Next Gen Sequencing Survey

What Laboratory Directors Are Saying About Next Generation Sequencing, GWAS and Stimulus

Life Science Tools & Diagnostics

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In an effort to better understand trends in the sequencing market, we recently surveyed 30 laboratory directors in the U.S. and Europe (24 US, 6 EU) to gauge the appetite for several new next generation sequencing platforms (HiSeq 2000 from ILMN, SOLiD 4 from LIFE), as well as third gen sequencing systems (PacBio, Ion Torrent, LIFE SMS) and microarrrays. Based on our survey, demand for new NGS instruments and upgrades remains healthy (estimated $540mm market, 22% 3-yr CAGR), with respondents, in aggregate, expecting to purchase or upgrade ~136 NGS systems through 2013, and estimating NGS-related activity to increase from ~37% of research today to 48% 12 months from now and 56% within two years. In conjunction, we are increasing our Dec. 2010 price target on ILMN from $44 to $48, as the company remains most exposed to growth in the sequencing market and a recovery in GWAS, while we maintain our Overweight rating on both ILMN and LIFE, based on our favorable outlook for academic research and other key markets.

- **Interest in HiSeq remains high.** As the market leader in next gen sequencing (JPMe of ~53% share), ILMN continues to lead in terms of demand for the recently-launched platform, HiSeq 2000, as well as GAIIx, with lab directors, in aggregate, expecting to purchase or upgrade 46 systems through 2013. As a reminder, ILMN unveiled HiSeq 2000 ($690K list, initial spec of 200 Gb of data/run) earlier this year, along with a record 128 system orders from BGI, and demand YTD has exceeded expectations (record backlog growth ex-BGI order), with ~85% of initial customers coming from non-genome centers. ILMN should reach full production volume for HiSeq in 2Q, and expects to begin bulk customer orders by 3Q.

- **Demand for SOLiD 4 appears better than we had expected.** With the second largest market share in NGS (JPMe of ~19% share), demand for LIFE's recently launched SOLiD 4 was solid, with respondents, in aggregate, expecting to purchase or upgrade 28 systems through 2013. Also notably, LIFE's SOLiD 3 Plus received the highest rating (vs. GAIIx or GS FLX) for data accuracy, which was considered the most important metric for making NGS purchasing decisions. As a reminder, LIFE introduced SOLiD 4 in January, with an initial spec of up to 100 Gb of data/run at $6K per genome, and along with a significantly enhanced sample prep system (EZ Bead), and is expected to release a SOLiD 4hq upgrade package (300Gb/run, 99.99% accuracy, $3K/genome) in 2H10. Although NGS represents <5% of revenue for LIFE, it remains an important growth driver (strong double digit growth in 1Q10), offsetting the slowdown in CE research (~13% of revenue).

- **Laboratory budgets remain stable.** Turning to lab budgets, respondents expect total budgets, and budgets for NGS, to remain the flat or, more likely, to increase going forward. On ARRA grants, only ~30% of respondents have received or expect to receive funding, with the greatest proportion of spending expected to occur between July and Dec. 2010. Over 60% of funds allocated have not been spent, with the greatest allocations expected to go to new research projects (34%), followed by NGS reagents and consumables (18%), and the hiring of scientists (17%). That said, with funds largely allocated for research projects and reagents, the ARRA impact may be more difficult to break out than previously anticipated, which is consistent with recent commentary from ILMN and other life science tools companies.

See page 53 for analyst certification and important disclosures.

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- **"Third generation" gets closer to reality.** While still early, our survey indicates ample interest for third generation platforms, including PacBio and Ion Torrent systems, with respondents expecting to purchase or upgrade 9 and 8 systems, respectively, through 2013, and only behind already commercially available HiSeq, SOLiD 4 and GAIIx systems. Notably, respondents in our survey estimated that third generation sequencing will replace ~8% of all next generation sequencing activity in the next twelve months, ~26% of NGS activity in the next two years, and ~47% in the next three years.
- **Microarray demand remains lukewarm, but GWAS recovery could provide cushion.** Given recent setbacks to the microarray market in 2009 (AFFX product sales growth of ~3%, and JPMe estimate of a double-digit decline for ILMN's microarray segment in 2009), the outlook for the array market remains cloudy vis-à-vis the impact from NGS technologies, although in the near term, ILMN and others should benefit from easy comparisons and a partial recovery in GWAS demand. With 19 of our survey respondents also microarray owners, ~68% of respondents noted expectations for an increase or no change in microarray usage for 2010, in light of the NGS impact, while ~58% expect to increase or not change usage in 2011, and ~53% in 2012. That said, on average, respondents expect that ~16% of microarray usage in their labs could be replaced by NGS in the next 12 months and ~33% in the next three years. Finally, on GWAS, which contributed significantly to ILMN's softness in the microarray business last year (although it still represents ~50% of revenues, GWAS was down an estimated 20-30%), respondents anticipated modest declines going forward, with ~26% of microarray usage representing GWAS in 2009, declining to ~22% in 2010, ~21% in 2011, and ~20% in 2012, although we expect that some of this could be offset this year by new rare variant product cycles, such as Omni 2.5 and 5.0 arrays from ILMN. In total, we estimate the current commercial platform-based microarray market is now ~$700mm growing at a 3-year CAGR of ~9%.

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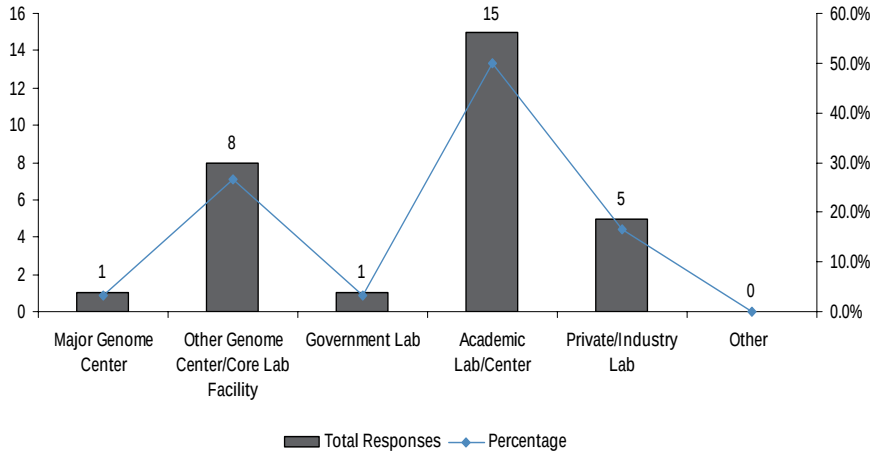
Survey Results

Respondent Background

In order to capture laboratory directors most qualified to share opinions on next generation sequencing, we limited our survey to laboratories that currently own or intend to own one or more next generation sequencing platforms in the near future, and laboratory directors who have major input in capital equipment purchasing decisions.

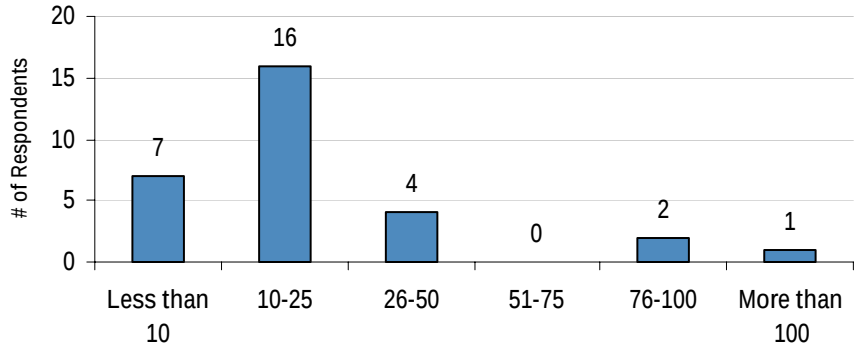
Our target group was primarily located in the U.S. (24 out of 30), with the majority of respondents from academic and government laboratories (15 out of 30), and others representing a major genome center (n=1), other genome centers/core laboratories (n=8), government laboratory (n=1), and private/industry laboratories (n=5), including diagnostic labs, a pharmaceutical laboratory, industrial laboratory, and a laboratory within a private research foundation.

Figure 1: Type of Laboratories Represented



Source: J.P. Morgan survey.

Figure 2: Number of Employees at Respondent Labs



Source: J.P. Morgan survey.

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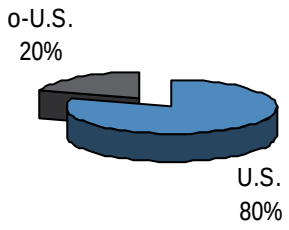
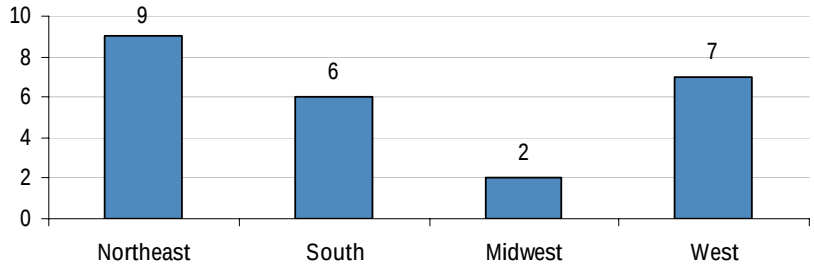
Survey respondents represented diverse geographic regions across the U.S., with seven labs located in the West, two in the Midwest, nine in the Northeast, and six in the South. The remaining six labs were located in Europe.

Figure 3: US vs. OUS



Source: J.P. Morgan survey.

Figure 4: Major Regions in US Represented

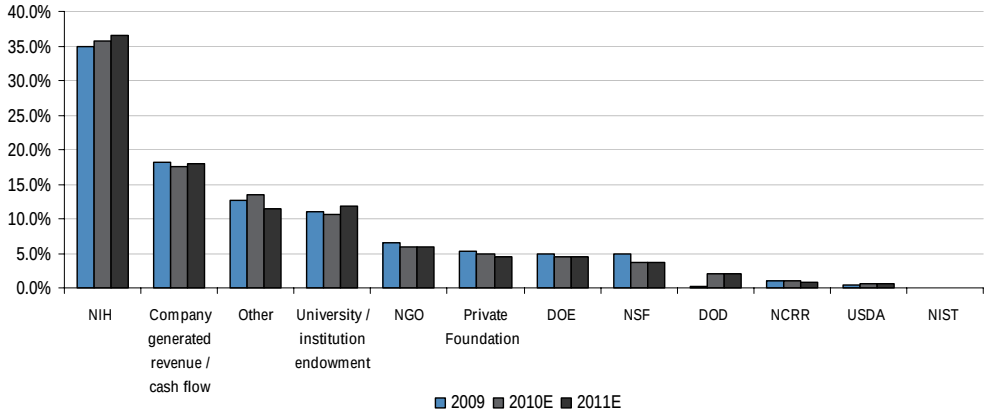


Source: J.P. Morgan survey.

Lab Budgets and ARRA Funding

Of the laboratories that we surveyed, the most significant funding source was NIH, comprising ~35% of funding in 2009, on average, followed by company generated revenue/cash flow (largely for private/industry labs), and university/institution endowments. Other funding sources listed include non-U.S. government funding (e.g., Spanish government, U.K.), various private foundations, venture funding, state government funding, various medical societies worldwide, etc.

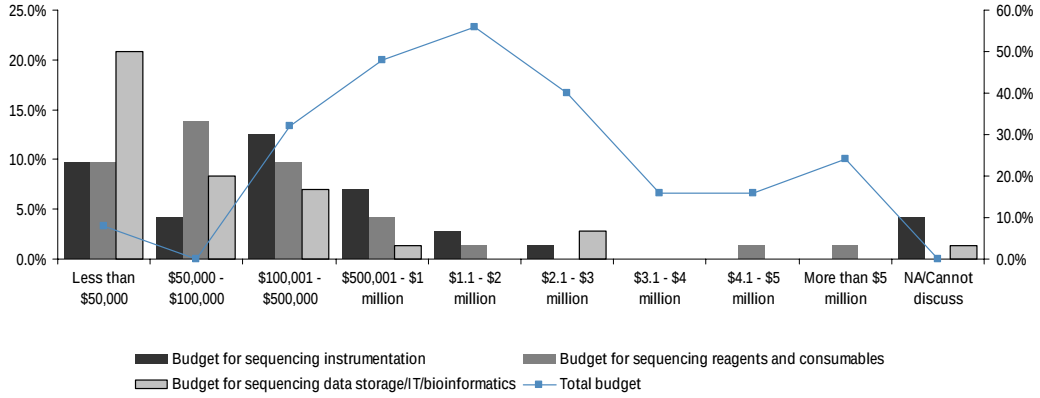
Figure 5: Laboratory Funding Sources



Source: J.P. Morgan survey.

On annual lab budgets, the largest proportion of the respondents had total annual budgets of $1.1-2 million, while the largest percentage of directors indicated annual sequencing instrumentation budget of $100-$500K, reagent and consumable budget of $50-$100K, and data storage/IT/bioinformatics of less than $50K.

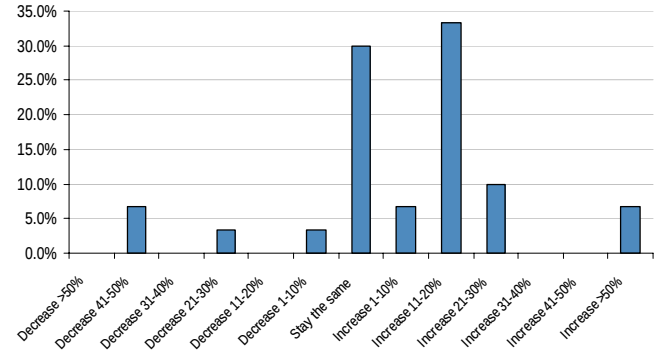
Figure 6: Annual Lab Budgets



Source: J.P. Morgan survey.

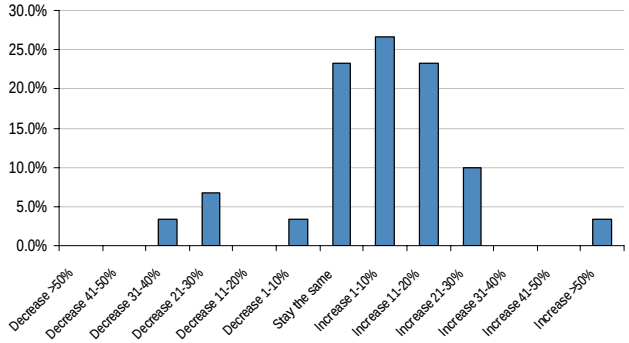
In general, respondents estimated their annual lab budget, as well as sequencing budgets will remain the same, or increase in 2010 over 2009, as well as in 2011 over 2010.

Figure 7: Total Annual Budget, 2010E over 2009



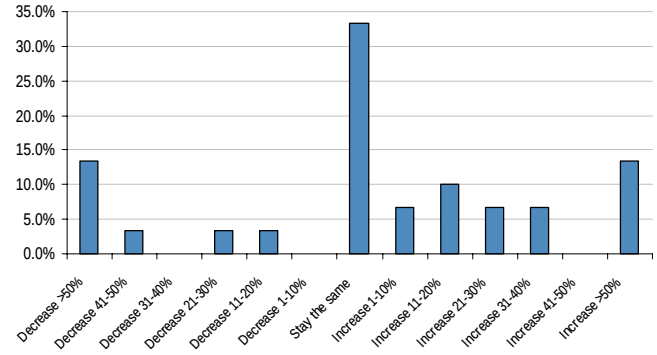
Source: J.P. Morgan survey.

Figure 8: Total Annual Budget, 2011E over 2010E



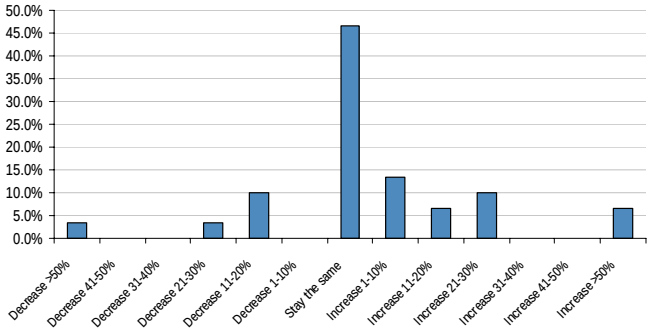
Source: J.P. Morgan survey.

Figure 9: Budget for Sequencing Instrumentation, 2010E over 2009



Source: J.P. Morgan survey.

Figure 10: Budget for Sequencing Instrumentation, 2011E over 2010E



Source: J.P. Morgan survey.

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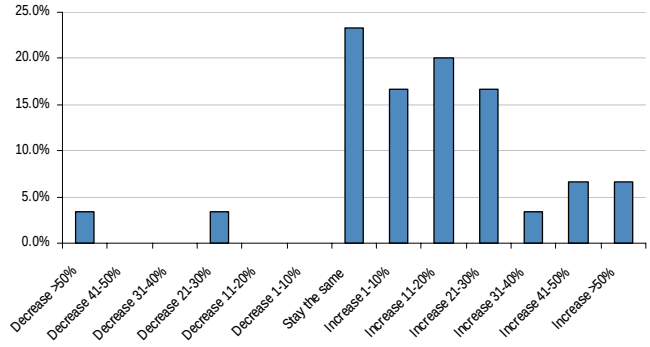
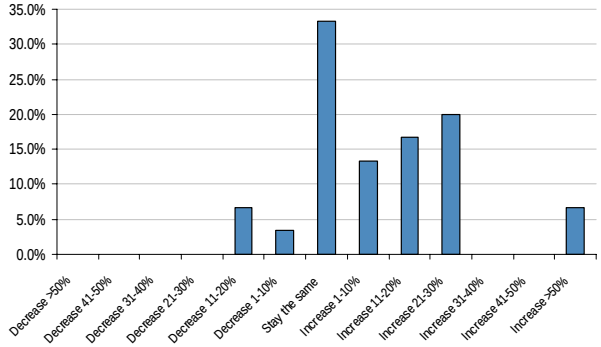
Figure 11: Budget for Sequencing Reagents and Consumables, 2010E over 2009



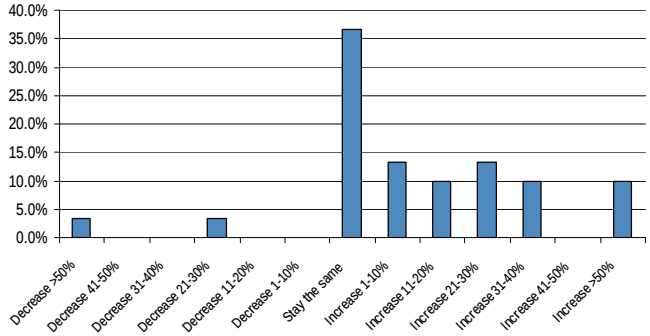
Source: J.P. Morgan survey.

Figure 12: Budget for Sequencing Reagents and Consumables, 2011E over 2010E



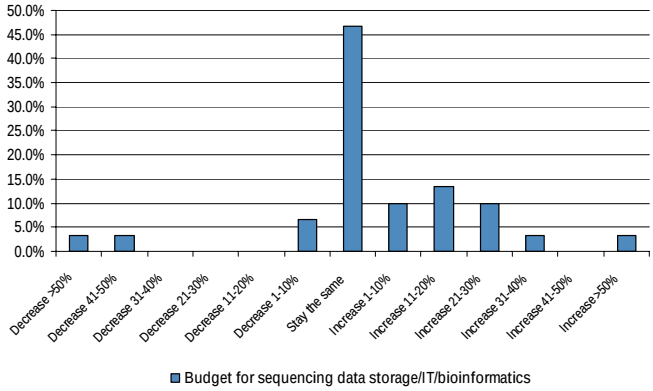
Source: J.P. Morgan survey.

Figure 13: Budget for Sequencing Data Storage/IT/Bioinformatics, 2010E over 2009



Source: J.P. Morgan survey.

