

# Next-Generation Sequencing Survey

## Results From Our Survey of 73 Researchers

In conjunction with our initiation of coverage on Illumina, we conducted an e-mail-based survey of researchers in an effort to understand their sequencing instrumentation and consumable purchasing and utilization trends. The survey was conducted in November 2010. Respondents (n=73) primarily came from academic research labs and small to midsize core labs (84% of the total) in the United States (63% of the total) and abroad. Our key findings are summarized below.

**Next-generation sequencing (NGS) instrument and consumable usage trends appear positive for 2011.** The vast majority of NGS users expect daily capacity (80%) and annual consumable utilization (78%) to trend upward in 2011. Given the high-margin, recurring nature of consumable-based revenue, this bodes well for NGS platform manufacturers next year, in our view. Trends appear especially positive for HiSeq users (HiSeq is Illumina's sequencing platform launched in early 2010). Although our survey included only a small sample size of HiSeq owners (10) and it is early in the product cycle, as users are only just receiving and validating machines, responses and our subsequent follow-up support company guidance that average consumable utilization per HiSeq 2000 should be at least double that of the Genome Analyzer (Illumina's existing sequencing platform). In addition, almost half of HiSeq users expect consumable usage to be up 30% or more in 2011 (of the other respondents, three expect usage up 20% to 25% and three were unsure).

**Illumina's HiSeq and Life Technologies' 5500xl are the most popular platforms cited for future purchase.** Almost 60% (42) of respondents are evaluating or plan to purchase at least one NGS platform and just over 40% expect to purchase an instrument in the next 12 months—survey participants identified a total of 49 machines. When asked for their top three priorities in choosing a new NGS platform, 12 of 42 respondents identified throughput as a key driver. Thus, it is not surprising that Illumina platforms (22% of machines identified) and Life's 5500xl (20% of machines identified) were the most-cited next-generation platforms for potential purchase. We suspect some of the 5500xl machines identified will be upgrades from Life's SOLiD 4, based on the company's rollout of its new 5500 platform in late 2010.

**The survey reflects excitement around newer sequencing technologies.** Over 60% of respondents expressed interest in sequencing technology under development and 12% of respondents indicated they were part of an early access program. Ion Torrent (a unit of Life Technologies) was the most popular platform (representing 24% of identified machines); Pacific Biosciences also had a strong showing with 12% of instruments. The strong interest in Ion Torrent's Personal Genome Machine (PGM) may have been driven by its recent launch—the PGM costs significantly less (at \$49,500), has much shorter run times (an hour), and has lower throughput (starting at 10 megabases per run). Thus, it is likely to be used for targeted resequencing (rather than whole genome sequencing)—and will likely complement instead of cannibalize Illumina's market opportunity.

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## Introduction and Methodology

In conjunction with our initiation of coverage on Illumina (see our report titled "Initiation of Coverage With an Outperform Rating," published January 7, for more information about our investment thesis on the company as well as an overview of the sequencing space), we conducted an e-mail-based survey of researchers in an effort to understand their sequencing instrumentation and consumable purchasing and utilization trends. The goal of the survey was to understand: 1) overall funding trends, 2) capillary electrophoresis (CE) and next-generation sequencing (NGS) utilization trends, 3) expectations for future CE and NGS usage/purchasing decisions, and 4) perspectives on newer technologies (e.g., third generation).

The survey was conducted in November 2010 and included 73 completed responses. We primarily targeted professionals who conduct genomic research that have peer-review publications based on sequencing and array applications, including targeted re-sequencing, RNA-seq, ChIP-seq, and genome-wide association studies (GWAS), as well as professionals who work in core labs, genome centers, and other areas of the industry. Respondents were primarily researchers from academic labs and core labs (84% of the total) and to a lesser extent commercial sequencing service providers, genome centers, and other labs (such as hospital/diagnostic labs). The focus of responses on individual principal investigators (PIs), academic labs, and small to midsize core labs provides an interesting perspective on trends outside the major genome centers.

In sum, our survey results support our view that the HiSeq conversion should sustain Illumina's momentum for the next couple of years through instrument sales, consumable pull-through, future upgrade cycles, and gross margin improvement as the company continues to optimize the platform. It is difficult to draw distinct correlations between our assumptions for the number of HiSeq instruments Illumina will ship in the next two years and the number of HiSeq machines identified in the survey. Results suggest, however, the HiSeq platform continues to be a popular solution outside the large genome centers, which provides us with comfort that HiSeq instrument sales should extend beyond GAllx conversions. Most importantly, given our belief that reagent sales represent the largest potential source of upside in 2011, HiSeq utilization trends identified in our survey (although admittedly early in the product life cycle and a small sample size of 10 HiSeq users) suggest our estimate of an average of \$315,000 in reagent sales per HiSeq in 2011 could be conservative. We estimate HiSeq reagent usage could provide \$0.10 in upside to our 2011 EPS estimate of \$1.46 (assuming average per unit reagent usage of \$400,000 and gross margin of 65%).

## A Brief Background on Sequencing

For readers unfamiliar with the space, the following section provides a brief background on sequencing and the competitive landscape. We discuss these concepts in more detail in our report initiating coverage of Illumina.

DNA sequencing is used to determine the order of nucleotide bases—adenine (A), cytosine (C), thymine (T), and guanine (G)—of a DNA strand, which carries information for building and maintaining an organism. Human DNA contains 3 billion base pairs, 99.9% of which are identical between individuals and across populations. The 0.1% that varies drives unique genetic traits or phenotypes (hair color, height, etc.) as well as predisposition to medical conditions. As a result, researchers have a strong interest in identifying and comparing genetic variation across individuals and populations as well as within and between other species (plants, animals) in an effort to better understand the heritability and mechanism of disease.

For 30 years labs have used a sequencing technology called capillary electrophoresis (CE), which was initially developed by Frederick Sanger and commercialized by Applied Biosystems (ABI, now part of Life Technologies), which manufactures and sells CE/Sanger-based sequencing machines to this day. In 2005, companies such as 454 Life Sciences, ABI, and Solexa began to commercialize a new generation of sequencing technology (referred to as next-generation sequencing), which dramatically improved the throughput (amount of DNA sequenced per run) relative to CE sequencing through improved chemistry and by leveraging massive parallelism (or a number of sequencing reactions performed at once). Over the past five years, scientists have improved these technologies and platforms, leading to a dramatic reduction in sequencing cost. As an example, the Human Genome Project, which sought to sequence the human genome for the first time, took 13 years and cost more than \$3 billion. Now, Illumina offers whole genome sequencing to consumers for as low as \$9,500 for a single patient when sequencing could provide direct clinical value.

Although many labs still use CE-based sequencing instrumentation, the sequencing market has evolved rapidly since the next-generation platform was first developed. There are three primary next-generation instrumentation vendors that have been widely adopted: 454 (now owned by Roche), ABI, and Solexa (owned by Illumina). Although next-generation platforms use similar workflows, each of these platforms is based on different chemistry and therefore has different advantages and disadvantages. In 2005, 454 Life Sciences introduced the first next-generation platform, the GS 20, which was based on pyrosequencing and emulsion PCR; the company introduced its updated version, the FLX, in 2007. In 2006, Solexa (acquired by Illumina in 2006) introduced the first “short-read” platform, the Genome Analyzer (Illumina recently launched an updated version, the HiSeq). ABI introduced another short-read platform in 2007, the SOLiD (and at the end of 2010, introduced an improved version, the 5500xl). Illumina’s platforms have historically provided the greatest throughput and thus have become more widely adopted; Illumina has an estimated 60% of the NGS market and Roche/Life split the remainder at 20% each.

