections – MRSA treatment</td>
</tr>
<tr>
<td>Sanofi-Aventis, Afibercept</td>
<td></td>
<td>Orthotopic renal cancer</td>
</tr>
</tbody>
</table>

### In Clinical Trials

**Phase I:**
- **Nereus Pharma, NPI-0052**
  - Multiple myeloma
- **Novartis, AEE788**
  - Advanced Cancers
- **Millennium, PS-341 (combo)**
  - Non-Hodgkin’s Lymphoma, others
- **Insert Therapeutics, IT101**
  - Solid tumors
- **Novartis, CHIR-258**
  - Metastatic melanoma
- **Abbott, ABT-888**
  - Multiple diverse tumor models
- **Amgen, RANKL inhibitor**
  - Denosumab and bone metastasis models

**Phase II,III:**
- **Sanofi-Aventis, Afibercept**
  - Multiple indications
- **EntreMed, Panzem**
  - Recurrent Glioblastoma
2010 Innovation for Experimentation Series

- China, EU, West Coast, and Hopkinton Headquarters meetings
- Expect 450 global attendees including thought leaders / investors
- FDA Momentum: Amgen, Pfizer & Biogen, training FDA on GX
- 09 Novartis: Keynote Martin Mackay, President R&D, Pfizer
- 10 Hopkinton: Keynote George Church, Father of Next Gen Sequencing
- Key NextGen, MDx and Biologics thought leaders, vendors and customers
## Collaborator Strategic Fit Assessment

<table>
<thead>
<tr>
<th>Large BioPharma</th>
<th>2008 R&amp;D Spend</th>
<th>GX*</th>
<th>EZ*</th>
<th>IVIS</th>
<th>% Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most Penetrated Accounts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pfizer-Wyeth</td>
<td>$11,318</td>
<td>7</td>
<td>10</td>
<td>5</td>
<td>55%</td>
</tr>
<tr>
<td>Merck-Schering Plough</td>
<td>$8,334</td>
<td>7</td>
<td>9</td>
<td>16</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Novartis</strong></td>
<td><strong>$7,217</strong></td>
<td>7</td>
<td>10</td>
<td>16</td>
<td><strong>75%</strong></td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>$6,698</td>
<td>3</td>
<td>12</td>
<td>3</td>
<td>40%</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>$5,013</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>30%</td>
</tr>
<tr>
<td>Amgen</td>
<td>$3,030</td>
<td>9</td>
<td>3</td>
<td>4</td>
<td>55%</td>
</tr>
<tr>
<td>Takeda Millennium</td>
<td>$2,665</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>50%</td>
</tr>
<tr>
<td>Merck-Serono (EMD)</td>
<td>$1,807</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>50%</td>
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<tr>
<td>Biogen-Idec</td>
<td>$1,072</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>40%</td>
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<tr>
<td>Vertex</td>
<td>$516</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Least Penetrated Accounts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche-Genentech</td>
<td>$9,911</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>20%</td>
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<tr>
<td>GSK</td>
<td>$6,433</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>35%</td>
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<td>Johnson &amp; Johnson</td>
<td>$5,095</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>20%</td>
</tr>
<tr>
<td>Bayer Schering AG</td>
<td>$3,884</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>5%</td>
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<tr>
<td>Eli Lilly</td>
<td>$3,841</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>15%</td>
</tr>
<tr>
<td>BMS</td>
<td>$3,585</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>25%</td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>$3,088</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>25%</td>
</tr>
<tr>
<td>Abbott</td>
<td>$2,689</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>20%</td>
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<tr>
<td>Genzyme</td>
<td>$1,308</td>
<td>1</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Allergan</td>
<td>$798</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>15%</td>
</tr>
</tbody>
</table>

* GX units include predecessor LC 90 installations; EZ includes LC3000 units
Rick’s Mom, Eva Bernal 104 years!
Passed in January 2009
In Loving Memory

My Mom, Eileen Hrusovsky 81 years!
BUCKEYE Grandma
Passed in July’07
In Loving Memory

Randy Pausch

Willard Scott
Key Themes Revolutionizing Medicine & Pharma Industry

The pharmaceutical & medical industries will be transformed

- Innovation and imbalances in wealth, population, and disease will catalyze healthcare revolution
- Pharmacoeconomics & personalization will steer R&D efforts and focus onto next generation diagnostics and therapeutics
- Another major advance in global life expectancy is becoming more probable

Advanced technology will continue to give progressive organizations advantages

- Technologies providing high fidelity models will enable a transformation in discovery strategies
- Paralleling into 96 – 384 testing formats will continue its evolution into newer technologies
- Next gen sequencing, biomarker and imaging platforms will help enable personalized medicine
- Imaging, microfluidics, sequencing and sample prep platforms will underpin IIH Bridge drug discovery models
Our Quest

A Unified, Noble Vision: Health Care

We will **fight** for cures and the highest possible quality of life

We will **not give up** or let down those that urgently need our innovation

We are a **chosen group** of people and this is our moment to **fulfill the promise**

*in vitro – in vivo – human (IIH)*
Thank You!

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