Figure 14: Budget for Sequencing Data Storage/IT/Bioinformatics, 2011E over 2010E

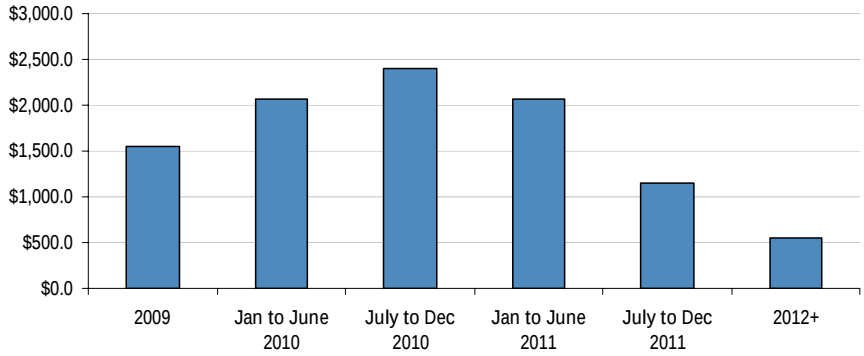


Source: J.P. Morgan survey.

Nine out of 30 respondents expected to receive ARRA funding.

On ARRA funding, nine out of the 30 respondents have or expect to receive grants, with the greatest proportion of the funding expected to be spent in the July to December 2010 timeframe.

Figure 15: Expected ARRA Funds Spending Timeline ($000)



Source: J.P. Morgan survey.

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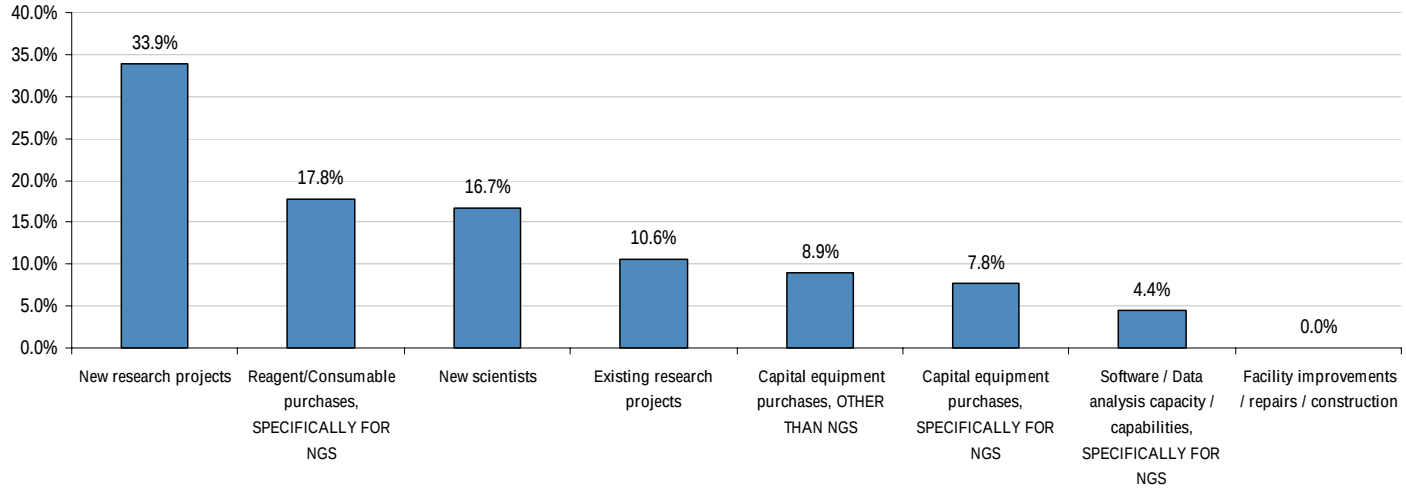
Looking closer, the majority of the funding is anticipated to come from the National Institutes of Health (NIH), or on average ~98% of funding from NIH, with a couple citing NCRR (National Center for Research Resources) as a funding source.

When asked about spending priorities for ARRA funds, new research projects were listed as the highest priority (average of ~33.9% of ARRA grant allocation), followed by reagents/consumables purchases for next generation sequencing (average of ~17.8% allocation). Other priorities included new scientists (average 16.7% allocation), existing research projects (average 10.6% allocation), and capital equipment purchases for next generation sequencing (average 8.9% allocation). Rounding out ARRA fund allocations were non-next generation sequencing capital equipment purchases (7.8%), and software/data analysis capacity/capabilities for next generation sequencing (4.4%). None of the respondents anticipated to use ARRA funding for facility improvements/repairs/construction.

Figure 16: ARRA Funding Allocation Priorities



Source: J.P. Morgan survey

Impact of non-governmental funding on lab budgets

When asked whether they expected non-governmental funding sources to impact the overall laboratory budget and/or next generation sequencing budget, most respondents replied they did not anticipate an impact from institutional endowments and other private/NGO funding mechanisms. For the several respondents who believed lab budgets would change, responses were skewed towards an overall increase in laboratory and/or next generation sequencing budgets in 2010.

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Table 1: Sample Comments on Whether Non-Governmental Funding Sources May Impact Overall Lab or NGS Budgets in 2010

"Spanish government grants may shrink somewhat."

"We have not seen any major impact for 2010."

"Two factors will affect our budget. The first will be ongoing income and utilization from core facility customers. The second, which is harder to predict, will be institutional recognition of the importance to increase NGS investment to keep pace with other research organizations."

"Our college dean is actively working to increase our endowment for research. Our endowment has also done reasonably well for the last two years, so we should start seeing an increase next fiscal year in payout."

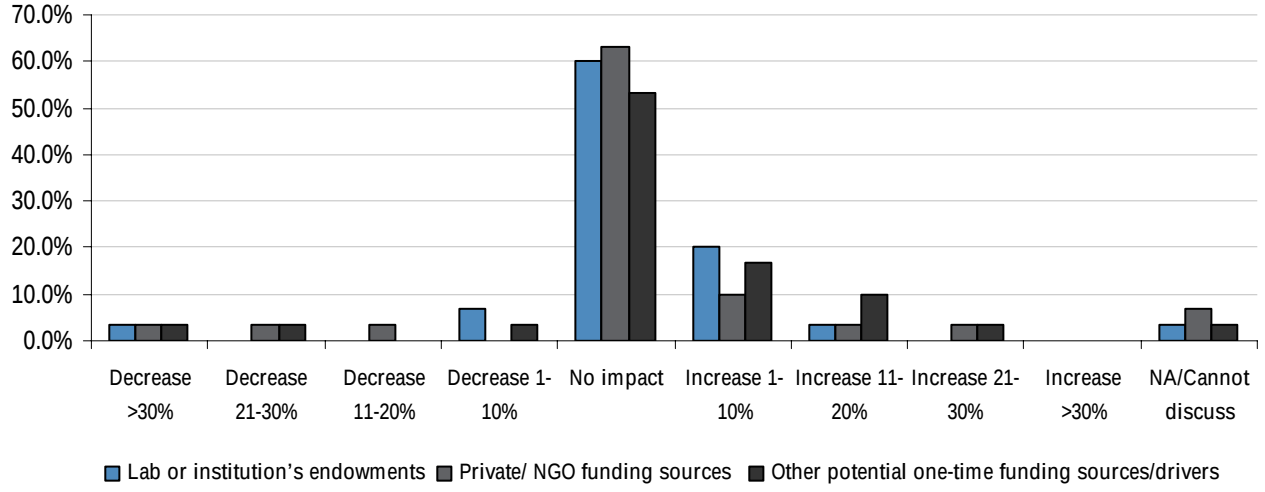
"The success rate for cancer charity grants is much lower than in previous years."

"An estimate is really difficult; Several grant applications are running, but we currently design our projects to not depend on their approval."

"We used private donations to fund our past next generation sequencing, and may do so again this year, if we obtain the funds."

Source: J.P. Morgan survey.

Figure 17: Impact of Non-Governmental Funding Sources on Overall 2010 Budget



Source: J.P. Morgan survey.

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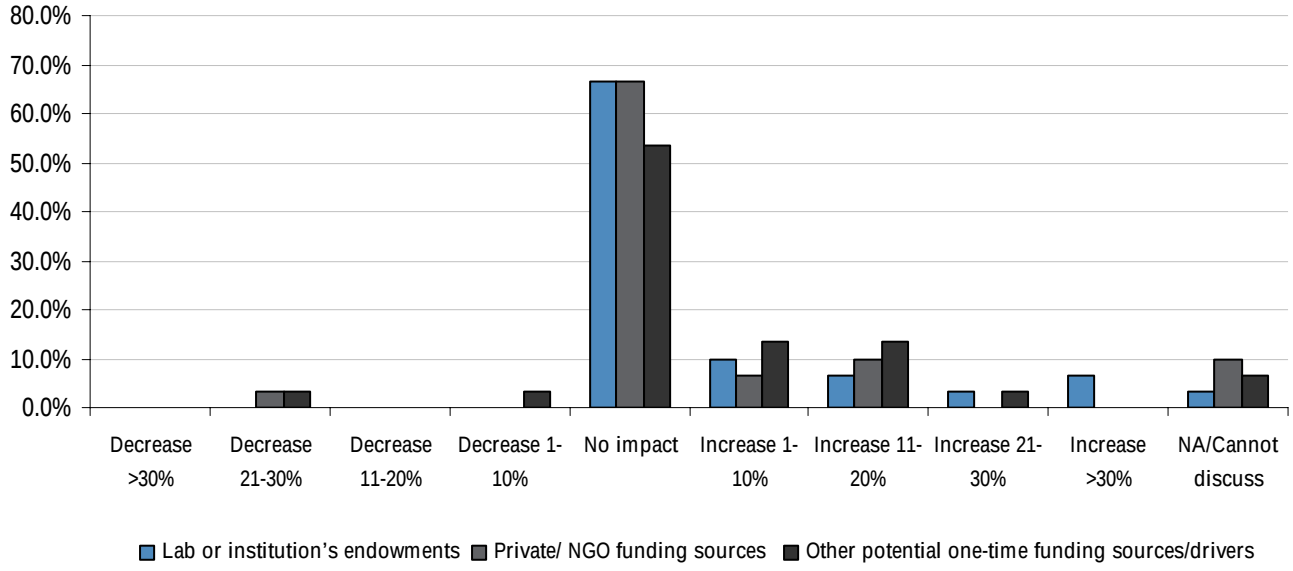
Figure 18: Impact of Non-Governmental Funding Sources on NGS Budget for 2010



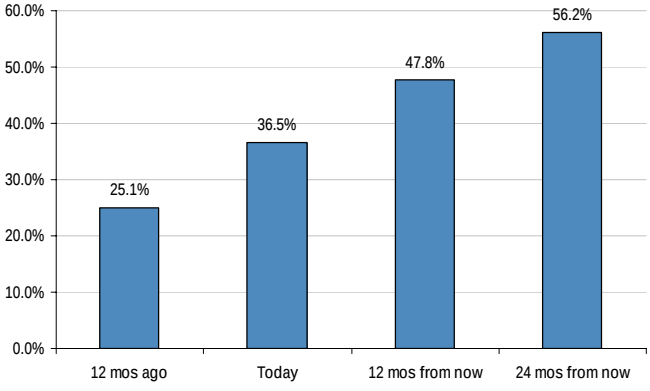
Source: J.P. Morgan survey.

Current Sequencing Needs

Demand for next generation sequencing remains strong

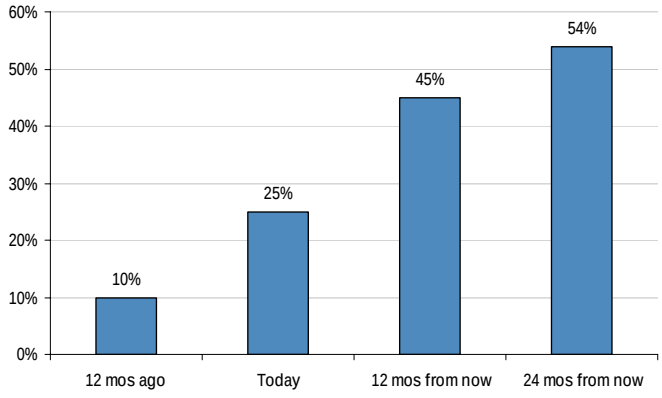
Among the laboratories that we surveyed, approximately 37% of research activity involves next generation sequencing. This has increased from ~25% of research activity a year ago, and next generation sequencing is expected to constitute ~48% of research activity a year from now, and ~56% two years from now. Notably, expectations for sequencing activity ramp-up were modestly lower compared to expectations among respondents in our 2009 survey.

Figure 19: Lab Research Activity Involving NGS Systems (2010 Survey)



Source: J.P. Morgan survey.

Figure 20: Lab Research Activity Involving NGS Systems (2009 Survey)



Source: J.P. Morgan survey.

RNA-Seq and ChIP-Seq are NGS applications respondents were most excited about.

When asked to list top three next generation sequencing applications respondents are most excited about, RNA sequencing was cited most frequently (15 responses), followed by ChIP sequencing (10 responses), whole genome sequencing (6

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responses), resequencing (6 responses), whole exome sequencing (4 responses), and cancer genome sequencing (4 responses).

Table 2: Top Three NGS Applications Respondents Are Most Excited About

Application	# cited
RNA Seq	15
ChIP-Seq	10
whole genome sequencing	6
resequencing	6
whole exome sequencing	4
cancer genome sequencing	4
methylation	3
mutation and structural DNA analysis	2
single molecule sequencing	2
SNP analysis	2
microbial/viral genome sequencing	2
bisulfite sequencing	2
RNA counting, novel pathogen discovery, metagenomics, proteomics, biomarker/diagnostic, forensics, non-coding RNA profiling, nuclear organization studies, RNA sequencing for chimeric transcript discovery, oligonucleotide capture sequencing, deep sequencing mutation/somatic hypermutation, global run-on (GRO) sequencing, prenatal screening	1

Source: J.P. Morgan survey.

Data storage / management / informatics are the biggest hurdle to expanding NGS usage.

When asked to name the largest hurdles to expanding next generation sequencing usage, the most cited reason was data storage/management/informatics (19 responses), followed by general cost (5 responses), sample prep/workflow (4 responses), and DNA sample access (4 responses). We note that several instrument vendors, including Illumina and Life Technologies, have recently undertaken major initiatives to improve data storage and handling costs.

Table 3: Biggest Hurdles to Expanding NGS Usage

Biggest hurdles	# cited
data management / informatics / storage	19
general cost	5
sample prep / workflow	4
DNA sample access	4
funding	3
quality and reproducibility	2
regulatory / legal constraints	2
capacity / access to more sequencers	2
scaling up, cost of WGS, switching cost, limited read-length, educating investigators about technology, automated SNP detection, instrument and software maintenance	1

Source: J.P. Morgan survey.

Table 4: Sample Comments on the Biggest Hurdles to Expanding NGS Usage

"Being stuck with an obsolescing platform (i.e., heavily invested in SOLiD as better technologies emerge, so when to shift and buy new equipment)."
"Funding for capital equipment purchases. Currently, we would like to get additional sequencers, but there are limited resources of funding available. Data analysis is another hurdle. A lot of data are being generated, but it is difficult to get through all the analyses."
"Although bioinformatics will be a challenge, we are not directly responsible for data handling and analysis. Our most serious challenge is educating investigators about the technology so they will understand how to use it efficiently and will recognize what is involved in generating high-quality libraries and data."
"Resources for equipment purchases; I moved from a $70 M research facility in Canada. Unfortunately, NIH currently has no equivalent funding mechanism for equipment infrastructure."
"Legal issues related to storing person-sensitive data on online servers."
"Instrument time. Because of the length of time these instruments take to actually do a run, we are pretty backed up. It's a major hurdle. Informatics and data management are also a problem, but they scale better than instrument time."

Source: J.P. Morgan survey.

Illumina's NGS portfolio continues to garner significant interest

Illumina's next generation sequencing platforms continue to lead the way in terms of current ownership or expectations for purchases/upgrades in the next three years. Forty-three percent of the respondents in our survey currently own or expect to purchase/upgrade Illumina's GAIIx, slightly behind 47% of respondents who currently own or expect to purchase/upgrade CE platforms in the next three years.

As for the newest versions of next generation sequencers, 33% of the respondents own or expect to own Illumina's HiSeq 2000, while 23% of the respondents own or expect to buy Life Technologies' SOLiD 4 and 17% expect to purchase the SOLiD 4*hq* upgrade. Notably, more than a quarter of the respondents expect to purchase a third generation sequencer, with 27% of the respondents indicating interest for either PacBio or Ion Torrent systems, and 23% for Life Technologies' single molecule sequencing platform. Other third generation systems as potential purchases included Oxford Nanopore and NABsys systems.

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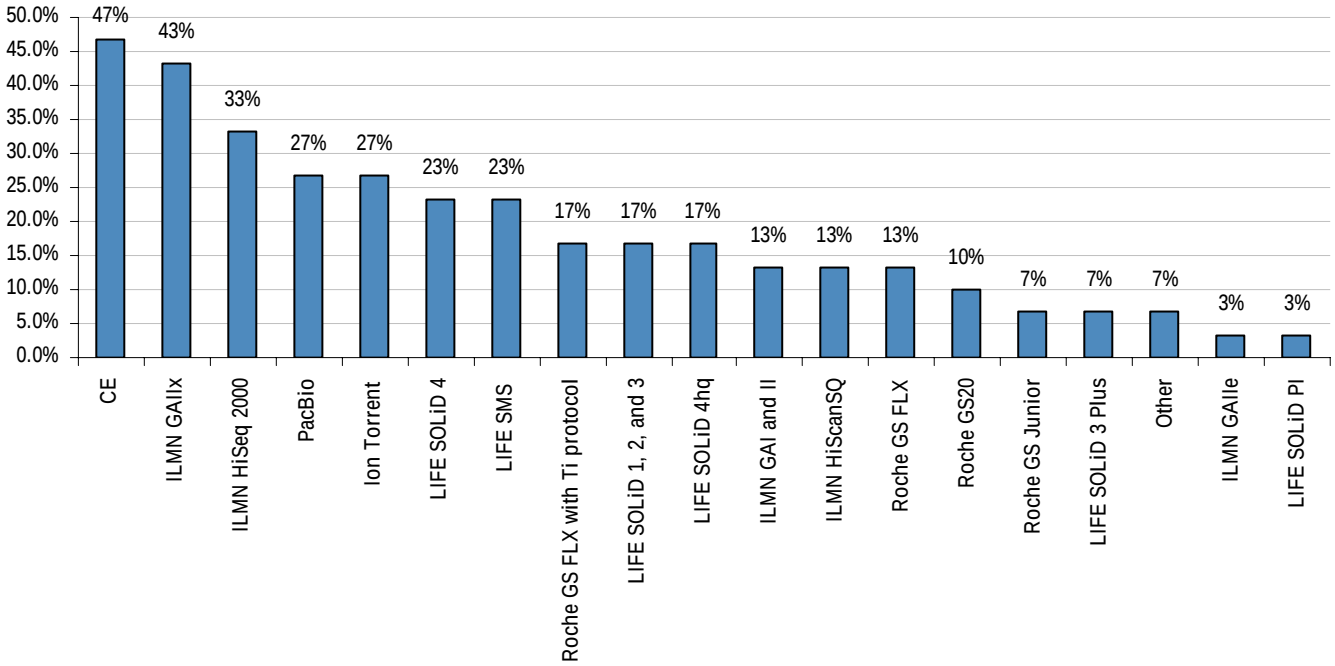
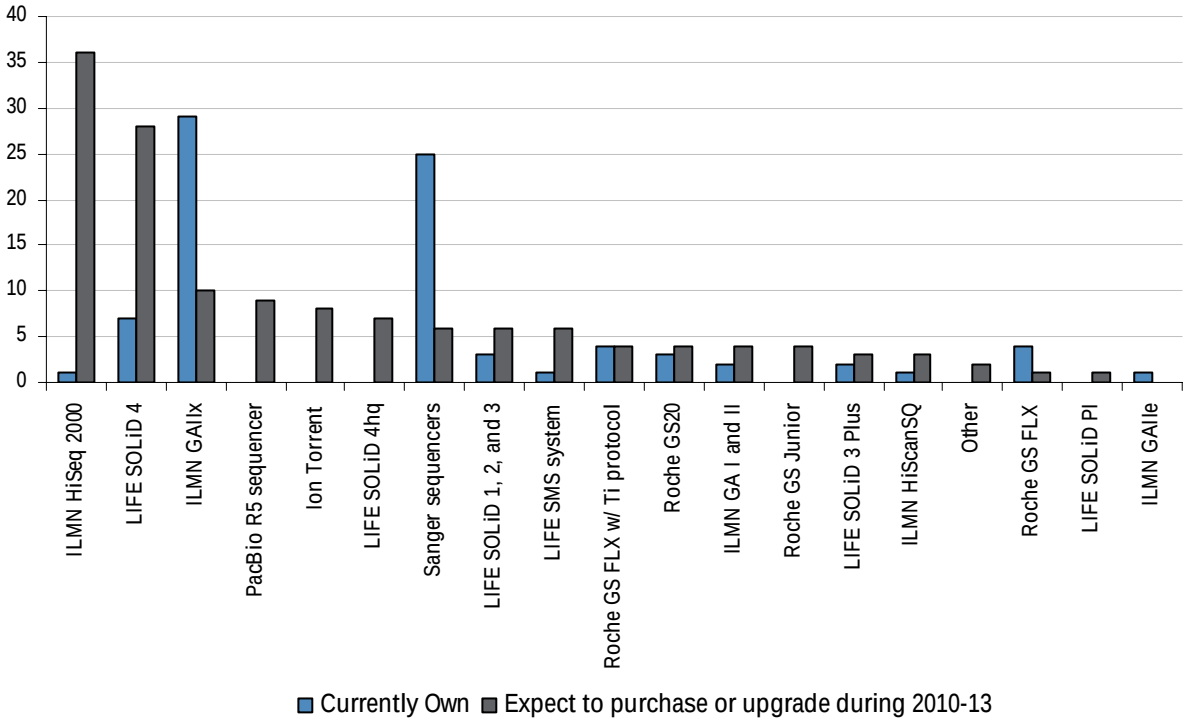
Figure 21: Sequencers Currently Own or Expect to Purchase/Upgrade in the Next Three Years



Source: J.P. Morgan survey.