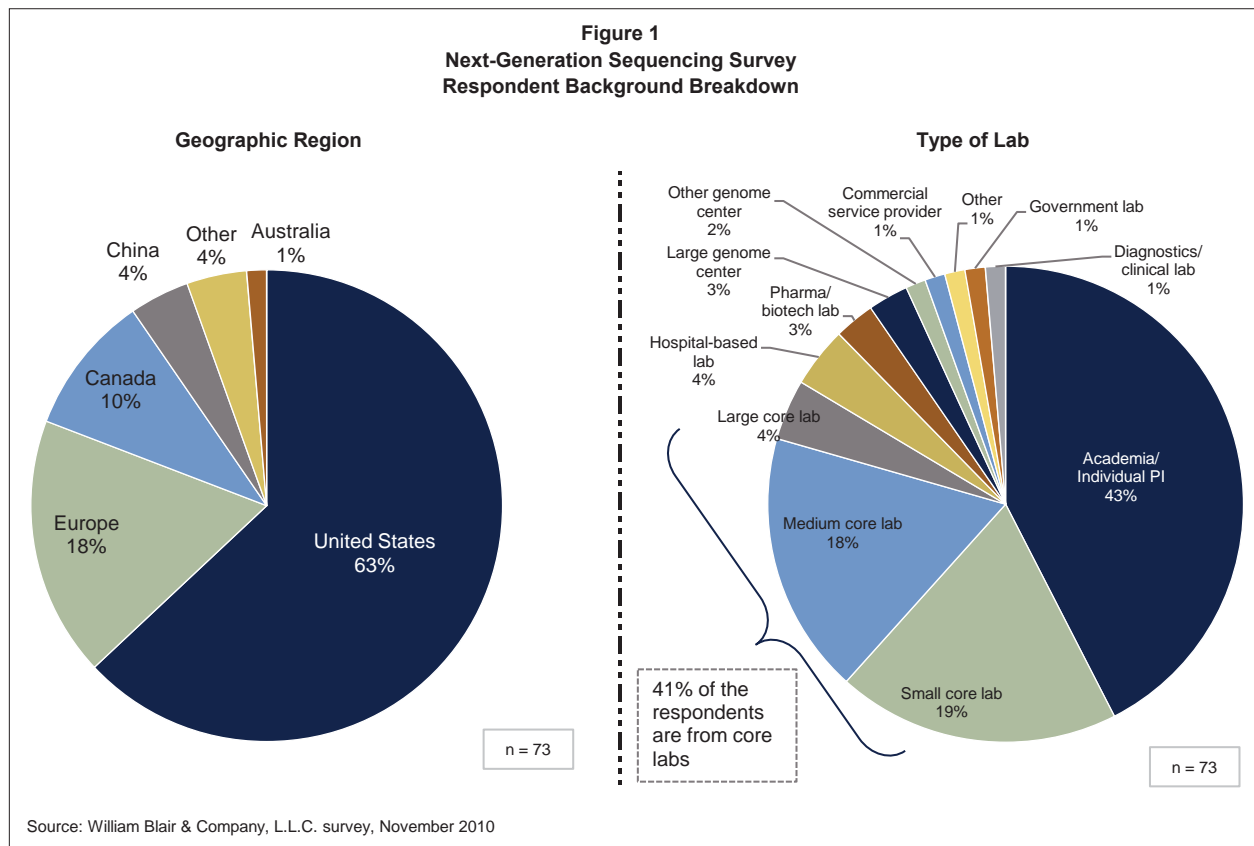
The majority of sequencing instrument vendors recognize revenue based on a razor/razor-blade model—generating revenue from machine sales, which then translate into a recurring revenue stream of higher-margin reagent sales over time. As an example, roughly 50% of Illumina’s revenue is generated by NGS-related sales (instruments and reagents)—an estimated 23% from sequencing consumables and 29% from sequencing instrument sales. Another 40% of revenue is generated by the company’s microarray business, which has been around longer and is much more weighted toward consumables (36% of revenue, compared with instruments at 4%). Thus, future revenue growth and margin expansion, as well as earnings upside, are driven not only by instrument sales, but also by consumable utilization (e.g., whether researchers on average use more or less reagent than expected). We conducted this survey in an effort to gain insight into these variables (future instrumentation purchasing as well as consumable usage patterns).

## Respondent Demographics and Research Interests

### Respondent Background

As shown in figure 1, 63% of respondents are based in the United States, 18% in Europe, and 10% in Canada. The remaining 9% of respondents are from the Asia-Pacific region, such as China (4%), Singapore, and Australia. In terms of job responsibility, 55% of respondents are at the management level in scientific labs (principal investigator and lab director/manager); graduate students and post-doctoral fellows made up another 24%. The remaining respondents serve in a variety of roles, including lead manager for a university's core DNA sequencing facility, core facility analyst, and applications specialist from a hospital-based lab.

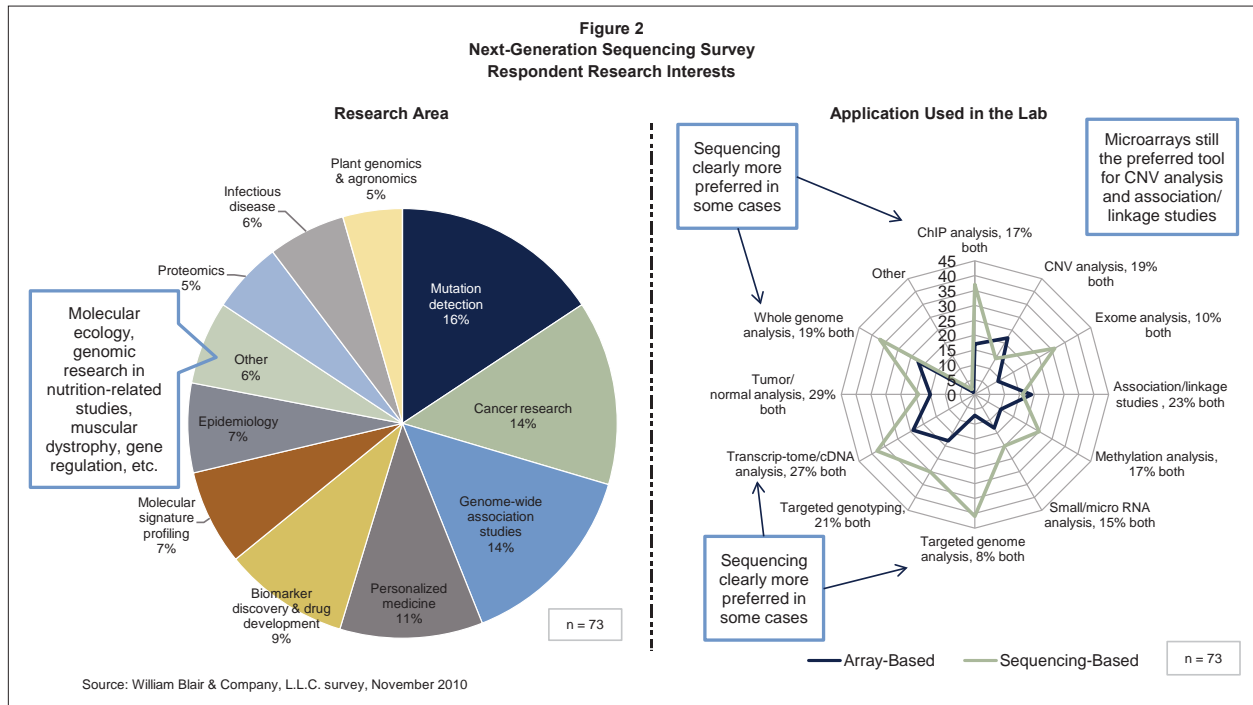
As mentioned, the majority of survey participants work in individual PI labs (43%) and core labs (41%). Core labs are typically part of academic institutions and offer research services such as sequencing to internal constituents (individual PIs, for example). Core labs offer competitive pricing to internal users, as they are typically set up using government funding and are not-for-profit organizations. The adoption of the HiSeq outside the larger genome centers has been surprising, given its high price tag (\$690,000), which has helped fuel greater-than-expected HiSeq instrument sales. Thus, the higher weight of responses toward smaller laboratories (academic labs and small/midsize core labs) provides an interesting perspective into the purchasing and utilization trends outside the genome centers.



### Respondent Research Interests

We also asked respondents to identify their research interests and the types of technologies they apply to their research studies. As shown in figure 2, on the following page, cancer research (14%), genome-wide association studies (GWAS, 14%), and mutation detection (16%) are the top three areas of interest. Technologies used in respondents' labs included bioinformatics (82% of respondents), RT-PCR (75%), PCR (72%), next-generation sequencing (69%), microarrays (60%), biostatistics (58%), CE sequencing (34%), mass spectrometry (23%), protein/immune-based assays (18%), cell imaging (14%), flow cytometry (14%), pyrosequencing (5%), and oligo synthesis (11%).

Many research applications can be performed via microarrays and sequencing—some argue that microarray technologies will become obsolete as NGS costs continue to drop at a rapid pace, while others argue that microarrays will remain the most cost-effective mechanism to rapidly analyze multiple markers for some time. Our survey suggests (the right chart of figure 2) that sequencing-based methods may be preferred for some applications (whole genome analysis, exome analysis, ChIP analysis, targeted genotyping and genome analysis, and transcriptome analysis) while microarrays continue to be the preferred technology in linkage/association studies (such as GWAS) and CNV (copy number variant) analysis.



## 10 Key Survey Conclusions

**1. Overall funding trends are more positive for the space in 2011.** Fiscal 2009 and 2010 were difficult years for the life sciences space, as the economic downturn led to cutbacks in government and endowment spending. Based on our survey results, although uncertainty around the NIH budget remains, the overall funding environment appears to have stabilized with a positive skew, which bodes well for life science vendors (including Illumina) in the coming year. While 40% of respondents expect general research project funding to be flat in 2011, 40% expect an increase (versus 9% down) in 2011. Thirty-six percent of respondents expect sequencing instrumentation funding to be up over the next year (versus 41% flat and 3% down).

**2. The first phase of stimulus funding disbursements seems to have run its course, although only about 39% of funds have been dispersed.** The American Recovery and Reinvestment Act of 2009 (ARRA) included \$10.4 billion in funds for the National Institutes of Health (NIH); these funds have been dispersed to researchers somewhat more slowly than originally anticipated. Illumina’s management indicated that the company had access to roughly \$100 million of the first phase of funding. Based on management commentary throughout the past year, Illumina has received orders for roughly 80% of that amount, suggesting that at least the funds from the first phase of ARRA awards have made their way from the NIH to researchers to Illumina orders.

Based on information provided by the NIH, we estimate 39% of total ARRA funds (or \$4.0 billion) have been released to researchers to date. Only 10% of respondents to our survey secured ARRA funding, and only roughly half of those that secured ARRA have actually

received funds. Although this is a small sample size, in our opinion, this response supports the view that the majority of ARRA funds have yet to be distributed—suggesting that the stimulus should continue to be a tailwind for life sciences equipment and consumable manufacturers for a year or more.

**3. CE sequencing still has a place in certain applications; utilization trends are mixed in 2010 and 2011, and some CE/Sanger users are still converting to next-generation platforms.** The cost of sequencing has declined by a factor of 100 over the past three years and continues to decline rapidly. Thus, there is a view that a shift to NGS has eroded and will continue to erode the CE/Sanger sequencing market, as the cost of NGS continues to fall. Based on commentary from Life Technologies (which manufactures the majority of CE-based sequencing platforms), the shift—at least within the major genome centers—has mostly occurred. Life has also seen success with its latest CE platform launch (the 3500), particularly in hospital labs and clinics, indicating it had placed 400 3500 machines as of the end of the second quarter.

Results from our survey were mixed. Overall, 54% of respondents (39) either own or share a CE sequencing machine. Slightly fewer respondents expected CE utilization to be up in 2011 versus 2010 (41% in 2010 versus 36% in 2011), while the percentage of respondents who expect utilization to be down in both years was similar (26% in 2010 versus 24% in 2011). In giving a reason respondents expect CE utilization to be down in 2010 and 2011 (19 total respondents), 13 cited that they had switched or are going to switch to an NGS platform. Our survey results suggest CE sequencing maintains a stronghold, which supports Life Technologies' comments that the dramatic decommissioning of CE machines that occurred over the past two years is largely complete. On the other hand, our survey also suggests that there is still some conversion of CE to NGS instrumentation under way.

**4. Researchers seem to prefer sequencing-based methods for most applications, although microarrays remain the preferred method for linkage/association studies (such as GWAS) and CNV (copy number variant) analysis.** Many research applications can be performed with both microarrays and sequencing—some argue that microarray technologies will become obsolete as NGS costs continue to drop at a rapid pace, while others argue that microarrays will remain the most cost-effective mechanism for some applications—e.g., rapidly analyzing multiple markers. Our survey pointed to clear examples where sequencing-based methods may be preferred for some applications (such as whole genome analysis, exome analysis, targeted genome analysis, ChIP analysis, and transcriptome analysis). Microarrays continue to be the technology of choice for linkage/association studies (such as GWAS) and CNV analysis. Respondents could select both sequencing and microarrays, which occurred 8% to 30% of the time depending on the application (illustrated in figure 2).

**5. Current NGS ownership trends are in line with overall market share, with the GAllx by far the most popular instrument.** As expected, given Illumina's estimated 60% share of the NGS market, the Genome Analyzer represented the most widely adopted platform (52% of respondents with a NGS platform have one or more Illumina machines). Life Technologies' SOLiD platforms represent a close second, with 26% of NGS machines identified in our survey, followed by Roche 454 at 19%.