Figure 22: Number of Systems Currently Owned and Expected to Acquire in 2010-2013 (in aggregate)



Source: J.P. Morgan survey.

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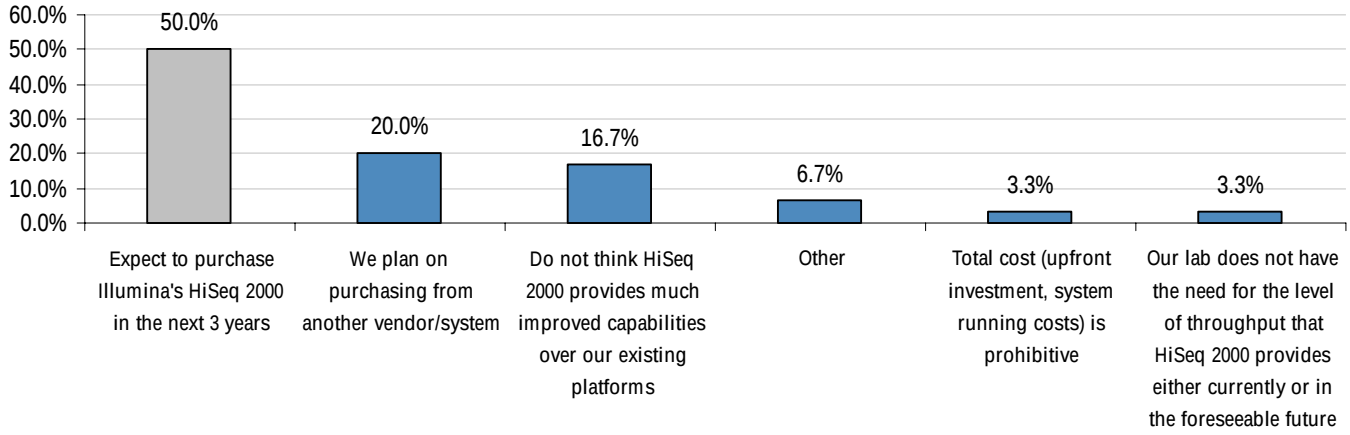
Fifteen lab directors expect to purchase Illumina's HiSeq 2000 system in the next three years. Of those who do not plan on purchasing a system, six plan on purchasing an alternative system or from a different vendor.

Figure 23: Reasons for Not Purchasing HiSeq 2000 in the Next Three Years



Source: J.P. Morgan survey.

Table 5: Sample Comments on Why or Why Not Lab Directors Plan on Purchasing HiSeq 2000

"Upgrade to SOLiD 4 and beyond, then Pacific Biosystems later?"
"The GAIIx is fine for us right now, but for the future we are looking to get to the next level sequencer beyond the HiSeq 2000."
"We have a GA IIx that we are going to upgrade to a HiSeq 2000 this year."
"PacBio. We might, however, purchase another GAIIX or HiSeq 2000."
"There is value in having overlapping technologies as well as in continuing to invest in ones which are already purchased. It is too soon for us to know which direction we might take as platforms continue to evolve. Our current plans are to follow the latter model."
"We have two. We will evaluate further as circumstances require. Maybe, maybe not."
"Our applications are not based on HT but on accuracy of the data."
"We will expand in about two years, but because of the rapid development of these technologies, it is impossible to foresee which system we will go for."
"We currently have a SOLiD 3 system and will most likely buy another similar system as the technology improves for compatibility with developed pipelines."

Source: J.P. Morgan survey.

Eleven lab directors plan on purchasing Life Technologies' SOLiD 4 or 4*hq*. For those not planning on purchasing SOLiD 4 or 4*hq*, seven stated they do not think SOLiD 4 or 4*hq* provide much improved capabilities over existing platforms, while six plan on purchasing an alternative system or from a different vendor.

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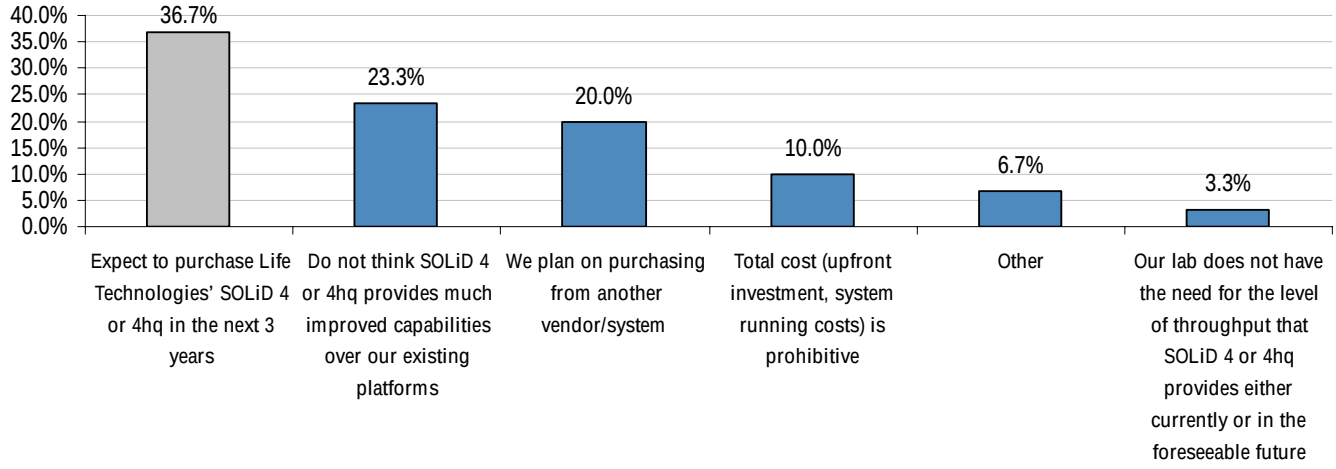
Figure 24: Reasons for Not Purchasing SOLiD 4 or SOLiD 4*hq* in the Next Three Years



Source: J.P. Morgan survey.

Table 6: Sample Comments on Why or Why Not Lab Directors Plan on Purchasing SOLiD 4+

"Throughput should be similar to HiSeq, and up-front sample prep via emulsion PCR is a nightmare, which makes the platform a non-starter."

"Will have three HiSeqs."

"We'll have two - depends upon performance and future needs. Mostly performance."

"Our applications are not based on HT but on accuracy of the data."

"We will expand in about two years, but because of the rapid development of these technologies, it is impossible to foresee which system we will go for."

"Illumina, Roche are our current preferences - We are currently completing our 5-year review, which will determine our future budget and experimental direction."

Source: J.P. Morgan survey.

CE sequencing demand

Eight lab directors indicated they plan on purchasing additional Sanger sequencers or upgrading in the next three years, largely because there are applications for which Sanger sequencing is still most cost effective. One respondent stated they use capillary sequencing for fragment analysis for microsatellite instability assays.

Table 7: Reasons for Purchasing or Upgrading Sanger Sequencer (5=extremely important, 1=not at all important)

There are applications where Sanger/capillary sequencing is still most cost effective	4.25
There are applications where Sanger/capillary sequencing still produces the most accurate data	2.38
There are applications where next gen sequencing does not have appropriate capabilities	2.25
There are applications where Sanger/capillary sequencing is still most time efficient	1.88

Source: J.P. Morgan survey.

Seventeen (57%) of the respondents expect third generation sequencing will impact a second generation purchasing decision.

Seventeen (57%) of the thirty respondents indicated that the timing of the availability of third generation single molecule sequencing platforms or services would impact purchasing decisions for second generation systems. The most frequently cited platform was the PacBio system (7 respondents), with Oxford Nanopore, Life Technologies SMS, Ion Torrent and Complete Genomics all mentioned once. Please see our recent report from AGBT ("AGBT 2010: Notes from Marco Island" for a more complete description of third generation platforms).

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Others did not have a specific system in mind, but had the following comments:

Table 8: Impact of Third Generation Technology on Second Generation Sequencing Purchases

"They are still not real systems. The answer depends on costs, specs, throughput, etc."

"I have only heard second-hand information about Life technology's SMS and Ion Torrent's system. I have heard a presentation from Pacific Biosciences and know some details about the timing of their manufacturing and sales plans. We will need to monitor these technologies to see if they are complementary to further upgrades of the SOLiD systems or if they will totally replace them for our purposes."

"We currently have a Roche 454 and anticipate using our equipment funds to purchase "third generation" technology in the next 2 years, depending on the quality of the technology."

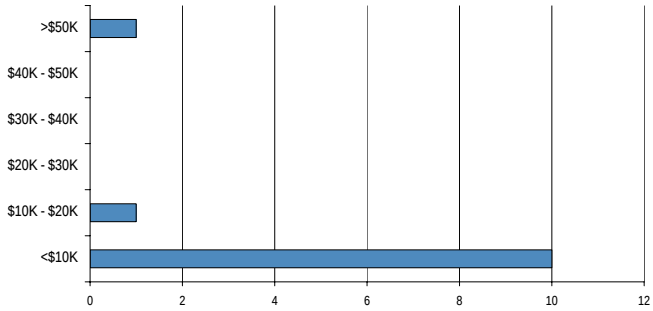
"We have no strong views at the moment but the key for us would be cheaper sequencing costs per sample and increased sensitivity (i.e., less DNA needed). We would evaluate what is on the market at the time of purchase."

Source: J.P. Morgan survey.

Data storage / IT / bioinformatics spending

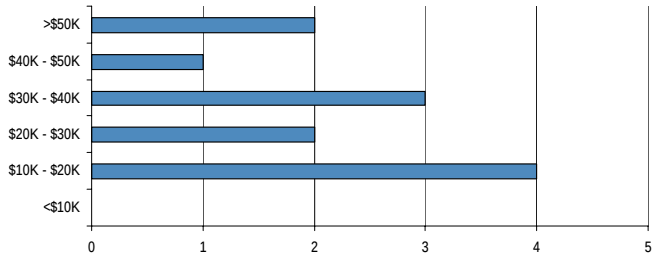
On how much laboratory directors expect to spend on data storage/IT/bioinformatics, with the exception of CE sequencing, the responses varied significantly. In addition to the small sample sizes, this could be largely due to the different data storage/IT/bioinformatics needs for different labs regardless of the next generation sequencer used.

Figure 25: Estimated Spending per Year on Data Storage / IT / Bioinformatics (Sanger sequencers)



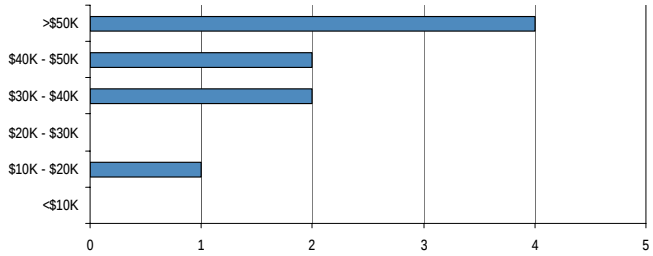
Source: J.P. Morgan survey.

Figure 26: Estimated Spending per Year on Data Storage / IT / Bioinformatics (ILMN GAIIx)



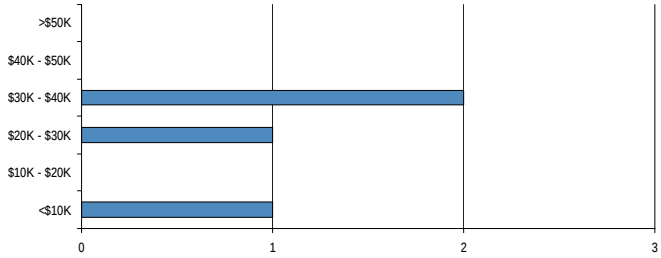
Source: J.P. Morgan survey.

Figure 27: Estimated Spending per Year on Data Storage / IT / Bioinformatics (ILMN HiSeq 2000)



Source: J.P. Morgan survey.

Figure 28: Estimated Spending per Year on Data Storage / IT / Bioinformatics (Roche GS FLX with Ti protocol)



Source: J.P. Morgan survey.

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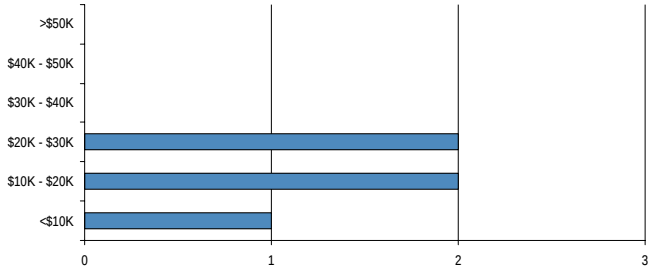
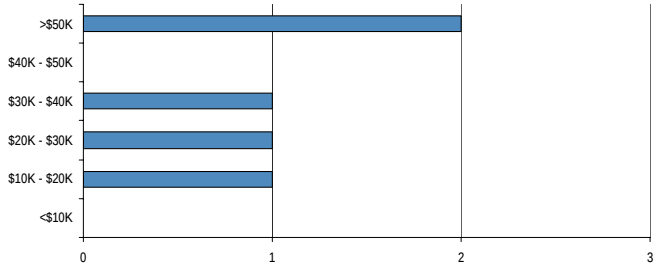
Figure 29: Estimated Spending per Year on Data Storage / IT / Bioinformatics (LIFE SOLiD 1, 2, 3)



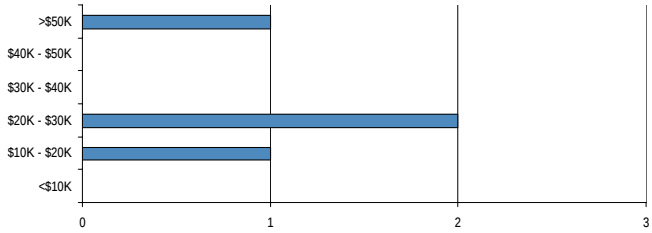
Source: J.P. Morgan survey.

Figure 30: Estimated Spending per Year on Data Storage / IT / Bioinformatics (LIFE SOLiD 4)



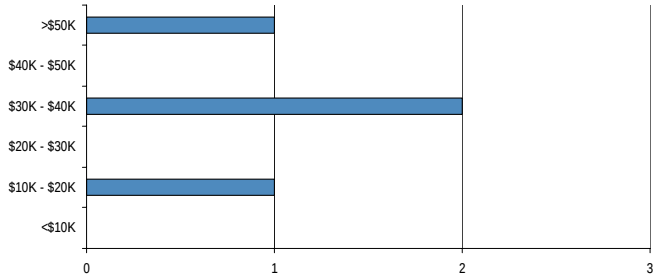
Source: J.P. Morgan survey.

Figure 31: Estimated Spending per Year on Data Storage / IT / Bioinformatics (LIFE SOLiD 4*hq*)



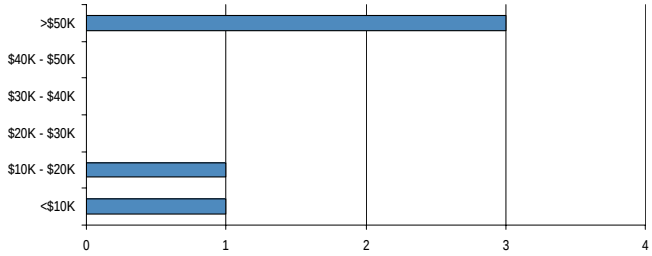
Source: J.P. Morgan survey.

Figure 32: Estimated Spending per Year on Data Storage / IT / Bioinformatics (LIFE SMS)



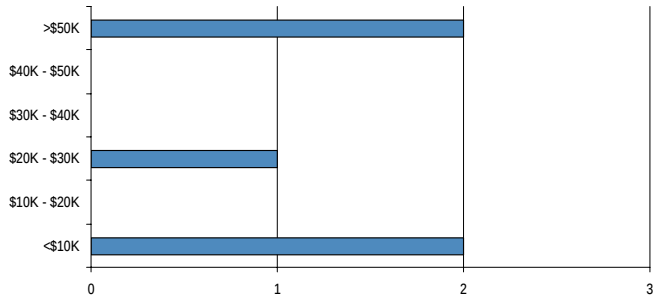
Source: J.P. Morgan survey.

Figure 33: Estimated Spending per Year on Data Storage / IT / Bioinformatics (PacBio)



Source: J.P. Morgan survey.

Figure 34: Estimated Spending per Year on Data Storage / IT / Bioinformatics (Ion Torrent)



Source: J.P. Morgan survey.

NGS reagent and consumable spending

The majority of respondents using CE sequencing estimated spending less than $100K per system per year, while reagent and consumable spending for Illumina's and Life Technologies' were more broadly distributed across a wider spectrum of budgets. Consistent with Illumina management's expectations, respondents generally expect to spend more on consumables for HiSeq 2000 versus GAIIx (i.e., on consumable pull-through per system, HiSeq is expected to bring in $300-400K, or double that of GAII systems given the dual (versus single) flow cells).