**6. Illumina's GAllx to HiSeq trade-in program appears to be on track to finish in the first quarter of 2011.** When Illumina introduced the HiSeq in January 2010, the company offered a trade-in program for researchers that had ordered or received a Genome Analyzer in fourth quarter 2009 (where they received a credit for the full cost of the Genome Analyzer toward the HiSeq) or received an instrument before fourth quarter 2009 (where they received a \$150,000 credit). Although the GAllx-to-HiSeq trade-in program bodes well for future consumable sales (since the HiSeq 2000 is expected to use roughly double the amount of reagent as the GAllx), the conversion will likely drive some margin compression in the nearer term. Illumina's management has indicated that it expects the trade-in program to reach a peak in fourth quarter 2010 and be mostly complete in the first half of 2011.

Of the 15 respondents who indicated they have traded in or plan to trade in their GAllx, roughly half have already received their platform and the other half expect to receive their platform in the next six months or less, with an average time to receipt of three months. Thus, our survey results seem to support the statement that the majority of the trade-in program should be complete by the first half of next year and most likely by the end of the first quarter of 2011.

**7. NGS-related utilization and consumable usage trends appear positive for 2011 and particularly for the HiSeq (although admittedly early in the product's life cycle).** Of the 35 respondents with an NGS platform, 80% expect their NGS utilization to be up in 2011. Seventy-eight percent of respondents expect 2011 consumables spending to be up from 2010, with 32% pointing to growth in reagent usage of more than 30%.

Trends look even more positive for HiSeq users. Our survey included responses from 10 HiSeq owners, which were more weighted toward smaller labs (medium core labs and academic/individual PIs). Many users own multiple NGS machines and thus it is difficult to assess specific per-machine HiSeq usage, and we admittedly have a small sample size to analyze. Still, survey responses and subsequent follow-up support management's estimate that HiSeq 2000 consumable usage should be at least roughly double that of the Genome Analyzer (or on average in the \$300,000 to \$400,000 range) and suggest that average annual per HiSeq consumable usage for these specific HiSeq users is roughly \$300,000. In addition, almost half of HiSeq users expect consumable usage to be up 30% or more in 2011 (with three users indicating use up 20% to 25%, and three stating that they are unsure).

In our view, this bodes well for the overall average per HiSeq machine consumable usage considering most HiSeq instruments shipped to date reside in genome centers or large core labs, which should have much higher utilization rates (and thus reagent usage) than those in smaller labs. Given that researchers are just receiving HiSeq machines, we also expect some ramp-up time. Our sensitivity analysis suggests that consumable utilization represents by far the greater upside opportunity (versus machine sales), and thus, in our view, these results bode well for Illumina's growth prospects in 2011. We note we have assumed average per HiSeq reagent usage of \$315,000 in 2011 and \$350,000 in 2012. We estimate consumable upside could add \$0.10 to our adjusted 2011 EPS estimate of \$1.46 for Illumina (assuming an average annual consumable usage of \$400,000 per HiSeq at a gross margin of 65%).

**8. Throughput is still the key factor in determining platform choice; HiSeq and Life's 5500xl are the most popular NGS platforms.** Almost 60% of respondents (42) are evaluating or plan to purchase at least one NGS platform in the future. Just over 40% expect to purchase an instrument in the next 12 months. Survey participants identified their intention to purchase a total of 49 non-CE-based machines.

We asked respondents for their top three priorities in choosing a new NGS platform. Twelve of the 42 respondents selected throughput as their top priority—the cost of reagents and software/data management support were also frequently cited drivers. Given throughput is the most-desired characteristic, it is not surprising that Illumina platforms (22% of machines identified) and Life's 5500xl (20% of machines identified) were the most popular next-generation platforms for future purchase. We suspect some of the 5500xl machines identified were upgrades from Life's SOLiD 4, based on the company's rollout of its new 5500 platform in late 2010—we estimate potentially 7 out of 10 platforms identified will be upgrades.

**9. Instrument price is still a major hurdle for those not planning to purchase an NGS machine.** Many respondents cited expense as a reason not to purchase a next-generation platform, including both the cost of maintaining the instrument (17 survey participants) and incremental resource needs (12), which we believe points to the high elasticity of the demand curve. Interestingly, only a few users (6) indicated they were waiting for commercialization of new technology before purchasing a sequencing platform, which bodes well for some of the less established vendors, in our view.

**10. Industry buzz around Life’s Ion Torrent, Pacific Biosciences’ RS system, and Oxford Nanopore was reflected in our survey.** A number of third-generation vendors, including Pacific Biosciences, Life Technologies (Starlight), Halcyon, and Oxford Nanopore, and other new platforms such as Ion Torrent (Life Technologies) have generated quite a bit of buzz at industry conferences, promising longer read lengths, higher quality, and higher throughput, all at a low cost. It is early in the life cycle of these companies and most do not have instruments available commercially—although Life Technologies (Ion Torrent) recently launched its PGM and Pacific Biosciences has an early access program in place, with a commercial launch target of first quarter 2011.

Over 60% of respondents expressed interest in the new sequencing technology under development and 12% of respondents indicated they were part of an early access program. Ion Torrent was the most popular platform of all (representing 24% of the 49 high-throughput sequencing machines respondents plan to purchase); Pacific Biosciences also had a strong showing with 12% of instruments. The strong interest in Ion Torrent (Life’s) PGM may have been driven by its recent launch. The PGM costs significantly less (at \$49,500), has much shorter run times (an hour), and has lower throughput (starting at 10 Mb per run). Given its low throughput and fast run times, we believe it is more likely to be used for targeted resequencing and potentially microbial genome sequencing (versus whole human genome sequencing), and thus we believe will likely complement rather than cannibalize Illumina’s market opportunity.

## Part I. Funding Sources and Budget Expectation for 2011

### Government Funds Are a Key (but Not the Only) Source of Funds

As illustrated in figure 3, government funding is an important financial resource for labs, as 25% of respondents received NIH/ARRA funds and the majority of the international respondents receive equivalent funding from their state governments. Chargebacks (23%) and institutional funds/cash flow (26%) also represent important resources.

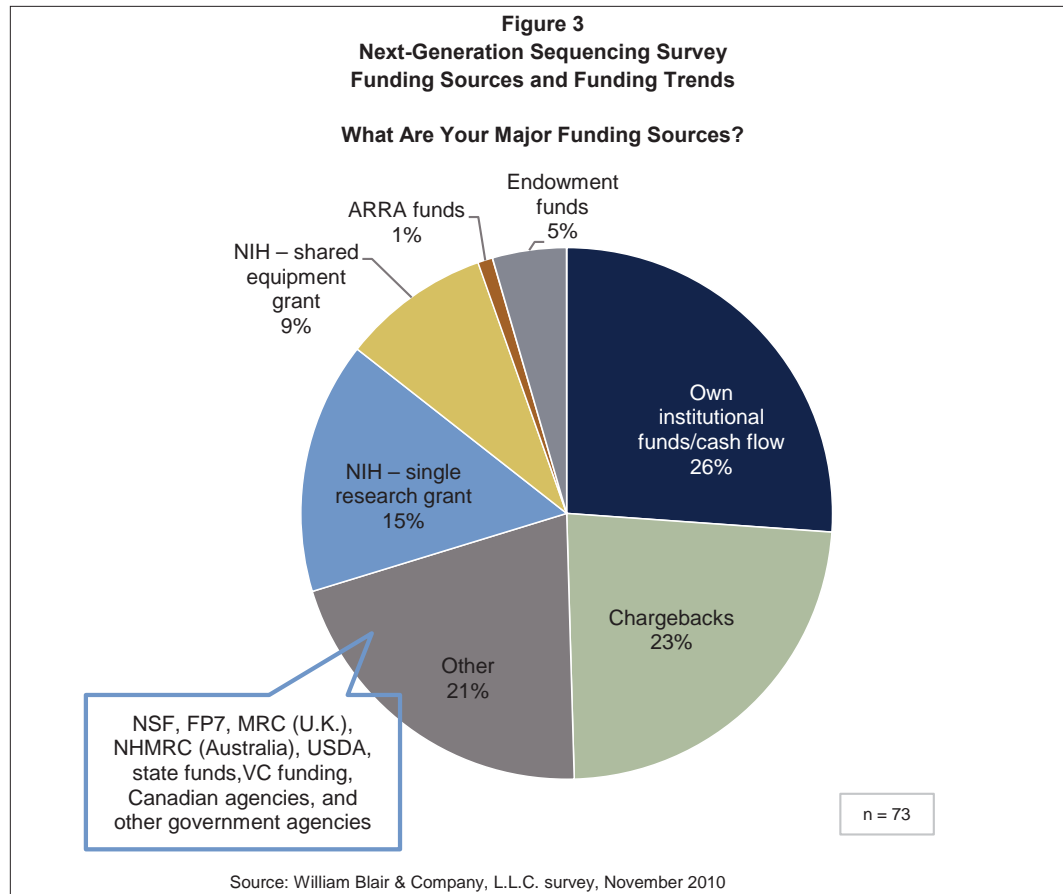
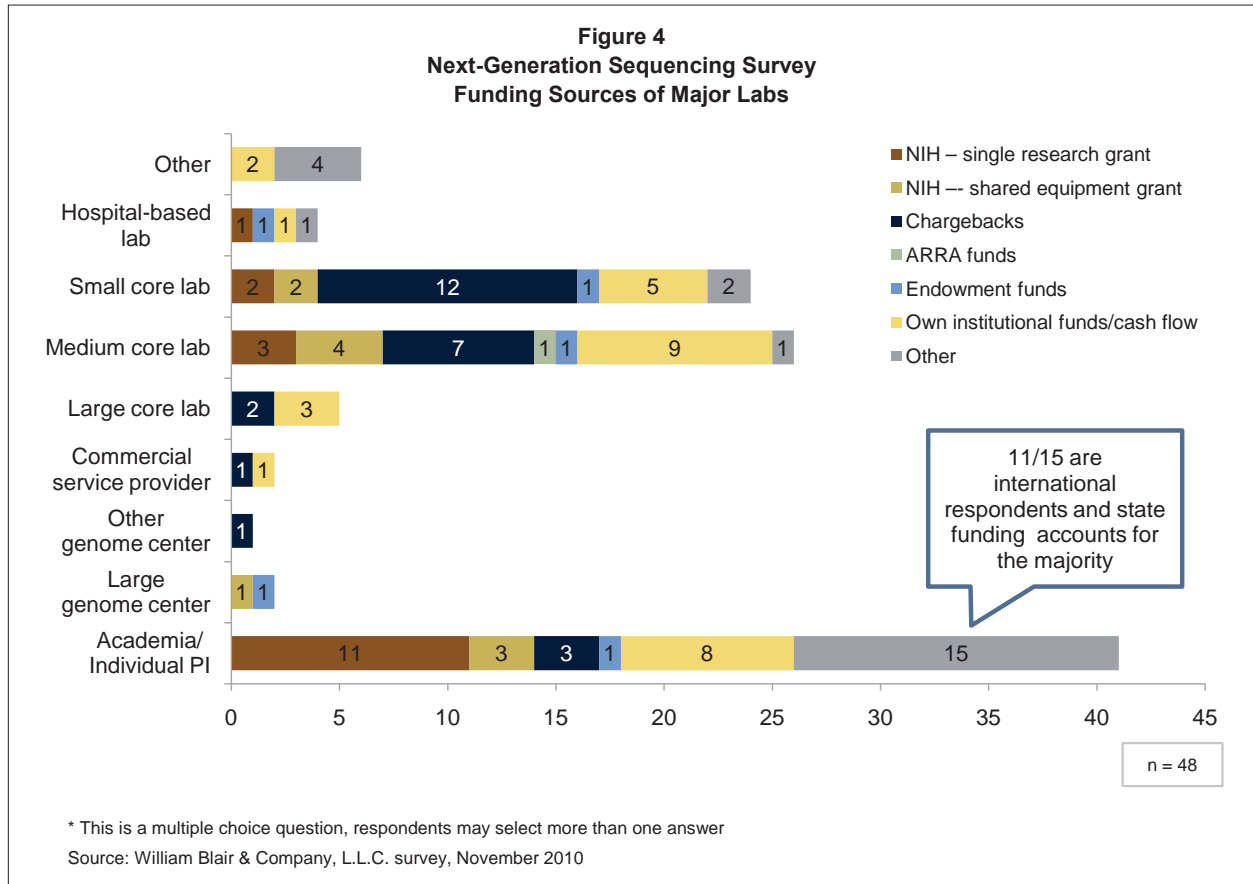