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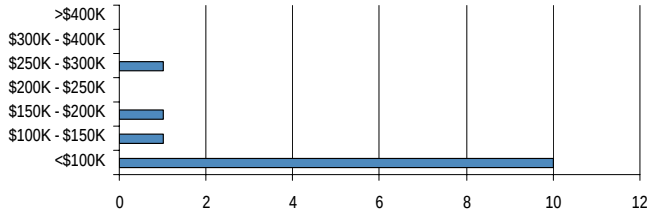
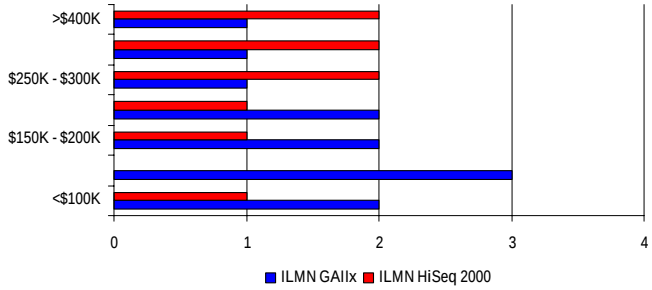
Figure 35: Estimated Spending per Year on Reagents and Other Consumables (Sanger)



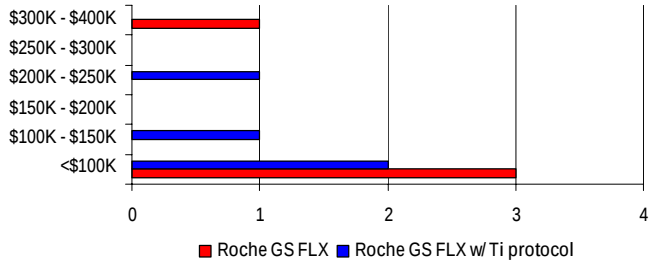
Source: J.P. Morgan survey.

Figure 36: Estimated Spending per Year on Reagents and Other Consumables (ILMN GAIIx vs. HiSeq 2000)



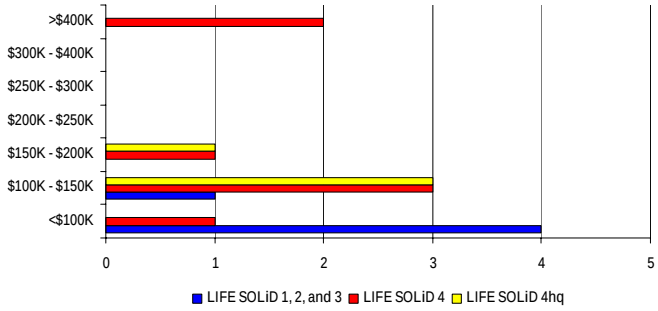
Source: J.P. Morgan survey.

Figure 37: Estimated Spending per Year on Reagents and Other Consumables (Roche GS FLX vs. GS FLX w/ Ti protocol)



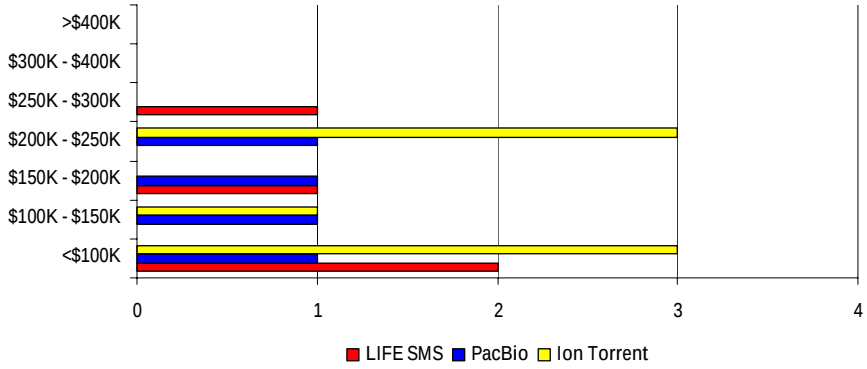
Source: J.P. Morgan survey.

Figure 38: Estimated Spending per Year on Reagents and Other Consumables (LIFE SOLiD 1,2,3 vs. 4 vs. 4*hq*)



Source: J.P. Morgan survey.

Figure 39: Estimated Spending per Year on Reagents and Other Consumables (LIFE SMS vs. PacBio vs. Ion Torrent)



Source: J.P. Morgan survey.

Sample prep performance by platform

Regarding sample prep, the prevailing perception was that Illumina's sample prep capabilities remain superior, regardless of Life Technologies' recent launch of EZ Bead or Roche's REM e system.

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Table 9: Advantages and Disadvantages of Sample Prep – By Platform

Illumina	Life Technologies
"For Illumina the sample prep is very easy. For 454/AB the prep is a bit more difficult (emulsion PCR step)." *"Illumina platforms are superior to Solid because they use cluster PCR (which is fully automated) rather than emulsion PCR (which is manual and kludgy)."* *"cBOT makes ILMN have the easiest sample prep."* *"GAIIx among the next generation sequencers currently has a robust sample preparation."* *"GAIIX: disadvantage: have to make and test libraries by Sanger Seq."* *"Sample Prep is easiest and fastest with the Illumina HiSeq 2000 as compared to the other systems."* *"Capillary sequencers require sample preparation for every fragment sequenced. The Solexa requires more upfront preparation of a sample, but only one run is needed per sample."* *"The sample prep Illumina is pretty straightforward. A computational graduate student with very little experience got it to work the first time. The 454 and SOLiD instruments both use emulsion PCR, which is a disadvantage."*	*"SOLiD advantage is throughput."* *"SOLiD 4hq has to get better than sample preparation for SOLID3 which currently is more cumbersome than GAIIx."* *"Illumina has had some advantages in ease of library prep and amounts needed for its paired-end protocol. However, AB has had advantages for some applications and has consistently reduced amounts."* *"Solid: easiest and most cost-effective."* *"AB- library prep. They're moving to automate this with EZ Bead, etc. so may be less of a problem in the future. Illumina best and simplest prep."* *"Sample and library preparation: not much difference in the effort, with SOLiD in the mate-paired version more lengthy. The difference is more that we tend to use 454 for the bisulfite sequencing, the solid for ChIP-Seq, RNA-Seq."*
Roche	**Third Gen Sequencers**
"454 Titanium: Emulsion PCR is a problem." *"Roche 454 requires a lot of DNA, which means we're limited in some of the experiments we'd like to do."*	*"Pacific biosciences will be useful for our specific studies of somatic cancer mutations in that it employs single molecules."* *"Single molecule sequencing will be much faster, cheaper and more straightforward since no amplification and library production is needed."* *"Third-generation systems could make library preps unnecessary."*

Source: J.P. Morgan survey.

Important attributes in NGS

When asked to rate factors important for next generation sequencing purchases, respondents rated data accuracy as the most important, followed by overall cost and cost of reagents. Instrument footprint, installation and set-up time as well as sample volume required for library construction were rated the least important. Other important factors listed by respondents included: availability and delivery time, sequence modification detection (e.g., methylation) and cost per base.

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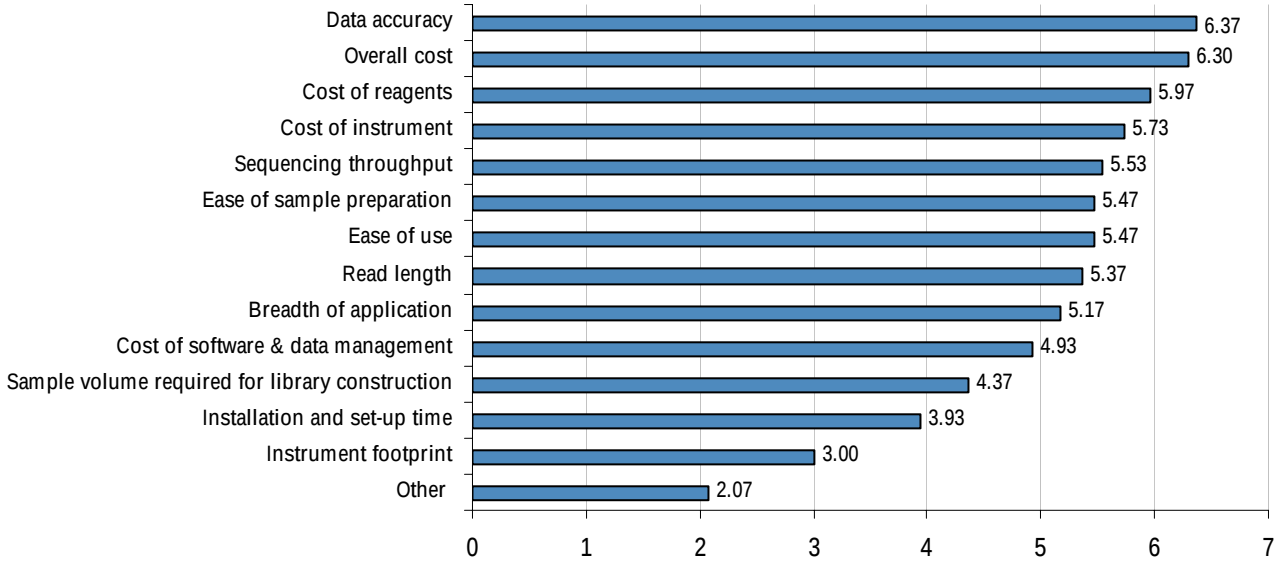
Figure 40: Importance of Factors in Choosing Next Generation Sequencing Platform (7=Extremely Important, 1=Not Important At All)

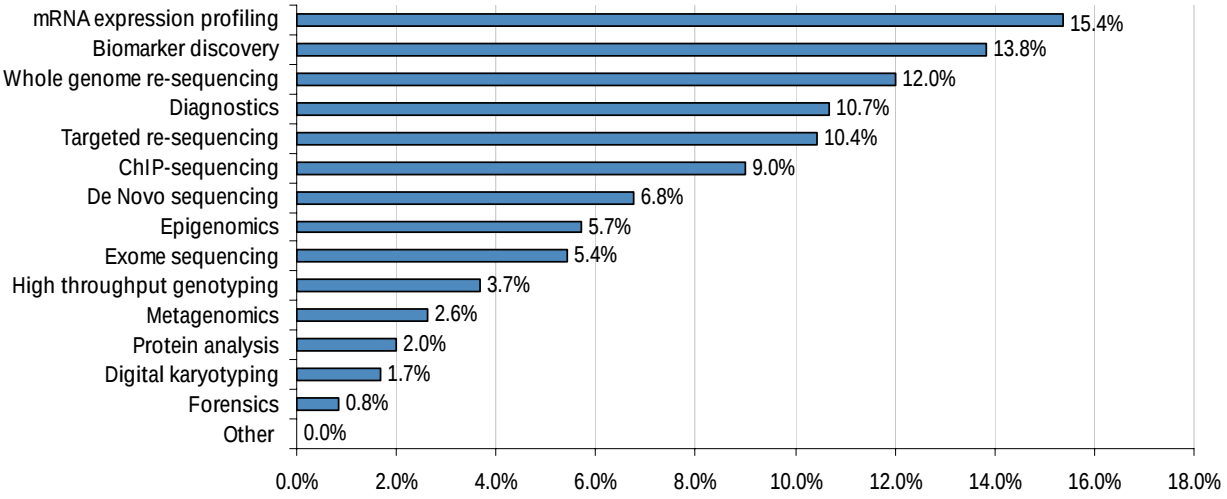


Source: J.P. Morgan survey.

Most frequently used applications for NGS

Among our respondents, mRNA expression profiling was the most frequently used application on next generation sequencing in the laboratory, followed by biomarker discovery and whole genome re-sequencing. Other applications representing high proportion of next generation sequencing usage included diagnostics and targeted resequencing. This compares with the top five applications in our 2009 Next Generation Sequencing Survey of de novo sequencing, mRNA expression profiling, ChIP-sequencing, targeted re-sequencing, and biomarker discovery.

Figure 41: Percent of Application Representing Next Generation Sequencing in the Laboratory over the Next 2 Years



Source: J.P. Morgan survey.

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Table 10: Sample Responses Elaborating on "Other" Applications

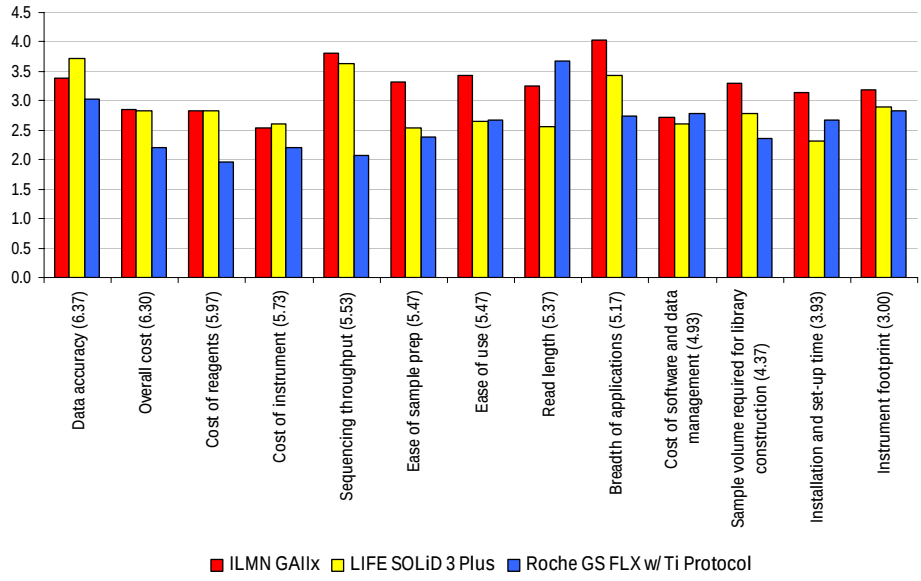
"All of this depends on cost. If the cost of WGS falls low enough, then exome sequencing applications are moot."
"We are a cancer genomics group looking at 1. mutational targets within areas of recurrent del/UPD and 2. polycomb study identifying target promoters - this reflects on our specialised requirements."
"Epigenomics means bisulfite sequencing of targeted regions in several samples (human and animal samples) using tagged primers (bar coded). As alluded to above, the machine is used by several laboratories at the institute, my laboratory does not use the machine(s) to full capacity. Other uses at the institute include biomarker discovery, targeted re-sequencing, exome sequencing."
"Right now, we are principally doing RNA sequencing. We are looking to get into epigenomics. We anticipate exome-sequencing being important for the next two or three years, and then moving to whole genome resequencing."

Source: J.P. Morgan survey.

Side-by-side comparisons of next generation sequencing platforms

We asked respondents to rate Illumina's GAIIx, Life Technologies' SOLiD 3 Plus and Roche's GS FLX with Titanium Protocol on a scale of 1 to 5, with 5 being excellent and 1 being poor, against important metrics for next generation sequencing purchasing decisions. Overall, Illumina's GAIIx received the highest average rating (3.21), followed by Life Technologies' SOLiD 3 Plus (2.88) and Roche's GS FLX with Titanium Protocol. Notably, for the most important metric, data accuracy, SOLiD 3 Plus came out on top, as well as for the fourth most important metric, cost of instrument, while GAIIx came in ahead for overall cost (2nd most important metric), sequencing throughput (fifth most important), ease of sample prep (sixth most important), and ease of use (7th most important). GAIIx and SOLiD 3 Plus tied for first with respect to cost of reagents (third most important). The following chart shows ratings for each system against the important purchasing decision metrics (number in parenthesis represents importance rating on a scale of 1 to 7, with 7 representing extremely important and 1 not at all important.

Figure 42: Comparison of GAIIx vs. SOLiD 3 Plus vs. GS FLX w/ Ti Protocol



Source: J.P. Morgan survey.

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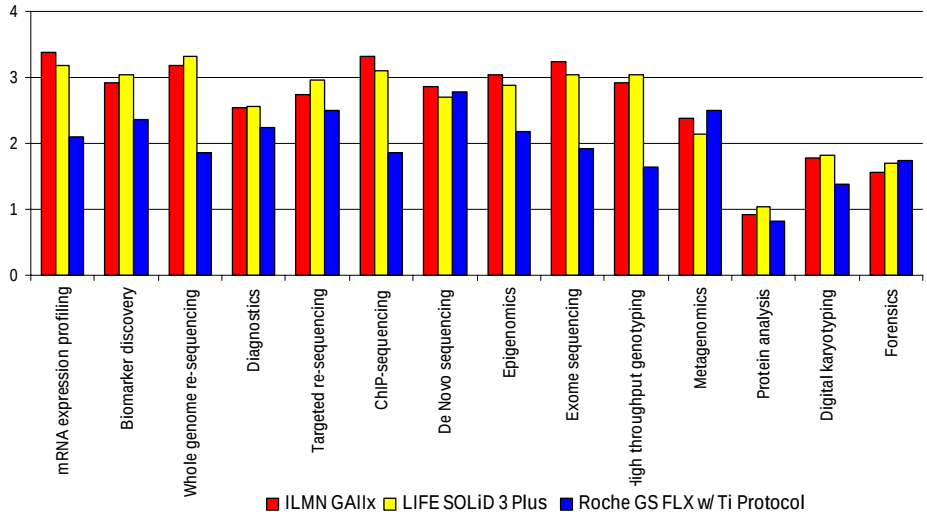
For the most frequently used next generation sequencing applications, GAIIx received the highest rating for the most frequently used application, mRNA expression profiling (~15% of NGS usage), while SOLiD 3 Plus was rated ahead of GAIIx for biomarker discovery (~14% of NGS usage), whole genome resequencing (~12% of NGS usage), diagnostics (~11% of NGS usage), and targeted re-sequencing (~10% of NGS usage).

Figure 43: Comparison of GAIIx vs. SOLiD 3 Plus vs. GS FLX w/ Ti Protocol



Source: J.P. Morgan survey.

We also asked respondents to rate Illumina's HiSeq 2000 and Life Technologies' SOLiD 4 and SOLiD 4*hq*, recognizing that these systems are still in early stages of commercialization or expected to be launched later this year, and as best summarized by one respondent.

"These are pure guesses. Most are just coming on line and no-one outside the company knows about the 4hq. Many answers are projected based on current info."

Not surprisingly, respondents were least familiar with SOLiD 4*hq*, reflected in the lowest average overall rating (2.08 out of 5), while HiSeq 2000, which started shipping in 1Q10, received the highest rating (3.19 out of 5). The following charts show ratings for HiSeq 2000, SOLiD 4 and SOLiD 4*hq* against important metrics for next generation sequencing purchases, as well as frequently used NGS applications.

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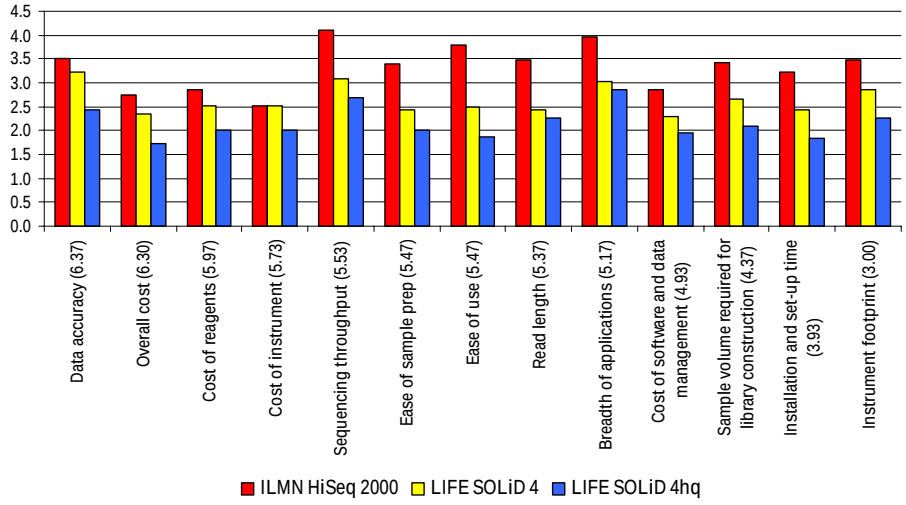
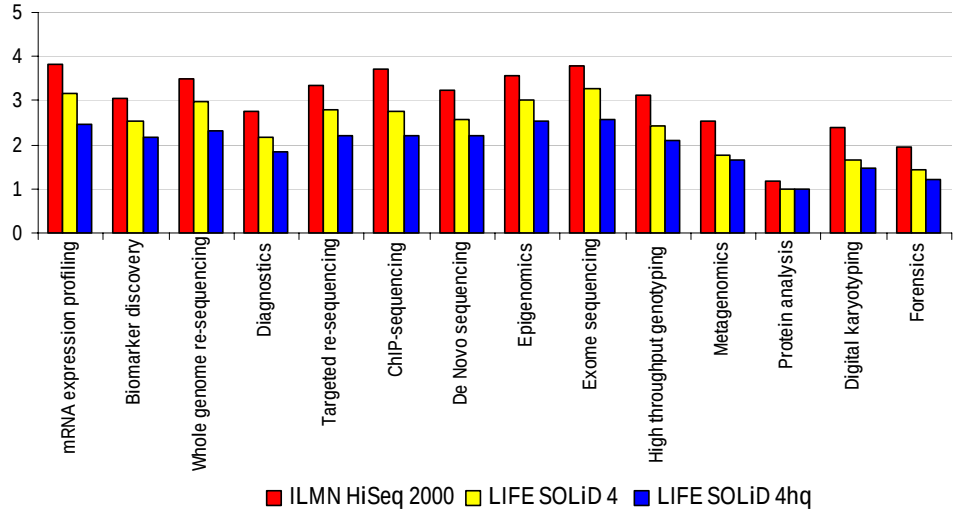
Figure 44: Comparison of HiSeq 2000 vs. SOLiD 4 vs. SOLiD 4*hq*



Source: J.P. Morgan survey.