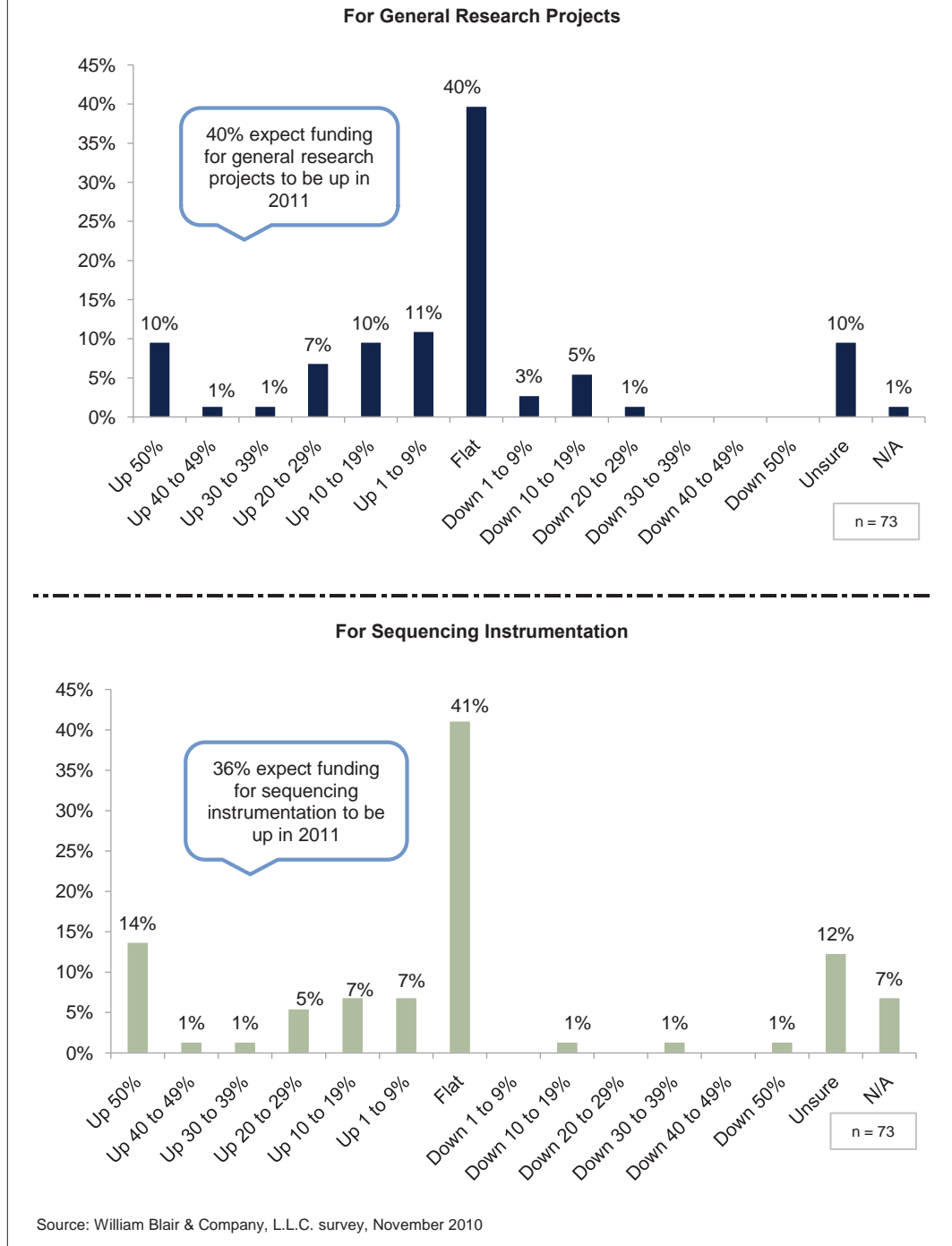
Figure 4 provides funding source by lab type. Individual PI labs receive funding from the widest variety of sources, but more so from the NIH than other lab types, as one would expect. Core facilities tend to be funded by their own institution's funds and chargebacks, as well as to a lesser extent the NIH.



**Funding Trends Appear Stable to More Positive**

As illustrated in figure 5, although a good percentage of respondents expect funding trends to be flat (which is not surprising considering the uncertainty around NIH funding trends), many also indicated they expect funding to be up in 2011 (which perhaps suggests the NIH continues to prioritize sequencing projects). Forty percent of respondents indicated they expect general research project budgets to be up next year, and 36% of respondents suggested their sequencing instrumentation budget should increase in 2011. This bodes well for both instrumentation purchases (especially given the relatively high price tag of Illumina's HiSeq) and consumable utilization (which is also addressed more directly below).

**Figure 5**  
**Next-Generation Sequencing Survey**  
**Funding Sources and Funding Trends**  
**How Do You Expect Funding to Trend in 2011?**

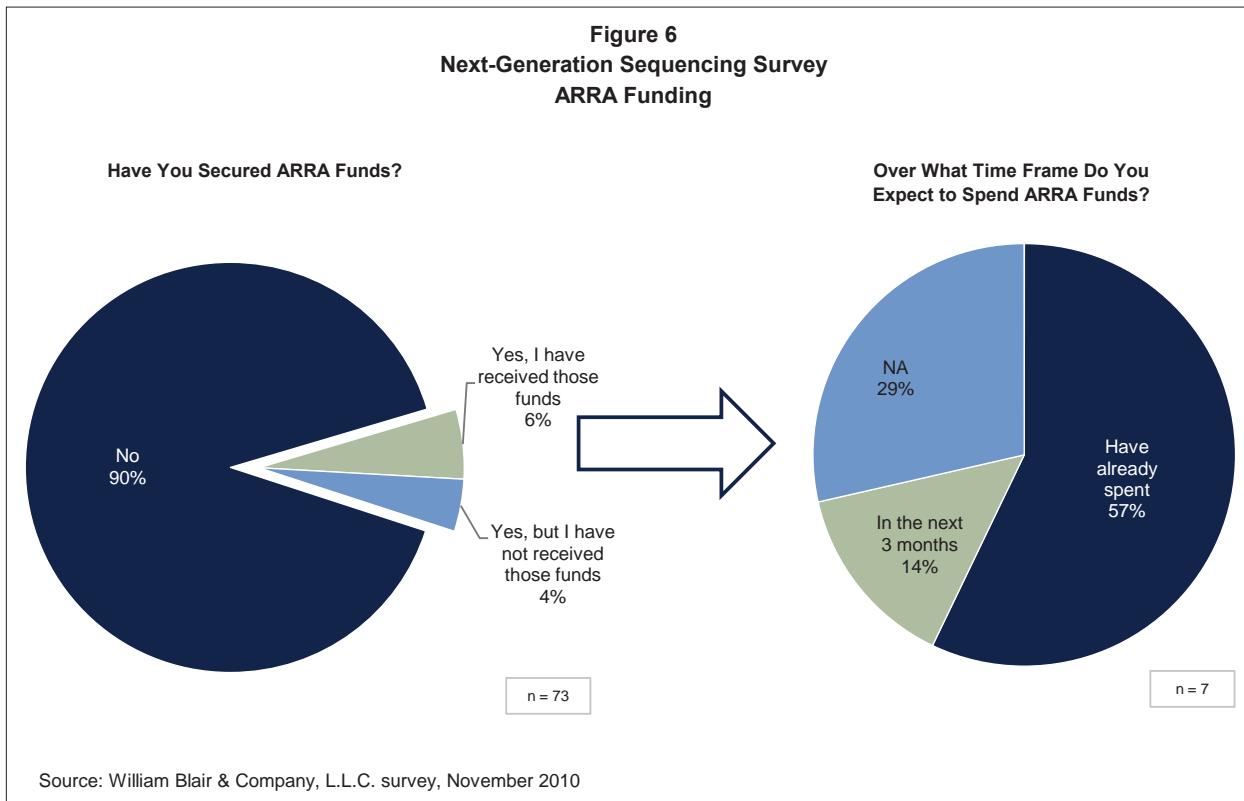


**First Phase of ARRA Funding Has Run Its Course**

Although disbursements have been slower than expected, we believe ARRA funding has accelerated microarray and NGS instrument purchases over the past year. According to the National Center for Research Resources, 55% of ARRA funding that was allocated to the purchase of protein/DNA analysis instruments under shared equipment grants was allocated to Illumina machines (about \$9.7 million), 15% toward Roche 454 (about \$2.6 million), and 8% toward Life SOLiD (about \$1.4 million).

Illumina has suggested that it has access to about \$100 million of the first phase of ARRA funds. Based on management commentary over the past four quarters, the company has received roughly \$80 million in orders related to the stimulus, which suggests that at least the first phase of the ARRA disbursements has been spent.