Figure 45: Comparison of HiSeq 2000 vs. SOLiD 4 vs. SOLiD 4*hq*



Source: J.P. Morgan survey.

CE sequencing usage continues to decline.

Sanger sequencer usage continues to decline, with the respondents indicating Sanger sequencing usage comprising ~28% of all sequencing activity twelve months ago and ~21% today, whereas 12 months from now, Sanger sequencing is expected to represent ~16.5% of all sequencing activity and 24 months from now ~14.6% of sequencing activity.

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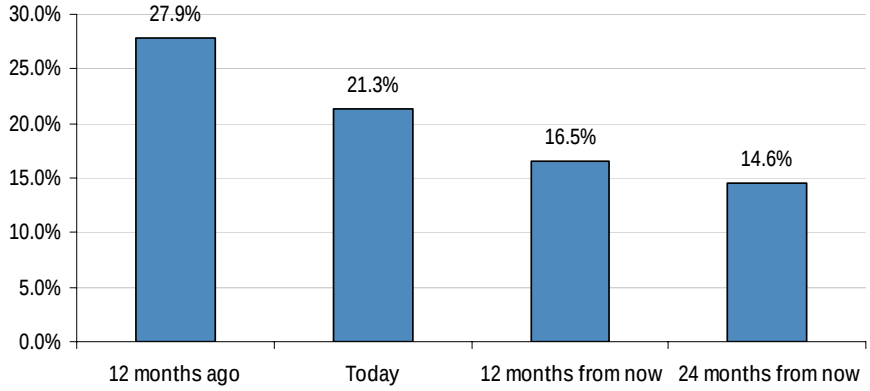
Figure 46: Sanger Usage



Source: J.P. Morgan survey.

Regarding technical problems by vendor, respondents had the following to say:

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Table 11: Technical Problems by Vendor

Illumina
"Not aware of any. We are routinely getting over 60 billion bases per flow cell on the GAIIx."
"Only technical problem aware of is on the GAII; the immersion oil sometimes spills out around the prism and causes imaging failures."
"We have had problems with the paired-end module reliability."
"Hard to get good libraries, must test extensively, long sequencing times (3-8 days or more)."
"Low accuracy at longer read lengths."
"I expect them to compare to their typical issues related to sample prep."
"The Illumina Solexa GA IIx that my department owns had multiple technical problems at start-up. However, these were mixed with some human errors due to the learning curve in running the instrument, so it is difficult to assign the cause. Essentially, some included bad flow through the instrument or cluster station due to blocked reagent lines, manifolds needed adjustments, etc."
"GAIIx sensitive to room temperature."
"We have had GAIIx-lanes out of focus. Also a crash with the cBot library construction."
"For the GAIIx, you still have to run a control lane, which takes 1 of 8 lanes away."
Roche
"Homopolymers are not sequenced as accurate as other sequences."
"The major hurdle is to improve sequence speed and length of runs in order to reduce costs per GB."
"Reagent quality and reproducibility."
"I do not like the indel problem inherent in the pyrosequencing chemistry."
"Low throughput."
"GS FLX has issues with library representation of rare clones."
Life Technologies
"The emulsion PCR is the largest technical problem. It is tedious, not automated, and the largest point of failure/data variability in the system."
"Data pipeline has been problematic. Buggy software. Poor reagent quality control."
"The sample preparation protocol has been relatively cumbersome compared to Illumina. Overall it is more complex than Illumina and thus needs more training to get used to workflow."
"Main problem is need for a template to do anything."
"Library quantitation prior to deposition."
"I am only aware of occasional reports of mapping problems/accuracy for methods producing short reads."
"Nothing special that could not be helped. Remote monitoring is very helpful."
"For SOLiD 3, need to have a reference genome is a problem. I understand that has been overcome."

Source: J.P. Morgan survey.

On recent improvements for sample preparation, while Roche's REM and Life Technologies' EZ Bead were perceived as improvements, laboratory directors

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continued to view Illumina's sample prep capabilities, particularly with the new cBot system, as being superior.

Table 12: Recent Improvements on Sample Prep Capabilities

Roche REM e System
"An improvement, but not as simple as the ILMN cBOT."
"The REM system is a very solid system and performs well compared to the other systems, however the workflow is somewhat different due to the difference from the Illumina type sequencer compared to the FLX."
"This new platform makes it more comparable to workflow on other systems."
"Less reproducible, more sensitive to failures."
"Sample prep is simplified and enhanced with this new sample prep platform."
"We've actually been looking at other systems for sample preparation. We like the Fluidigm system."
Life Technologies EZ Bead System
"Much more complicated and error-prone than the Illumina cluster station/cBot."
"Not as easy to use as the ILMN cBOT."
"The EZ Bead System is a significant improvement and will help to streamline the SOLID sample prep."
"It should improve things, but sample prep will still be more challenging than for Illumina."
"Prefer Illumina or Roche for ease of use and sample, preparation, volume, time."
"We are avidly looking forward to the release of the EZ bead System as the emulsion PCR/bead enrichment steps and time-consuming and laborious."
"Library prep is the sticking/difficult point in use of the SOLiD. Should take much of that away."

Source: J.P. Morgan survey.

As for what laboratory directors expect to pay for a new next generation sequencing instrument or upgrade, respondents, on average, expect to pay the most for Illumina's HiSeq 2000, followed by Illumina's GAIIx and Life Technologies' SOLiD 4, although as we have noted in the past, visibility around pricing – in particular, on SOLiD – remains low.

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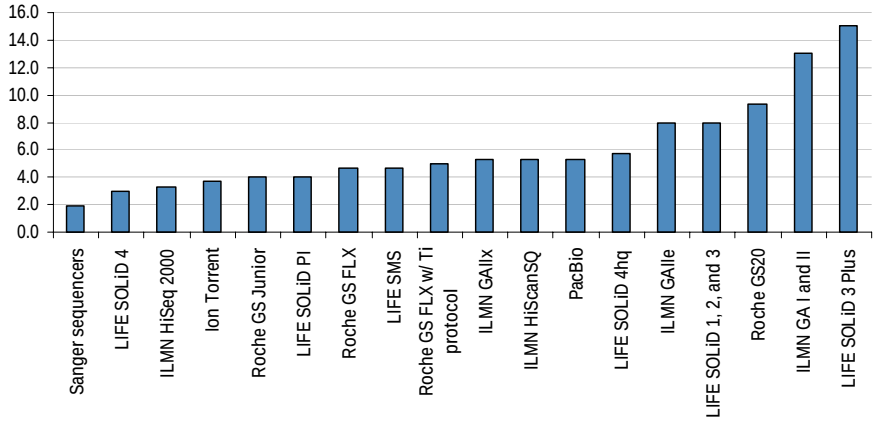
Table 13: NGS Platform Price – Expected to Pay

	Pay (in $USD) for the New Instrument	Pay (in $USD) for the Upgrade
Sanger sequencers	$44,333.33	$11,000.00
ILMN GA I and II	$20,000.00	$5,666.67
ILMN GAIIx	$110,016.67	$10,340.00
ILMN HiSeq 2000	$162,666.67	$13,000.00
ILMN HiScanSQ	$50,000.00	$1,333.33
Roche GS20	$11,666.67	$5,000.00
Roche GS FLX	$6,666.67	$1,666.67
Roche GS FLX w/ Ti protocol	$40,000.00	$3,000.00
Roche GS Junior	$10,000.00	$3,333.33
LIFE SOLiD 1, 2, and 3	$11,833.33	$4,500.00
LIFE SOLiD 3 Plus	$13,333.33	$1,833.33
LIFE SOLiD 4	$86,666.67	$5,466.67
LIFE SOLiD 4*hq*	$53,333.33	$3,833.33
LIFE SOLiD PI	$16,666.67	$0.00
LIFE SMS	$65,000.00	$1,666.67
PacBio	$89,166.67	$33,166.67
Ion Torrent	$18,333.33	$5,000.00

Source: J.P. Morgan survey.

On the length of time from installation to full utilization, aside from CE sequencers, lab directors, on average, expect the fastest installation and ramp-up for Life Technologies' SOLiD 4 and Illumina's HiSeq 2000 systems.

Figure 47: Length of Time from Installation to Full Utilization



Source: J.P. Morgan survey.

Generally speaking, respondents expect to run Illumina's systems in excess of 100 hours per week. Also notably, while Life Technologies' SOLiD 3 and earlier generations are or have been used ~40 hours per week, SOLiD 4 and SOLiD 4*hq* are expected to be used more than double that amount of time.

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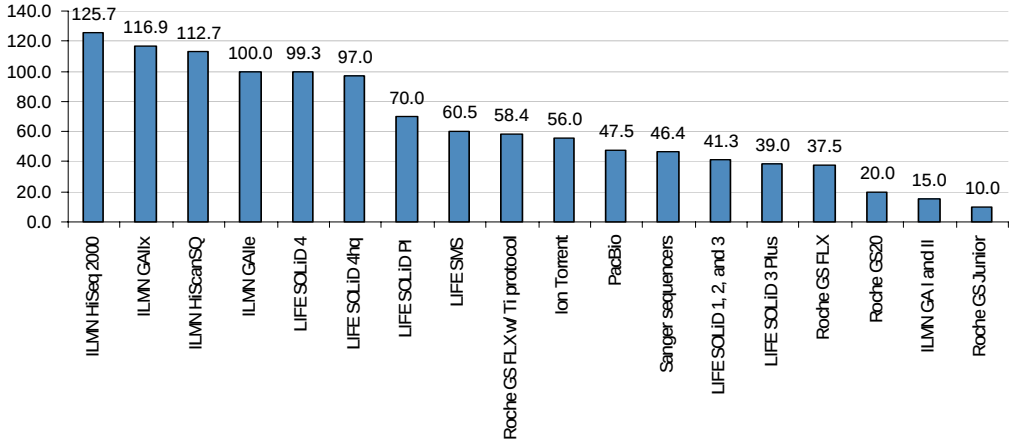
Figure 48: Number of Hours Respondents Anticipate Running the System per Week



Source: J.P. Morgan survey.

Table 14: Additional Thoughts on HiSeq 2000, SOLiD 4 and 4*hq*

"The HiSeq2000 increased throughput will be transformational for my lab and our research."
"HiSeq2000 is an amazing instrument right now and will be able to positively compete with Life Technologies, however it is significantly more expensive than SOLID4. SOLID4hq will potentially compete with Illumina if priced right."
"HiSeq 2000 is very promising given lower costs; same with SOLID 4 / 4hq; neither is a fundamental advance in the area of high-throughput sequencing."
"Too little is known about the 4hq at present to judge."

Source: J.P. Morgan survey.

Sequencing for diagnostics

Sequencing for diagnostics was perceived as a significant possibility pending improved accuracy and more affordable cost. Lab directors had the following comments:

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Table 15: "What are your thoughts on the broader use of sequencing for diagnostics? How do you envision the market evolving between CE sequencing and next generation sequencing for diagnostics?"

Appropriate platform / technology / applications	Cost
"For unknown disorders we are already sequencing clinical samples. Don't think it will be capillary at all. It will either be a cheap whole genome platform or a chip based genotyping method with millions of variants or complete sequencing of a set of disease related genes (but not using Sanger - it's too expensive)." *"Will be a role for capillary sequencing for single gene analysis for the foreseeable future (i.e., next 5 yrs)."* *"Next gen sequencing will enter diagnostics as soon as whole genome sequencing is affordable enough. It is likely that in the future everyone will have their genome sequenced."* *"Will eventually go to next gen approaches."* *"Exciting niche for capillary sequencing: samples are not readily available, small volumes makes capillary sequencing for biomarker important in clinical diagnostic."* *"There will be an initial slow progression from capillary with an exponential increase."* *"NGS will fit a different space in diagnostics than CE sequencing does. The throughput will allow people to perform sequencing of groups of genes in a disease-based or pathway-based fashion. There is also tremendous interest in how NGS can be used to detect genomic rearrangements. The chief challenges for NGS in the clinical lab will be simpler operation and linking to automation."* *"NGS will likely only be really viable when simultaneous multi-testing is needed. Single assays Sanger will be ahead for the foreseeable future."* *"As companies further develop bar-coding strategies, next-gen sequencing will become more and more affordable for rapid and high-volume diagnostics."* *"For diagnostics and resequencing in general, the third generation sequencing platforms have their niche."* *"I would expect about half to use next generation sequencing."* *"In my own field, oncology, I see a huge potential for sequencing for diagnostics. Tumor profiling for correct diagnosis, and also to identify personalized biomarkers for improved and personalized follow-up of the individual cancer patient. And many more applications."* *"I can envisage sequencing of a finite number of genes, typing of SNPs become part of a diagnostic platform and slowly supersede capillary tried and tested methods."* *"If annotation can be automated and instruments/assays are certified."* *"Definitely will increase in value especially for cancer screening."*	*"If costs will be brought down, it will blossom. Otherwise, it won't (and clinicians will disdain it)."* *"Demonstrations of accuracy, and cost per sample compatible with current industry standards, will be requisite for widespread adoption of NGS. Capillary will never have a large share because of its relatively high cost.."* *"When the genome is less than $1000, every cancer patient will have their somatic and gerrmline genomes sequenced."* *"As costs come down, sample prep becomes easier and more robust and analysis software is simplified, then this will undoubtedly switch to next generation sequencing. However costs would have to drop by at least 2 magnitudes."*
	Accuracy / ease of use
	"For clinical diagnostics, sample preparation and throughput must be vastly increased. Costs must come down as well. I still think we are 5-10 years away from this." *"Broader need for sequencing in cancer detection and classification."* *"I think sample preparation is a big hurdle for next generation sequencing for diagnostics. As the number of clinically useful markers increases over the coming years, next generation sequencing would quickly become more cost-effective and more efficient."*
	Potential timing comments
	"It all switches to NGS over the next 5 years." *"Will continue to grow by 10 - 15%/year."* *"Not in common clinical use for at least the next 3-5 years."* *"The first clinicians base their decision on how to proceed with a treatment or surgery on sequencing results. With more and more GWAS results finding their way into application, sequencing will play a greater role in diagnostics. My estimate, though, is that this process will take 5-10 years, rather than 1-3. My estimate for wider use of NGS in diagnostics) thus is also 5-10 years."*

Source: J.P. Morgan survey.

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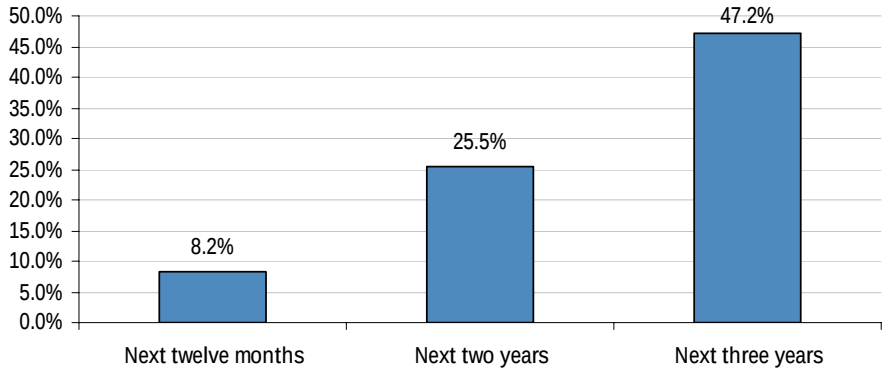
Third Generation and Other Emerging Technologies

Approximately ¼ of all NGS predicted to be replaced by third generation in the next two years.

Respondents projected roughly a quarter of all next generation sequencing could be replaced by third generation sequencing in the next two years, and near 50% of all next generation sequencing activity could be replaced by third generation sequencing in the next three years.

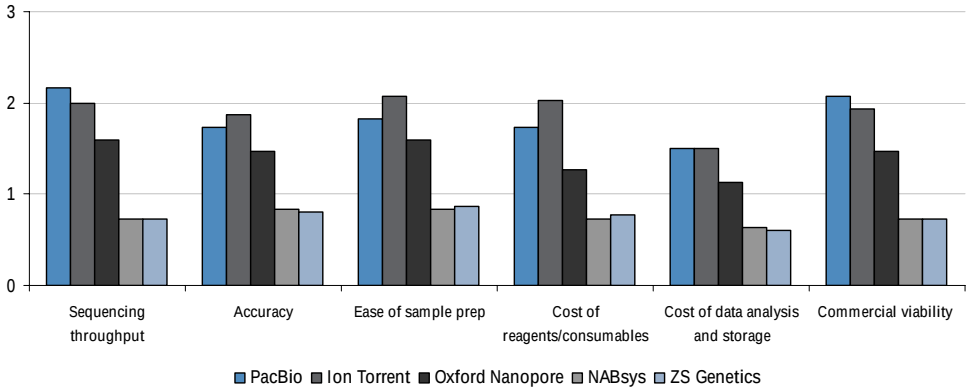
Figure 49: Percent NGS Activity That Could Be Replaced by Third Generation Sequencing



Source: J.P. Morgan survey.

We asked lab directors to rate third generation sequencing platforms based on their expectations for sequencing throughput, accuracy, ease of sample prep, cost of reagents/consumables, cost of data analysis and storage, and commercial viability. Not surprisingly, lab directors were largely unfamiliar with the specifics of third generation sequencing platforms, as reflected in the low ratings given for the aforementioned metrics.

Figure 50: Third Generation Sequencing Ratings (Scale of 1-5; 1=poor; 5=excellent)



Source: J.P. Morgan survey.

Perception on Illumina's Avantome

Six (20%) of respondents were familiar with Avantome, Illumina's longer read-length platform under development. Cost and throughput were considered some of the advantages or disadvantages of the Avantome system. Specific comments include:

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Table 16: Advantages/Disadvantages of Avanome vs. CE systems or Other NGS Platforms

"Main advantages could be cost and throughput. Disadvantages will be that it's not tested whereas Sanger is the gold standard for sequencing."
"In principle Avantome is similar to the Roche FLX, pyrosequencing. However it will have greater read length and more GB per run than FLX. It will thus fit a niche for competing with FLX. However, it is unlikely to compete with HiSeq 2000, SOLiD or third generation."
"Avantome - intermediate-length reads but if in high-throughput format, can combine long reads with throughput which is an advantage; currently system is in very early stages, however."
"The cost should be lower while maintaining the long run and accuracy."

Source: J.P. Morgan survey.

Perception on Complete Genomics

On Complete Genomics, and whether they would consider using the large-scale human resequencing service within the next two years, respondents mostly said that the service does not fit in with their needs (i.e., large-scale whole human genome resequencing). Sample comments include:

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Table 17: Interest in Complete Genomics

Does not fit the need	Depends
"I do not think it will be necessary for our activities." *"Not compatible with a diagnostics business at this time."* *"No, our uses need to be customized. Wonder what their customer service will be like."* *"No, because we do pathogen metagenomics, not human resequencing."* *"We need to have the capacity in house, and therefore will not use Complete Genomcis."* *"Not within the next two years, due to cost and other systems available for utilization."* *"Possibility but prefer to have instruments on site."* *"No. We don't do human genome sequencing. We're sequencing infectious disease agents (bacterial and viruses)."* *"No. There is not a market for that yet."* *"The service is good for institutions who do not want to make a large capital investment. But, for those of us who have, then it is not a great value."* *"Probably not since we have our own machines."* *"No - well it depends on cost - I envisage everything we do to be exome of capture exons."* *"Currently, the costs are too high for an academic setting (we would have to sequence hundreds, if not thousands of individuals), and our bioinformatic side is not yet set up for this."*	*"It depends on costs. If Complete Genomics is competitive with pricing and equal quality, we may use them."* *"The answer depends on cost and quality of the data."* *"In certain cases where there is a relational protein synergy. Particularly when the various expressed (over and/or under) cannot be readily attributed to a specific gene sequence and a complete genome is necessary to avail in narrowing the scope and source."* *"We would direct clients to Complete Genomics if they were interested strictly in whole human genome sequencing and were not pressed for time. However, there are many other applications which would not require whole genome data."* *"Depends on development of cost and funding."* *"We will consider if our system's capacity is not enough for our demand."*
Interested	**Service / quality issue**
"Probably. Human WGS is the single biggest market, and they have an approach that is great at doing one thing over and over again." *"Will be used in large scale as mass screening of population increase."* *"We could outsource specific projects where the experience is not available in house."* *"Yes for whole genome might be an economical possibility, not for whole exome, transcriptome or targeted resequencing."* *"Yes, a service model would be attractive. They are here today speaking."*	*"We tried early access and got tired of waiting so cancelled the work. So probably not. We like being able to assess the data quality for the runs and really learn what the technology is doing. Think you lose that a bit if you outsource the work."*

Source: J.P. Morgan survey.

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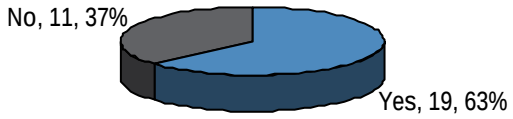
Microarray Usage

Nineteen of the 30 respondents are microarray users.

Nineteen of the thirty respondents currently own or expect to own microarray instruments over the next three years.

Figure 51: "Do you currently own, or expect to own over the next 3 years any microarray instruments?"

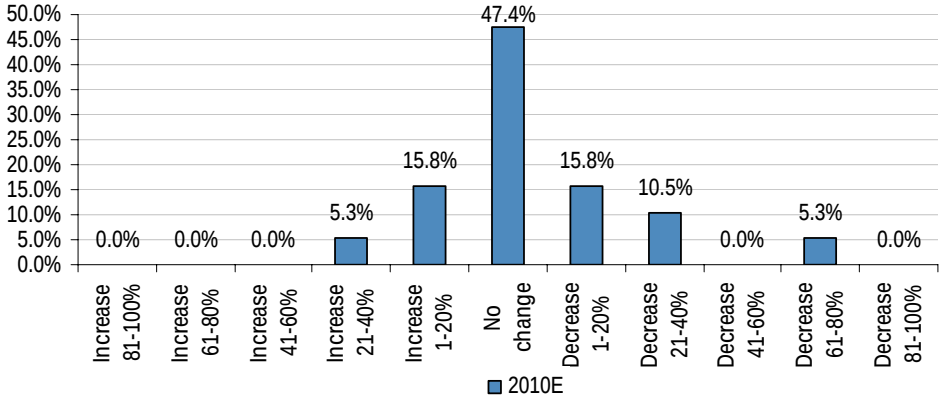


Source: J.P. Morgan survey.

Impact of NGS on microarray usage.

For 2010, most lab directors (9 of 19) do not anticipate next generation sequencing impacting y/y change in microarray usage, with the remaining respondents slightly biased toward decreased microarray usage as a result of the NGS impact.

Figure 52: Impact of NGS Sequencing on Microarray Usage in 2010E



Source: J.P. Morgan survey.

Notably, for 2011 and 2012, responses were more or less evenly balanced between those who expected to increase or decrease microarray usage as a result of next generation sequencing.

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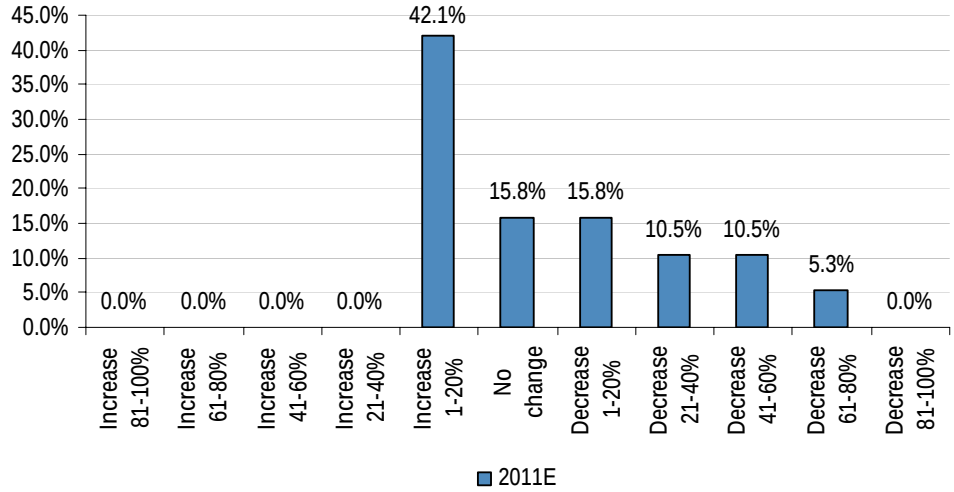
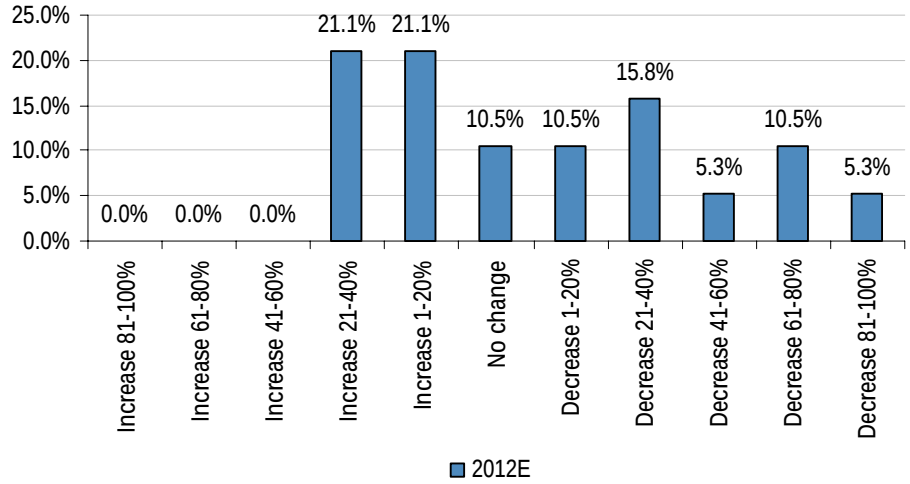
Figure 53: Impact of NGS Sequencing on Microarray Usage in 2011E



Source: J.P. Morgan survey.

Figure 54: Impact of NGS Sequencing on Microarray Usage in 2012E



Source: J.P. Morgan survey.

Respondents, on average, projected ~15.5% of current microarray usage could be replaced by sequencing in the next year, and ~33% of current microarray usage could be switched to sequencing in the next two years.

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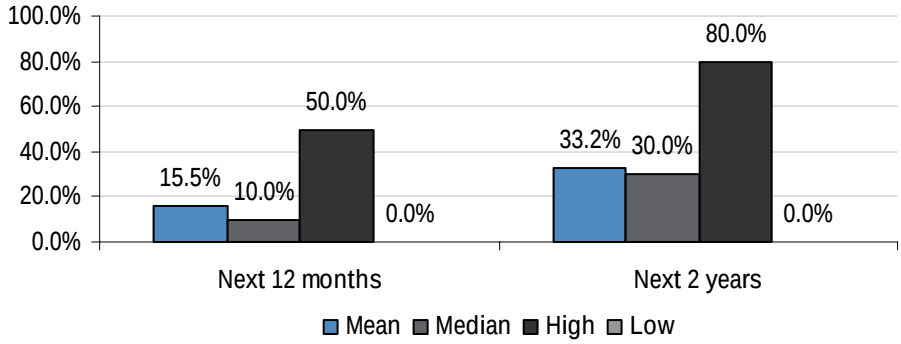
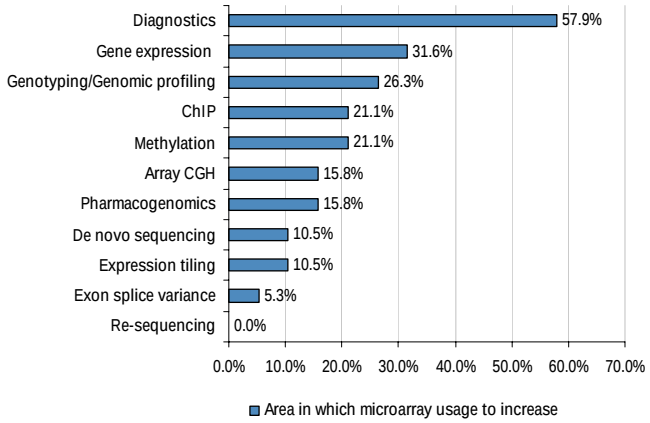
Figure 55: Percent of Microarray Usage That Could Be Replaced by Wequencing in the Next 12 Months and 2 Years



Source: J.P. Morgan survey.

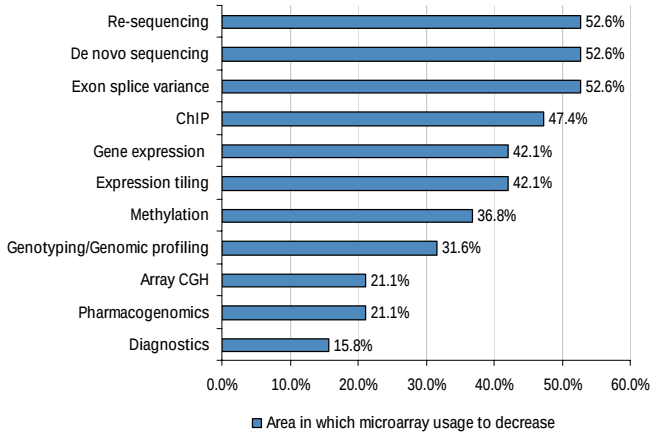
As for application areas in which microarray usage is expected to increase, the most popular response was diagnostics (58% of respondents), followed by gene expression (32%) and genotyping (26%), while application areas in which microarray usage is expected to decline were re-sequencing, de novo sequencing, and exon splice variance analysis (53% of respondents each).

Figure 56: Areas in Which Microarray Usage to Increase



Source: J.P. Morgan survey.

Figure 57: Areas in Which Microarray Usage to Decrease



Source: J.P. Morgan survey.

For areas in which microarray usage is not expected to change, the most frequently cited applications were array CGH and pharmacogenomics.

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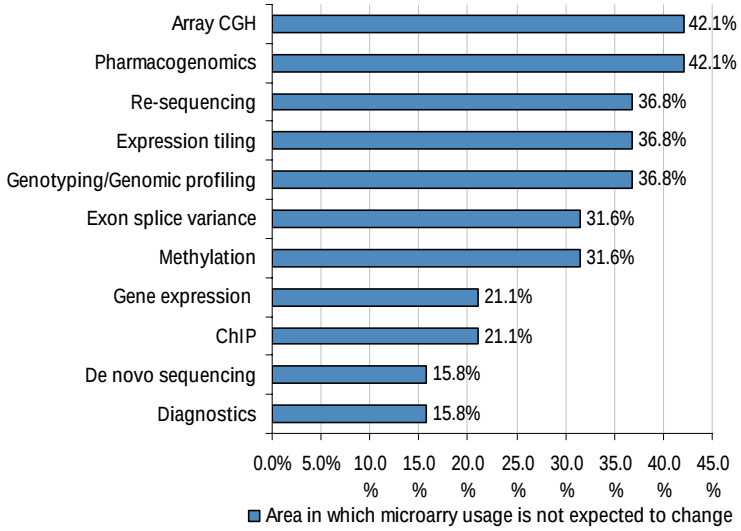
Figure 58: Areas in Which Microarray Is Not Expected to Change



Source: J.P. Morgan survey.

On the top three microarray applications being replaced the fastest by next generation sequencing or other alternative technologies, gene expression was the most frequently cited (9 respondents), followed by ChIP (8 respondents) and genotyping (7 respondents).

Table 18: Top Three Applications for Microarray Technology Being Replaced the Fastest

Application	# cited
gene expression	9
chip based expression assay	8
genotyping	7
methylation/epigenomics	5
resequencing	3
diagnostics	3
de novo sequencing	2
forensics	2
GWAS	2
not sure if replaced at all	1
metagenomics	1
chromatin regulation	1
chromosome analysis	1

Source: J.P. Morgan survey.

Comparison of microarray vendors

By vendor, ~38% of respondents using microarray systems used Affymetrix platform, followed by 34% that used Illumina platforms, and 17% that used Agilent platform. Other microarray platform used included custom arrays (two responses).

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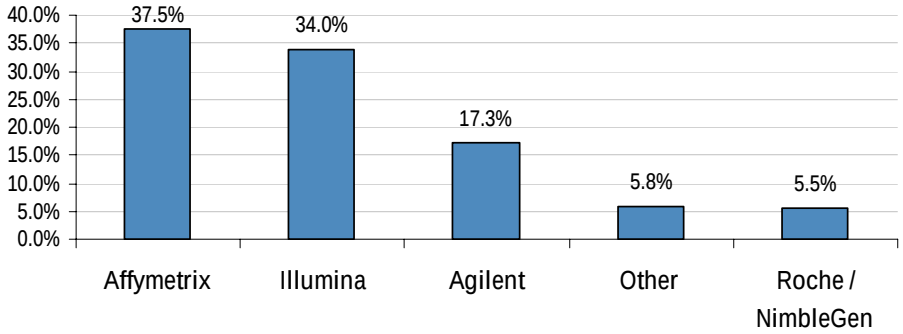
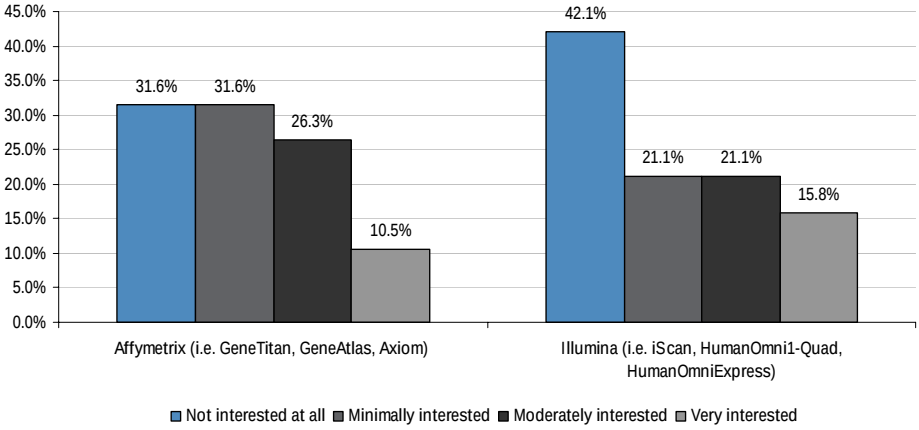
Figure 59: Microarray Vendor Currently Used



Source: J.P. Morgan survey.

Interest for Affymetrix versus Illumina microarray platforms were similar, with approximately 37% of nineteen lab directors moderately or very interested in acquiring either an Affymetrix or Illumina platform.

Figure 60: AFFX vs. ILMN



Source: J.P. Morgan survey.

Interest in Affymetrix's GeneTitan, GeneAtlas and Axiom

On the new platforms from Affymetrix, GeneTitan and GeneAtlas, as well as the new array technology, Axiom, with eight of the nineteen microarray owners not familiar with the products, others provided the following specific comments for the Affymetrix platforms compared to Illumina platforms:

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Table 19: Affymetrix's GeneTitan, GeneAtlas, and Axiom vs. Illumina's Platforms

"The Gene Titan platform works very well and enables high throughput on a 96 well platform which is compatible with all robotics systems. Axiom is interesting for high throughput and low cost per sample, but has much less content than what Illumina plans for their SNP arrays. Illumina has a larger share of the genotyping market, but is more expensive than Affymetrix."
"They appear to be a little better -- larger capacity."
"GeneTitan and Atlas are for super high throughput. We don't need."
"They are comparable, ease of use for Illumina is an advantage."
"Better accuracy and easier to use."
"Affymetrix's new systems provide some advantages for price and workflow over their classic cartridge-based systems and may make larger projects easier to achieve. However, investigators who have been using Illumina are unlikely to switch based on these new platforms."
"Higher throughput than Illumina. Fewer SNPs. Cheaper. Real advantage of new Affy is in targeted genotyping Illumina still has cost leadership, but Affy has better data concordance."
"These new systems are only incrementally better than existing platforms and do not compare with unbiased next-generation sequencing platforms."

Source: J.P. Morgan survey.

On whether the level of customization on Axiom (Affymetrix) is useful, of the nineteen microarray owners, six were not familiar (or did not have any comments), while five stated that it would be somewhat to very useful, and seven did not think it was useful. Sample responses include:

Table 20: Whether the Level of Customization Available on Axiom (AFFX) Is Useful for Microarray Applications Needs and Increases Interest in Purchasing AFFX Products over Other Brands

Useful	Other
"Customization is useful, but has no impact on accuracy and reliability of data." *"Yes. As stated above we see the chief advantage of the system being high SNP targeting of specific regions."* *"Yes is very useful and it does increase my interest in Affymetrix over other products."* *"Moderately useful."* *"Customization definitely increases our interest, currently this does not lead to entertain the idea of purchasing an Affymetrix platform, but rather to use these microarrays on platforms of collaboration partners."*	*"I have been sticking with Agilent, Illumina, and Nimblegen."* *"Good technology from Affy. We have invested 2 years ago in Illumina, we need to identify a clear superior system to justify an investment."* *"We find that Agilent has a nice model for custom arrays, and we will likely continue to use Affymetrix and Illumina for their non-custom arrays."*
Not useful	**Not sure**
"No, doesn't help us." *"Not that useful for us."* *"Not really."*	*"We currently do not have many projects that want to customize, but it will depend on what the investigators demand."*

Source: J.P. Morgan survey.

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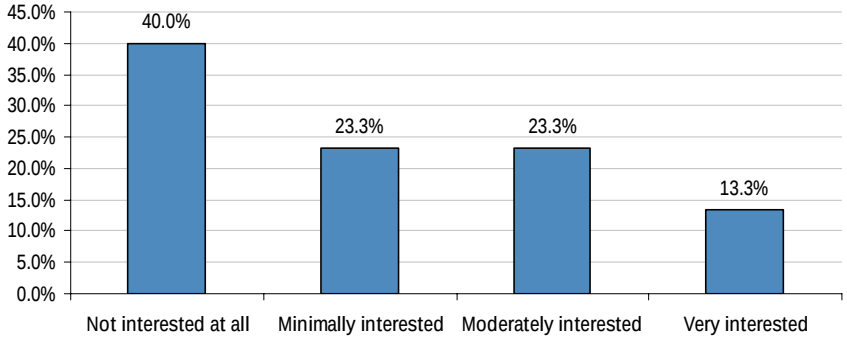
Interest in Illumina's 2.5mm and 5.0mm variant chips.

Of the nineteen microarray owners, eight respondents currently used Illumina's HumanOmni1-Quad or HumanOmniExpress BeadChips. Three of the respondents indicated they were likely to upgrade to 2.5mm and/or 5.0mm variant chips, while two expected to wait until there is demand or when there is further information available, while the remaining three did not plan on upgrading.

Interest in HiScanSQ

With regard to the Illumina integrated next-generation sequencing and array-based system, over 60% of the respondents (nineteen) indicated they were minimally interested or not interested at all in acquiring the platform.

Figure 61: Interest in Purchasing Illumina's HiScanSQ



Source: J.P. Morgan survey.