Based on information provided by the NIH, however, we estimate only 39% of the total \$10.4 billion in ARRA funds (or \$4.0 billion) has been released to researchers to date. Only 10% of respondents to our survey secured ARRA funding; however, only roughly half of those that secured ARRA funding have actually received funds. Although our sample size is small, we believe this supports the view that the majority of ARRA funds have yet to be distributed, suggesting that the stimulus should continue to be a tailwind for life sciences equipment and consumable manufactures for a year or more.



## Part II. CE Sequencing User Experience and Trend Analysis

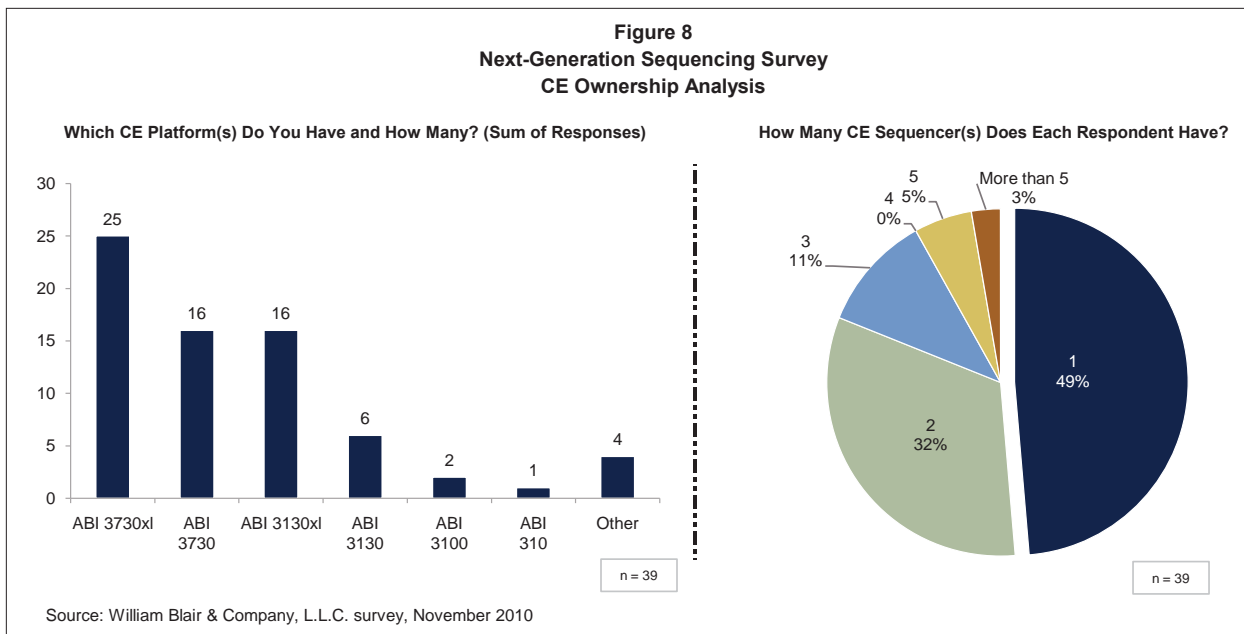
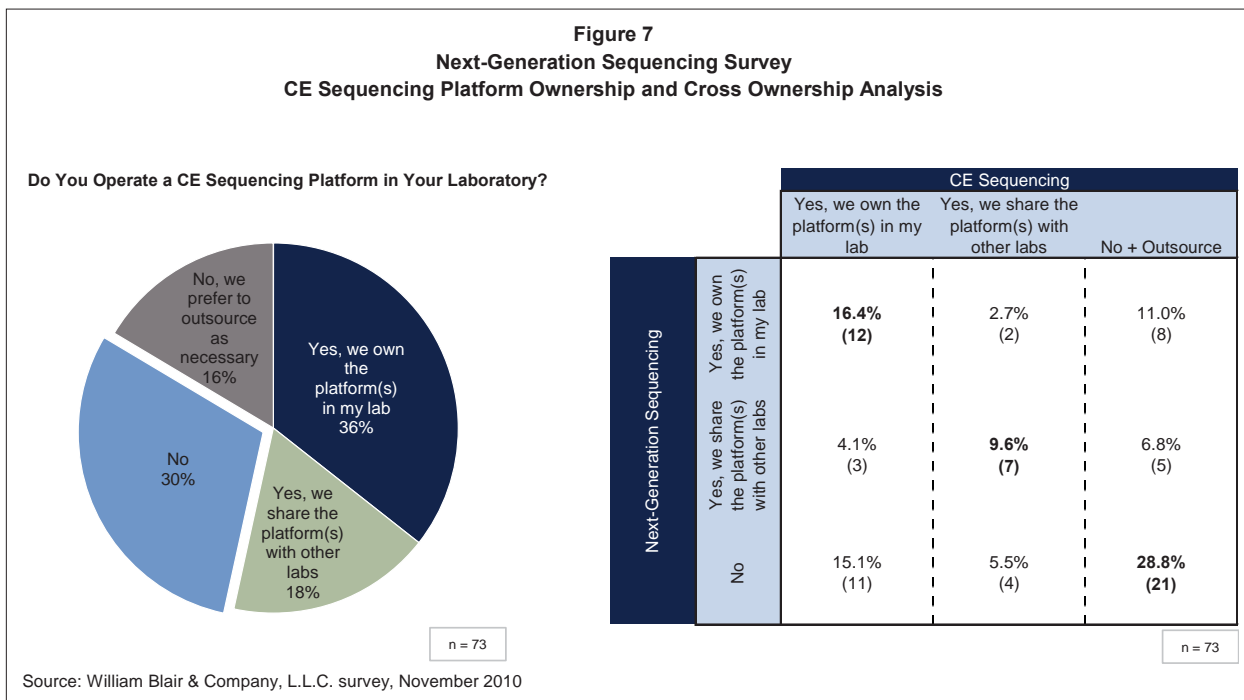
The cost of sequencing has declined by a factor of 100 over the past three years and continues to decline rapidly. Thus, it is difficult to reasonably estimate the longer-term potential market size for NGS platforms, as essentially the highly elastic nature of the market generates new demand.