In addition to the lack of familiarity with the platform, some of the comments from those not interested in purchasing HiScanSQ were:

Table 21: On Why Some Respondents Are Not Interested in HiScanSQ (Illumina)

"We are sequencing human whole genomes so don't have use for the lower throughput."
"Might be OK for small groups who already have an iScan."
"I have a workable platform in the form of SOLiD; I see no need to jump ship and outlay costs for new equipment plus time lost to training and adjusting work flow. In other words, there is considerable inertia toward changing platforms, unless there is a decisive advantage."
"If you have already an Illumina platform and want to include sequencing without major throughput it is OK."
"Not interested since I do not see much benefit in integration here."
"Mixed platform, not interesting to us. Need dedicated platforms."
"We have both iScan and GA's, HiSeq on order. We don't need it."
"I think most researchers are simply moving towards cDNA sequencing with next-gen approaches and giving up on microarrays for the most part."
"Not clear what it brings in addition to many other available tools."
"We would expect most of our NGS to continue on SOLiDs, but this might be a nice combination of microarray and Illumina NGS for us."
"Most sequencing projects I am interested in the near future do not require full-time use of a next generation sequencer for long periods of time."

Source: J.P. Morgan survey.

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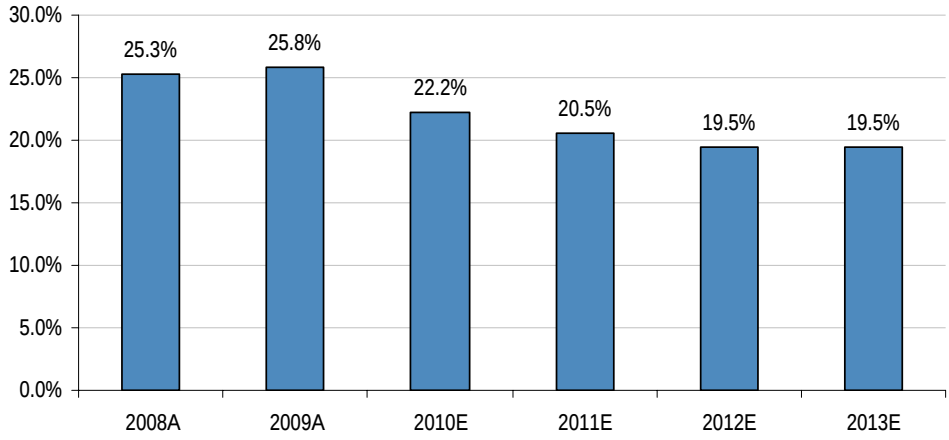
"GWAS-Chip" expected to decline steadily going forward.

As for genome wide association studies using microarrays, expectations are for a steady decline in activity from ~26% of total microarray usage in 2009 to 22% in 2010, ~21% in 2011, and ~20% thereafter.

Figure 62: Percent of Total Microarray Usage for GWAS



Source: J.P. Morgan survey.

While five respondents did not have additional thoughts on microarray-based GWAS trends, the rest of the lab directors largely believe microarray-based GWAS will be replaced by sequencing in the near future given various limitations.

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Table 22: View of Past, Current or Future Trends in GWAS (i.e. relevance for research applications using microarrays, etc.)

New platforms / technology for GWAS	GWAS-Seq limitations
"GWAS will continue, but be slowly displaced by NGS as costs continue to drop. Clearly full-genome data is better for identifying causative alleles, but cost remains prohibitive." *"Third generation sequencers is the new trend in research."* *"Switching from microarray platforms to next gen sequencing."* *"Numerous GWAS studies have been moderately successful at best. GWAS will be replaced by sequencing and resequencing."* *"GWAS studies will be revolutionized by NGS."* *"We are using Illumina GAIIx for GWAS studies, and I anticipate that this platform will dominate the field for several years to come."* *"GWAS were started with great expectations; will need the combination of novel statistical and systems biology (e.g. pathway analyses) approaches to produce more of meaningful information. This probably will result in diagnostic applications. I also believe that array-based methods will be gradually substituted by NGS (second and third), although pricing may be an issue."* *"Replaced by resequencing."*	*"GWAS detected common variation, but much of the action in human genetics/disease will be with rare variation (below say 3% minor allele freq). Need to sequence to get much below this."* *"Until there is a better way of dealing with rare variants, GWAS is not going to be viable."* *"Has limited potential in lead discovery and might be more valuable for diagnostics development."* *"The current trend is for a lot of resequencing. The industry will benefit from this effort in the short term. However, I think it is unlikely that this will lead to the easily interpreted results researchers are looking for. I think the real future will be in broad diagnostics that come from these GWAS studies as they identify many variants with some effect in limited population pools."* *"It is slowly gaining acceptance. It is limited because few grants can cover the costs of the research using this application."* *"My personal view is that the RR is very low for most of the variants detected and so the cost/benefit is unclear. That said, at least we know that the contribution of most variants is fairly low. Grant Committees are seeing these types of studies as being more speculative and hence the amount of funding for these fishing expeditions is likely to reduce."* *"GWAS is in trouble. I suppose you could say the glass is 3% full."*
Comments on timing	**GWAS-Seq demand near term**
"GWAS-Seq replaces GWAS-Chip over the next 3-4 years." *"GWAS has a shelf life that is fast approaching expiration. There are only so many diseases and populations that can be studied, and many have already been performed."* *"It will decrease significantly over time."* *"GWAS will largely be done by sequencing in the next 3-5 years, in my opinion."* *"Trend appears to be declining."* *"Decreasing at the moment relative to such things as NGS."*	*"We had a lot of GWAS business that somewhat slowed due to next gen sequencing data being released and will probably slowly ramp up again with new releases."* *"This is the niche for microarray as scientist will be looking for disease causes and association. Gene expression profiling has been completed and wealth of info exists in the literature."* *"There are a number of GWAS studies which will continue based on the built-in inertia of the planning and execution of such projects. However, as NGS costs drop, investigators will be seriously considering whether they will want to initiate new GWAS projects with microarrays."* *"Funding for GWAS is decreasing. However a number of studies I know are just now completing their GWAS, making it seem as if it is still popular. Also, several studies (2 I am involved with) are using the chops designed for GWAS to type thousands of markers in specific chromosomal regions because it is more cost effective per sample to type a GWAS-designed chip than to purchase custom chips."*

Source: J.P. Morgan survey.

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Appendix 1: NGS and Microarray Markets

Table 23: NGS Sequencing Market

Next Generation Sequencing Sales	2007E	2008E	2009E	2010E	2011E	2012E
Roche/454	$85.0	$150.0	$150.0	$157.5	$165.4	$173.6
		76.5%	*0.0%*	*5.0%*	*5.0%*	*5.0%*
Illumina/Solexa	$64.9	$166.3	$287.4	$380.3	$484.8	$581.7
		156.2%	*72.8%*	*32.3%*	*27.5%*	*20.0%*
Life Technologies	$0.0	$68.0	$100.0	$136.9	$178.0	$222.5
			47.0%	*37.0%*	*30.0%*	*25.0%*
Helicos	$0.0	$0.0	$2.3	$3.5	$4.4	$5.2
				50%	*25%*	*20%*
Market Total	$149.9	$384.4	$539.7	$678.3	$832.5	$983.1
Market growth rate (y/y)		*156.4%*	*40.4%*	*25.7%*	*22.7%*	*18.1%*

Next Gen Sequencing Mkt Share	2007E	2008E	2009E	2010E	2011E	2012E
Roche/454	56.7%	39.0%	27.8%	23.2%	19.9%	17.7%
Illumina/Solexa	43.3%	43.3%	53.3%	56.1%	58.2%	59.2%
Life Technologies	0.0%	17.7%	18.5%	20.2%	21.4%	22.6%
Helicos	0.0%	0.0%	0.4%	0.5%	0.5%	0.5%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Source: J.P. Morgan estimates, Company reports.

Table 24: Microarray Market

Microarray Sales	2007E	2008E	2009E	2010E	2011E	2012E
AFFX products sales	$279.8	$270.4	$279.2	$303.5	$324.8	$347.5
Growth y/y		*-3.4%*	*3.3%*	*8.7%*	*7.0%*	*7.0%*
ILMN BeadArray sales	$254.7	$346.2	$301.3	$318.9	$360.6	$396.7
Growth y/y		*35.9%*	*-13.0%*	*5.8%*	*13.1%*	*10.0%*
Agilent microarray sales	$80.0	$88.8	$88.8	$95.0	$101.7	$108.8
Growth y/y		*11.0%*	*0.0%*	*7.0%*	*7.0%*	*7.0%*
Roche/NimbleGen Microarray sales	$8.8	$25.5	$36.7	$49.6	$59.5	$68.4
Growth y/y		*190.6%*	*44.0%*	*35.0%*	*20.0%*	*15.0%*
Total	$623.3	$730.9	$706.0	$767.0	$846.5	$921.4
		17.3%	*-3.4%*	*8.6%*	*10.4%*	*8.8%*

Microarray Market Share	2007E	2008E	2009E	2010E	2011E	2012E
Affymetrix	44.9%	37.0%	39.5%	39.6%	38.4%	37.7%
Illumina	40.9%	47.4%	42.7%	41.6%	42.6%	43.1%
Agilent	12.8%	12.1%	12.6%	12.4%	12.0%	11.8%
Roche/NimbleGen	1.4%	3.5%	5.2%	6.5%	7.0%	7.4%
Total	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Source: J.P. Morgan estimates, Company reports.

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Appendix 2: NGS Background

Illumina

HiSeq

Although initial commercial shipments just began last quarter, early enthusiasm around the HiSeq 2000 Sequencing System ($690K list price) has been strong. As a reminder, the system is capable of generating two billion paired-end reads, with an initial spec of 200 Gb of data per run (7-8 days, 2x100 Gb) versus 50 Gb for GAIIx, and early access customers, such as The Broad, achieving >250 Gb per run.

Importantly, by increasing cluster density and read lengths, HiSeq has room for significant performance improvement (>500 Gb), and Illumina has already generated >300 Gb/run internally (1.5 billion clusters /run; >25 Gb/day).

As a reminder, HiSeq relies on the same underlying SBS chemistry as Genome Analyser, and the system features a state-of-the-art line scanner, dual-surface imaging, sub-10-minute total hands-on time to initiate a run, an easy-to-use interface (remote, iPhone-compatible monitoring), pre-configured reagents and the ability to sequence an entire human genome for <$10K (at launch specs), making the platform well-suited for sequencing entire genomes, transcriptomes (<$200 per trancriptome) and epigenomes, as well as for cancer and other complex disease research by large genome centers and core labs.

On annual consumable pull-through per system, HiSeq is expected to bring in $300K-$400K, or double that of GAII systems, given the dual (versus single) flow cells. Although the near-term impact on GAIIx (and potential cannibalization) remains unclear, what appears as healthy initial demand for HiSeq 2000 should position Illumina within the market, although the competitive dynamic should not be underestimated, as Life does appear to have become more aggressive on pricing (we believe for both reagents and instruments).

As a reminder, initial customers for HiSeq include the Beijing Genomic Institute (BGI), which previously announced a 128-system order that should be installed throughout 2010, as well as include the Broad Institute, which presented data on results from initial runs on HiSeq at AGBT (248 Gb/run with 0.48% error rate). The Broad currently has 94 GAII systems, generating >100,000 Gb per year, and we expect many of these systems will be upgraded to HiSeq over the coming year.

Longer term, by increasing cluster density, Illumina should be able to continue driving the performance specs on HiSeq to over 300 Gb in the coming months.

GAIIe, iScanSQ – not a significant focus for investors, but nonetheless important

As we noted coming out of AGBT earlier this year, Illumina has also introduced a “low-end” next-generation platform, GAIIe, with a list price of $250K for cap ex-sensitive customers looking for a low-cost, medium-throughput next-generation sequencing system. Importantly, GAIIe was designed with the same engineering and SBS chemistry as GAIIx (similar consumable pull-through), but with 200mm paired-end read capability initially and 20 Gb throughput per run, with headroom to reach

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40 Gb and 300mm paired-end reads, making it ideal for smaller core labs (vs. medium core labs and PIs in larger labs for GAIIx).

Additionally, rounding out the sequencing portfolio, Illumina also previously announced iScanSQ (formerly known as Harmonia), which is slated for launch this quarter. The system is capable of both sequencing and microarray processing, with an initial spec for sequencing of 20 Gb throughput and 200mm paired-end reads per run. Other new products include sample prep kits (2Q launch), which bring reduced hands-on time (75% of clean-up and 90% of gel steps eliminated), a 50% reduction in tubes with master-mixed reagents, parallel sample processing capabilities (96 samples at the same time, designed for 96 well plates).

Beyond sequencers, Illumina also continues to make progress on simplifying workflow and back-end requirements, most recently with the launch of cBot automation for clonal amplification of libraries (10/20) and IlluminaCompute (10/06). As a reminder, cBot eliminates user intervention and reduces up-front workflow (clonal amplification in <4 hours) and hands-on time (<10 minutes) for the Genome Analyzer. Combined with software updates released year that enable users to read more clusters per lane on a flow cell, Illumina continues to leverage system enhancements and workflow advantages to widen the gap with other next-generation platforms.

Oxford Nanopore and Avantome

Finally, Illumina continues to develop the longer read-length Avantome technology as well as a nanopore-based approach in collaboration with Oxford Nanopore Technologies. No recent details have been provided on either platform, but we continue to believe that Avantome, when launched, will prove highly competitive to the existing long read market (i.e., capillary and Roche/454).

Life Technologies

Although next generation sequencing is a relatively small portion of the Life Technologies portfolio (<5% of revenues), it remains an important component to the longer-term growth strategy for both research and clinical markets.

Looking closer at recent developments, SOLiD 4 marks an improvement from prior versions of the platform, with better chemistry and accuracy (>99.94%), lower error rates and an attractive cost structure ($6K per genome).

With an initial spec of up to 100Gb of mappable sequence data per run at $6K per genome (300K beads per panel versus 220K on SOLiD 3 Plus), SOLiD 4 uses improved sequencing chemistry and, as previously announced, is being made available as a one-day field upgrade for all SOLiD customers. The system currently relies on two base encoding, but LIFE will introduce reference free runs by year-end and five base encoding early next year, which should increase accuracy. Other enhancements include a decrease in bead size from the 1 micron beads previously used to 0.75 micron beads, which allows an increase in the numbers of beads per flow cell panel from 320K to 640K, thereby increasing throughput from 107 Gb (2 x 50 bp) to 214 Gb (2 x 50 bp) or 161 Gb and 322 Gb with 2 x 75 bp runs. A further reduction in beadsize to 0.5 microns would allow for >1000K beads and 501 Gb per run, while larger flow cells and five base encoding (2011) could get the system closer to 852 Gb. That said, although cluster densities will likely reach the diffraction limit

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of light within 1-2 years, this could prove a long-term disadvantage for LIFE, which scans on only one size of the flow cell (as opposed to Illumina, which scans on both).

As previously disclosed, in 2H10, LIFE will also introduce a SOLiD 4*hq* upgrade package in 4Q10, which increases capabilities to 300Gb/run (99.99% accuracy with five base encoding introduced next year) and $3,000/whole genome, getting closer to the accuracy and price point necessary for clinical applications, notably, coming in on par or below many established tests, such as Oncotype Dx ($,3800), Allomap ($2,900) and BRCA ($3,100). The move from four to five base encoding will entail six primers or two probe sets.

Regarding other products, feedback on workflow enhancements (i.e. EZ Bead Emulsifier, Amplifier and Enricher, which collectively reduced hands-on and turnaround time by up to 90%, with hands-on time now under 30 minutes) has generally been positive, and the new instruments ($46K) appear to address many, albeit not all, of the historical challenges around the emulsion PCR-based SOLiD platform, while feedback on the color spacing readout remains mixed.

SOLiD PI provides option for capex sensitive customers

Similar to GAIIe from Illumina, earlier this year, LIFE also introduced a “low-end” next generation platform, SOLiD PI, with a list price of $230K (versus $250K for the GAIIe) for cap ex-sensitive customers looking for a low-cost, medium-throughput next-generation sequencing system. Designed in partnership with Hitachi High-Technologies, SOLiD PI uses the same SBS chemistry as SOLiD 4, with initial spec of up to 50Gb mappable sequence data per 5-6 day run (up to 8 Gb per day), with 99.99% accuracy and a streamlined workflow. Initial demand for the PI appears largely from service labs, at which demand is more stochastic (i.e., do not want to wait to batch), and the system could help increase the competitive dynamic with core labs.

Starlight (single molecule) remains early

Prior to AGBT this year, LIFE had provided few details on the single molecule program, which is based on Visigen technology and incorporates Quantum Dots for continuous long read length (1,000-1,500 bp) sequencing, as well as dye chemistry from Molecular Probes.

LIFE plans to introduce initial systems via collaborations to early access customers in 4Q10, with broader commercialization plans to be announced later this year. Limited data has been provided on actual performance, although it was noted at AGBT that after five cycles, there was no loss in signal or gap in sequence, as the Qdot nanocrystals do not degrade.

In terms of the instrument, the bench-top system has no moving parts and relies on the use of highly-absorbent Qdot nanocrystals tethered to the DNA polymerase. After laser excitation, signals are measured in the 600-800nm range (630-800nm emission signal, 405nm excitation), with the dye then escaping out of the FRET zone.

Given that the polymerase is used as the sequencing engine, thousands of reactions can occur at one time under a microscope (a donor flourophor riding on back of the polymerase also equates to extra sequencing signal, thereby improving accuracy). The system monitors the real time incorporation of nucleotides into individual growing DNA strands, and as nucleotides are incorporated, they are energized by

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photons transferred from a Qdot nanocrystal, generating a colored flash of fluorescence light. The time and color series of light flashes are then used to determine the DNA sequence of each DNA strand. Real-time readout also means that the system is likely being targeted at applications in cancer diagnostics/patient management, RNA structure variation, viral analysis and methylation, while SOLiD will continue to be used for areas such as whole genome sequencing and expression profiling, longer-term.

While it is too early to say how LIFE will fare in the single molecule market longer term, in particular given the uncertainties around intellectual property (vis a vis Pacific Biosciences), near-term expectations also appear extremely low, with investor focus still largely on SOLiD and the remainder of the business, and we continue to exclude any contributions from Starlight in our estimates.

Pacific Biosciences

Earlier this year, Pacific Biosciences announced an early access program for the PacBio R5 sequencer ($695K ASP), including ten systems in North America to the Baylor College of Medicine, Broad Institute (MIT/Harvard), Cold Spring Harbor, U.S. Department of Energy Joint Genome Institute and Monsanto, among others.

2014 roadmap announced

Additionally, PacBio has also revealed that it is working on “version 2” SMRT technology, based on a newly integrated “detection core” developed in collaboration with partners from the semiconductor industry.

The new system enables higher scale multiplexing and marks a move away from the traditional optical-based detection platform, as the instrument will not have a camera, with the signal from each Optode cell assigned an individual smart pixel detector. This change should enable higher scale multiplexing, since the company can group several million Optode cells onto a single array, enabling ~100 Mb of sequence data/second. The change should also address a key bottleneck around signal detection, as no currently available technology was available to support the transfer of imaging data at that rate off a semiconductor chip.

Another key aspect of the new “detection core” is a structure underneath the illumination layer, which spatially separates the four distinct spectral frequencies associated with each nucleotide label (A, T, G or C).

Other performance enhancements going forward are also expected to be achieved by improving the enzymes (7x increase in throughput), ordered placement of ZMVs (emobilizing one and only one enzyme in a hole brings yield >90%) and higher density ZMV arrays (going from 80K to 160K doubles the throughput on a machine).

PacBio is targeting to launch V2 technology beginning in 2014, with a portfolio of two FDA approved systems. The system will be a high-throughput platform optimized for whole human sequence (several-fold coverage) in 15 minutes or less, while the low-throughput system will be a sub-$50K point-of-care instrument with the footprint of a “small copier.” PacBio plans to target the high-throughput platform to core labs and large genome centers, whereas the low-throughput instrument will be marketed to clinical labs and even physician offices for diagnostic applications. That said, given timing of the announcement, it remains unclear whether there will

be any impact on potential early customers, although it was noted by management that the company remains sold out through 2011.

Background

By way of background, since inception, Pacific Biosciences has pursued single molecule sequencing, with the goal of introducing a platform capable of enabling whole genome sequencing for routine medical care, which implies a cost per genome close to $1,000. Underlying the approach are the concepts that (1) long-reads are critical for broad genomic analysis (as opposed to a shorter-read, shotgun type approaches) and that (2) DNA polymerase strands themselves can be used to synthesize long strands of DNA, thereby eliminating PCR amplification (the system has low reagent use, 1K bases for $99) and lengthy cycle sequencing. Another key concept, as we see it, is that systems should offer flexibility – in other words, the ability to balance throughout versus read length, depending on the size and nature of an experiment (i.e. de novo sequencing requires longer read lengths and therefore, has lower throughput, while re-sequencing can be much quicker using short reads).

So how does it work? The SMRT system has no moving parts and relies on two core technologies: (1) a SMRT Cell, which contains 80K zero-mode waveguides (ZMWs) and enables observation of individual fluorophores (using a CCD camera) against a dense background of labeled nucleotides, and (2) phospholinked nucleotides, which produce a natural DNA strand through fast and accurate DNA synthesis.

Looking closer at the technology, the zero-mode waveguides – of which the initial instrument has 80K (the second generation instrument should have >1 million) – are tiny reaction chambers, tens of nanometers in diameter, fabricated on a 100nm metal film deposited on a silicon slide. Within each chamber, a single DNA polymerase molecule is attached to the bottom, while nucleotides labeled with a fluorophore are introduced. Upon incorporating a complementary nucleotide, the enzyme holds each nucleotide in the ZMW for milliseconds, during which the engaged fluorophore emits light corresponding to a particular base. Analogous to a microwave oven, in which wavelengths are larger than holes in the door, both excitation and detection occur in the ZMW without interruption. As part of the natural incorporation cycle, the polymerase then cleaves the bond, and continues incorporating bases.

For sample prep, the system will not require amplification, unless there is insufficient template material. Pacific Biosciences will also offer SMRTbell sample prep, which makes it possible to read both forward and reverse strands in one cycle, by turning the double-stranded linear DNA into a single-stranded circular template (shaped as a dumbbell, hence the name SMRTbell). Importantly, this should allow sequence information to be obtained from both the sense and antisense strands of the DNA, as well as providing greater consensus accuracy, since the polymerase can travel around the circular template multiple times. Although the SMRTbell method may take slightly longer (<4 hours hands-on, 5-6 hours all in), it should still enable results in half a day. Sample prep templates are packaged in 8-pack disposable containers, with 12 packs (96 samples) in a SMRT tray.

With the SMRT DNA Sequencing System, it will also be possible to run either linear or circular templates – and based on DNA, cDNA, and PCR products in a double stranded or single-stranded format – depending on what suits the application. Using circular consensus sequencing, it will be possible to read the same molecule multiple

times, enhancing the ability to find and confirm rare mutations when conducting deep re-sequencing.

Protocols on the SMRT platform can also be optimized for read length or throughput, depending on the application. When the system is released this year, customers will have the flexibility to run the instrument in "long read length mode" at 1,000-1,250 bp on average (longer than Sanger sequencing – i.e. 800-1,000 bp) for applications such as de novo sequencing, re-sequencing complex genomes and metagenomics, and for complex samples with repeats or structural variation. Currently, 5% of runs now fall between 3K-5K bp.

For applications that do not require long read lengths, such as re-sequencing or targeted mutation screening, protocols can be optimized for shorter reads and faster throughput. Furthermore, the number of reads per experiment and throughput remain a function of chemistry and number of holes on a chip. Since read length is also a function of the processivity of the enzyme, performance should improve over time as enhanced polymerases are developed and CCD technology and bandwidth improves.

On errors, Pacific Biosciences has worked to reduce insertion errors, which occur when a polymerase binds to a correctly-labeled nucleotide, but releases without adding. Deletion errors, in contrast, occur when a polymerase incorporates a nucleotide too rapidly, although one approach to the problem may be to hold the nucleotide in place for a longer period through modification of the enzyme.

Initial applications are expected to target infectious disease (influenza), in which time to result is highly important, as well as ribosome immobilization, HIV reverse transcriptase analysis, and agricultural biology – Monsanto is planning to sequence 1K genomes by 2014 (at an old Pfizer facility) all with PacBio systems – and de novo assembly (as mentioned earlier, data was presented on the Rhodopseudomonas palustris genome for biofuels). The system is also expected to have applications in DNA methylation, rare variation detection (beyond cancer) and characterization of complex structural variation.

Complete Genomics

Complete Genomics has developed high-density DNA nanoarrays and a sequencing byhybridization platform using probe-ligation chemistries, which it provides through a service-only offering for applications in biomarker discovery, diagnostics, clinical trial design, toxicology, functional genomics, cancer genomics and investigations of complex disease, such as cardiovascular and psychiatric disorders.

At this point, Complete has now delivered data for over 50 genomes to customers including Pfizer, Genentech, the Broad Institute, Riken, and Institute for Systems Biology, with applications in family studies, cancer genomes and tumor-normal pairs. As of mid-February, Complete had a healthy backlog, with orders booked for more than 500 human genomes (>$9 million).

To justify the $5,000 per genome cost, which applies only to complete human genomes, the company is assuming material costs at or slightly below $1,000, which is a notable drop from $4,000 in 2008 (computing remains the largest cost). While the sequencing method is ligation-based, the company has developed some interesting technology angles, including the development of DNA nano-balls (DNB),

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which are 200nm across (10 billion in a single 1 ml of liquid) and stick to the surface of an 8-inch wafer.

In terms of the model, Complete recently finished build-out of a new commercial sequencing wing for $12 million with capability for 5K genomes in annual throughput, and expects to build another $10 million expansion dependent on completion of additional financing rounds, which would enable 10K total output by the end of 2010.

This has required a significant increase in computing power (1.5K cores + 1.2 petabytes of disk storage to $6.3k cores + 1.5 petabytes of disk) and infrastructure (goal of ten genome centers worldwide), and accordingly, success is likely to be closely tied to the ability to raise additional capital and partner with genome centers and foreign governments.

Ion Torrent

Ion Torrent (private) recently introduced a $50K semiconductor-based sequencer, capable of <$500 runs. The system translates chemically-encoded information (A, C, G, T), using pH gradients, into digital information (0, 1) in a process labeled "ion semiconductor sequencing" (pH is measured by converting a hydrogen ion to voltage and subsequently measuring the gradient). The CMOS-based platform requires no camera, fluorescence or enzymes, and could prove disruptive based on price point alone, although a number of uncertainties remain around the commercialization strategy, sample prep, informatics, IP, etc.

Taking a closer look, the consumable stream for Ion Torrent (known as the Ion 314 chip) is sourced from a broad network of traditional semiconductor suppliers, thereby reducing supply chain costs, while electrochemical detection should reduce data storage costs over traditional optical images. Another aspect of the platform is that the company has adopted an open architecture approach to informatics, relying on third parties (DNASTAR, Geospiza, Partek, CLCbio and others) to develop software, which has proved a mixed strategy in the past (i.e., for the Danaher Polynator), but as price points come down, the market could open up to application developers.

Given that it is also an emulsion-based platform, however, it is unclear whether Ion Torrent will face some of the same traditional hurdles as 454 and LIFE, or whether it will ever be capable of true single molecule sequencing without sample prep. Either way, the potential around low cost, high throughput platforms (sequencing in an hour) could prove highly disruptive for both traditional research and importantly, clinical, applications. To that end, Ion Torrent is manufacturing the systems in an FDA certified facility (ISO 13485 certified).

Also, less clear, in our view, is the intellectual property landscape and to what extent the company could run into Illumina and Roche/454, in particular, around the use of beads (although Illumina is gradually moving away from beads for cluster generation).

Oxford Nanopore

Founded in 2005 to develop nanopore single molecule sensor systems, ONT has a development collaboration with Illumina (which also has an equity investment), and

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is working on a label-free, single molecule analysis system, using a protein bilayer to create a molecular hole. In February, the company raised an additional $28 million from existing investors including Lansdowne Partners, IP Group and Invesco Perpetual, new undisclosed U.S. institutions and Illumina UK Ltd. to accelerate development of the BASE technology, which uses real-time electronic measurement of current passing through the nanopores to identify molecules of interest.

The April 2009 issue of Nature Nanotechnnology featured the first published and peer-reviewed description of the method employed in the BASE sequencing system. Although the principle of label-free nucleotide detection by using a nanopore in combination with a non-covalent adapter had been previously demonstrated, the paper specifically solved a number of key technical problems, including the position of the adapter within the barrel of the pore to optimize data acquisition rates, high resolution of bases under operating conditions, and identification of a "fifth base", 5-methylcytosine, in the presence of G,A,T,C, which is particularly useful in epigenetics applications.

By way of background, in the BASE technology approach, as it is known, the alpha hemolysin protein used is well-characterized, highly-stable and provides a 3D scaffold that can later be manipulated and altered at a sub-nanometer scale. The lipid bilayer has a high electrical resistance, so when an electrical potential is applied across the membrane, current flows only through the nanopore. Once the bilayer is in place, a modified cyclodextrin is attached to the inner surface of the protein, which then becomes the binding site for an analyte (i.e., DNA base).

As the exonuclease directs individual DNA bases, in sequence, through the nanopore, each base transiently binds at the binding site (cyclodextrin). During the binding event, the nanopore current is disturbed, creating a characteristic signal for each type of base, which can then be easily distinguished and measured with traditional silicon chip technology.

One key advantage to the Oxford Nanopore approach, as we see it, revolves around electrical single molecule sensing, which should offer cost and throughput advantages to more expensive optical-based detection methods, such as those used in traditional CE and NGS instruments, as well as by Pacific Biosciences. ONT will not have to rely on third-party optics, while electrochemical detection on the system will eliminate the need for costly amplification and fluorescent labels. Furthermore, because the end result will be electrochemical, not optical, data storage and transfer costs should also be less.

Affymetrix

Valuation and Recommendation

We are maintaining our Neutral rating and December 2010 price target of $8. With shares trading at 1.3x our adjusted 2010 sales projection and better visibility around both manufacturing leverage and new product uptake, downside risk in the near term appears limited, in particular given the potential for stimulus spending as the year progresses, as well as a continued recovery in GWAS demand (although the trajectory remains debatable). The initial success of the GeneTitan and Axiom launches has helped reestablish investor confidence, while recent acquisitions (Panomics, TrueMaterials) should start to contribute more meaningfully. Technology obsolescence remains a longer-term concern given the pace of innovation in DNA

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sequencing, although demand for low-cost, rich variant studies and custom arrays should provide cushion.

At current levels, shares trade at forward EV/sales multiple of 1.3x our 2010 revenue projection, a ~64% discount to the peer group. We arrive at our December 2010 price target of $8 by applying 1.6x EV/sales multiple to our 2010 revenue projection, which we believe represents a fair valuation, given the aforementioned reasons and lower revenue growth expectations (+4% y/y versus 9% for the peer group).

Risks to Our Rating

Upside risks to our thesis include (1) missteps by competitors, in particular by Illumina and Agilent; and (2) faster-than-expected or more significant ramp for new products and/or faster-than-expected launch of differentiated next-generation products.

Downside risks to our thesis include (1) market growth uncertainties in an unstable funding environment, as certain Affymetrix customers rely heavily on government funded research grants; (2) continued declines in large-scale genotyping projects as alternative methodological frameworks to conduct genome-wide association studies (e.g. sequencing) become more affordable.

Illumina

Valuation and Recommendation

We maintain our Overweight rating and have raised our December 2010 price target to $48 in a separate note this morning. With a gradually improving end-market environment (better funding outlook for Europe and Japan, closer proximity to stimulus flow, 90% y/y increase in NIH GWAS budget in 2009 including stimulus funding), and what should be ongoing gains in 2010 from a refreshed product portfolio, we remain comfortable in our outlook for the company, and the broader genetic analysis opportunity.

At current levels, shares trade at 5.9x EV/2010E sales, a 63% premium to the peer group of life science research and diagnostic companies, while on a P/E basis, shares trade at 43.5x, a 130% premium to the same peer group. That said, given that ILMN continues to represent one of the best-positioned growth stories in healthcare, in our view, with opportunities for top- and bottom-line expansion in the next several years, we apply a premium 6.75x EV/sales to our 2010 revenue estimate (~88% premium to the peer group) and arrive at our Dec. 2010 price target of $48.

Risks to Our Price Target and Thesis

There are a number of investment risks, including: (1) competitive pressures within the emerging next-generation DNA sequencing landscape (from Life Technologies, Pacific Biosciences, Ion Torrent, Complete Genomics, etc.), while in molecular diagnostics, Illumina faces competition from a range of competitors, covering both content and instrument providers; and (2) market growth uncertainties in an unstable funding environment as a large number of Illumina customers rely heavily on government funded research grants.

Life Technologies

Valuation and Rating Analysis

We maintain our Overweight rating and December 2010 price target of $60. At current levels, shares trade at 15.2x our 2010 EPS estimate of $3.45, an 11% discount to the broader group of life science tool and bioproduction companies. With the near- to intermediate-term integration risks largely mitigated, in our view (i.e., the divestiture of the non-core mass spectrometry business completed February 1, and >$120 million of the target $175 million in synergies achieved ahead of schedule), we think upside potential from improved academic spending, new product cycles (SOLiD 4, Attune, etc.), and emerging markets throughout 2010 presents an attractive entry point, particularly at current valuations. We arrive at our December 2010 price target of $60 by applying a 17.4x multiple (in line with the peer group and a reasonable baseline, in our view) to our 2010 EPS estimate of $3.45.

Risks to Our Rating and Price Target

Downside risks to our price target and Overweight rating include: (1) longer-term integration-related risks (i.e., inability to drive revenue synergies); (2) slower-than anticipated uptake of the enhanced SOLiD 4 platform and/or a faster drop-off in the base capillary business; (3) stronger impact from competitive product introductions across the RT-PCR or DNA sequencing businesses; and (4) a greater-than-anticipated slowdown in demand from the emerging or applied end markets.

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Companies Recommended in This Report (all prices in this report as of market close on 11 May 2010)
Affymetrix (AFFX/$6.71/Neutral), Illumina, Inc. (ILMN/$42.16/Overweight), Life Technologies Corporation (LIFE/$52.45/Overweight)

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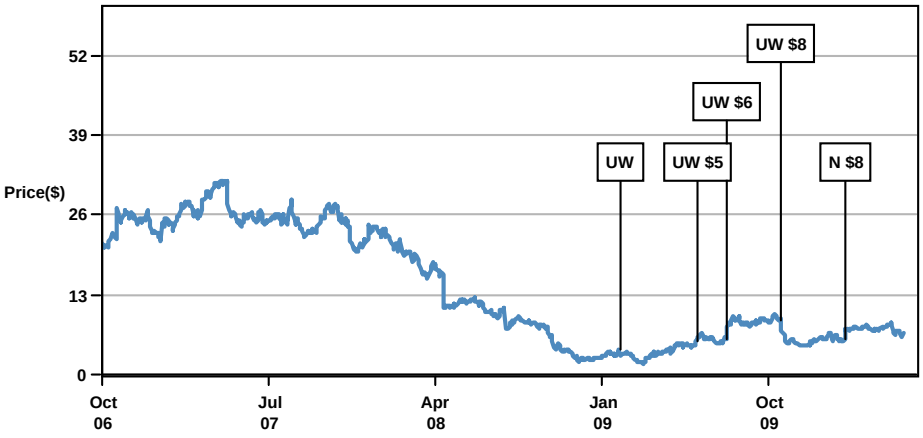
Affymetrix (AFFX) Price Chart



Date	Rating	Share Price ($)	Price Target ($)
29-Jan-09	UW	3.93	-
04-Jun-09	UW	5.33	5.00
23-Jul-09	UW	5.88	6.00
22-Oct-09	UW	8.86	8.00
04-Feb-10	N	5.67	8.00

Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.
This chart shows J.P. Morgan's continuing coverage of this stock; the current analyst may or may not have covered it over the entire period.
J.P. Morgan ratings: OW = Overweight, N = Neutral, UW = Underweight.

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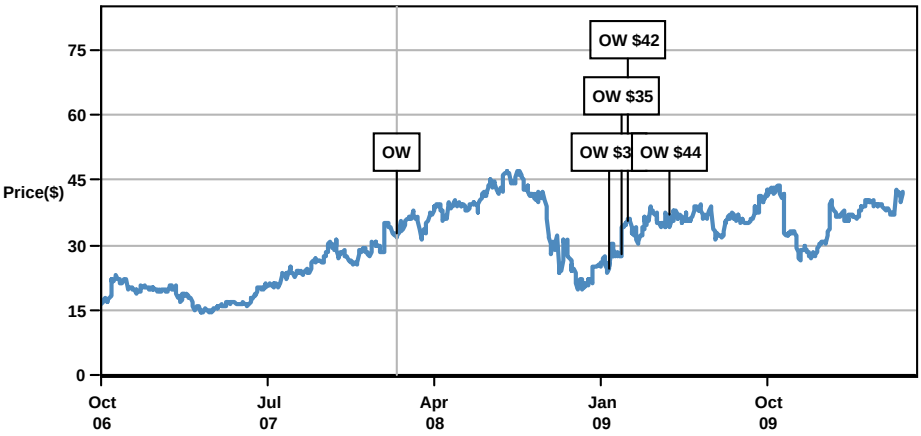
Illumina, Inc. (ILMN) Price Chart



Date	Rating	Share Price ($)	Price Target ($)
29-Jan-08	OW	32.58	-
12-Jan-09	OW	24.33	33.00
04-Feb-09	OW	27.99	35.00
13-Feb-09	OW	35.50	42.00
22-Apr-09	OW	37.16	44.00

Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.
Break in coverage Sep 12, 2002 - Jan 29, 2008. This chart shows J.P. Morgan's continuing coverage of this stock; the current analyst may or may not have covered it over the entire period.
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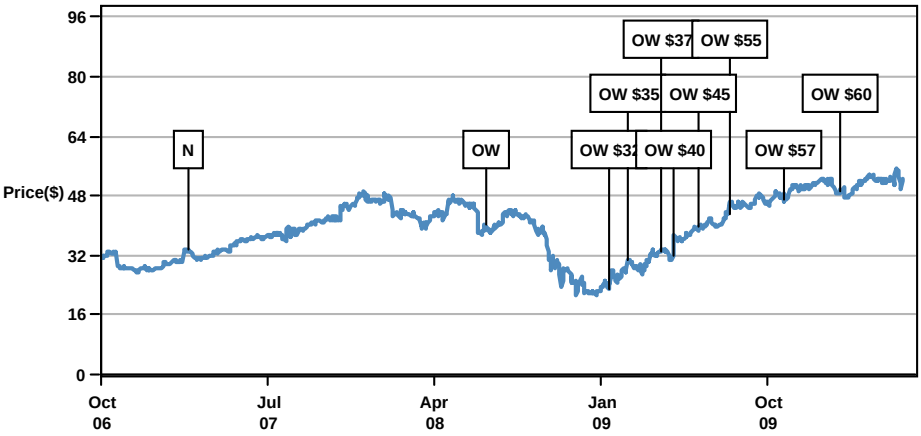
Life Technologies Corporation (LIFE) Price Chart



Date	Rating	Share Price ($)	Price Target ($)
22-Feb-07	N	33.50	-
24-Jun-08	OW	40.01	-
12-Jan-09	OW	22.99	32.00
13-Feb-09	OW	30.65	35.00
08-Apr-09	OW	32.77	37.00
29-Apr-09	OW	32.03	40.00
10-Jun-09	OW	39.57	45.00
29-Jul-09	OW	42.91	55.00
27-Oct-09	OW	47.05	57.00
29-Jan-10	OW	49.38	60.00

Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.
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IB clients*	70%	58%	48%

*Percentage of investment banking clients in each rating category.
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