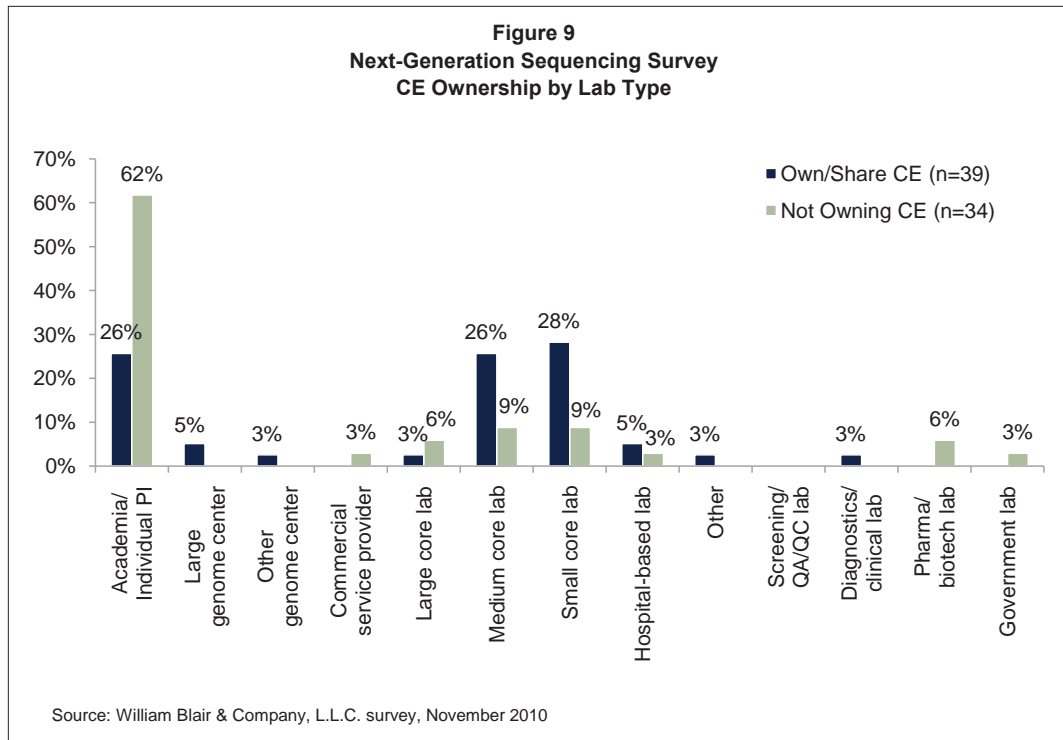
Minimally, in our view, Illumina and other next- and third-generation sequencing providers have the opportunity to convert the installed base of 15,000 ABI CE platforms to NGS. With an installed base of roughly 1,500 NGS machines, this represents a sizable opportunity, and therefore we attempted to ascertain users' CE utilization trends (e.g., whether CE sequencing utilization is going up or down, and why).

Our survey results were mixed, suggesting CE sequencing maintains a strong hold, which supports Life Technologies' comments that the dramatic decommissioning of CE machines that occurred over the past two years is largely complete. On the other hand, our survey suggests that there is still an underlying conversion of CE to NGS instruments under way.

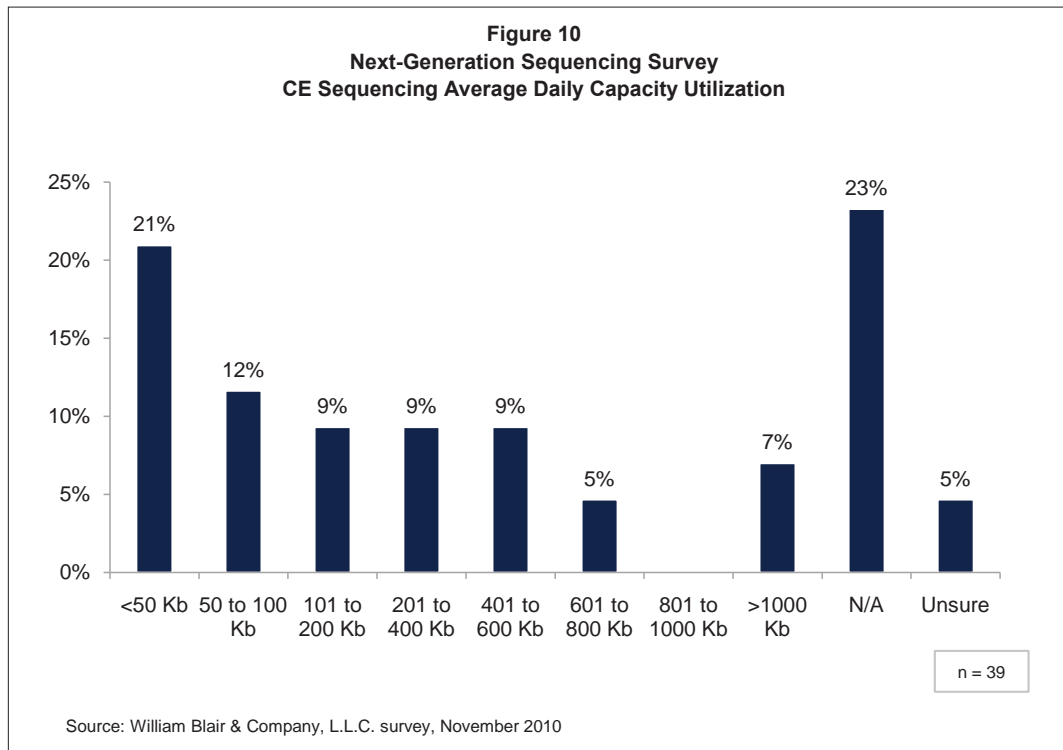
### CE Sequencing Platforms Maintain a Stronghold

Just over half of the respondents own or share a CE sequencing platform, with the ABI 3730xl the most popular platform (36% of total CE sequencers identified); 16% outsource their CE sequencing needs. As one would expect, academic/PIs are more likely to share equipment than core labs, which are more likely to own instruments.





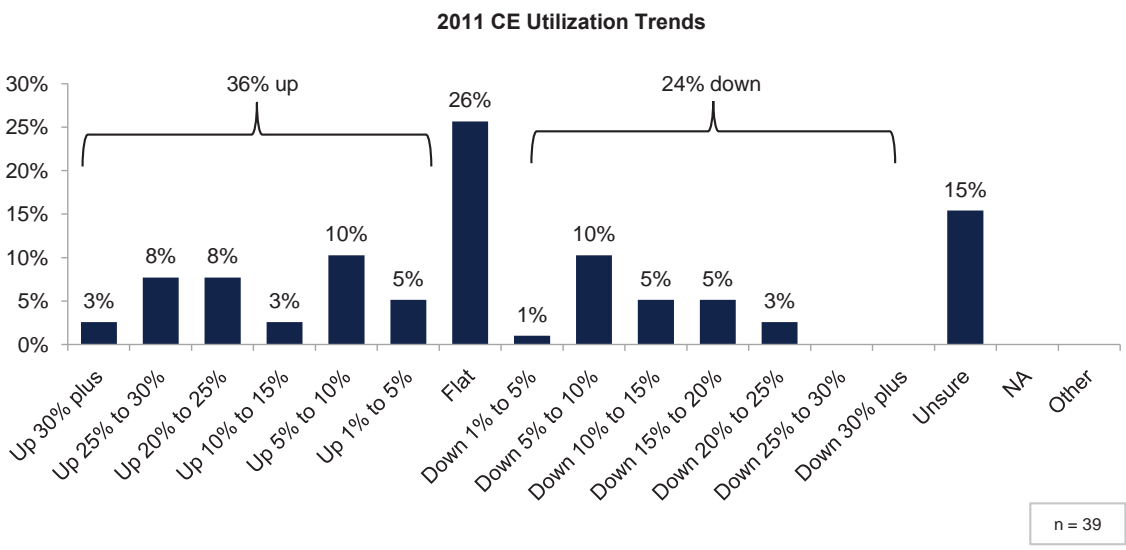
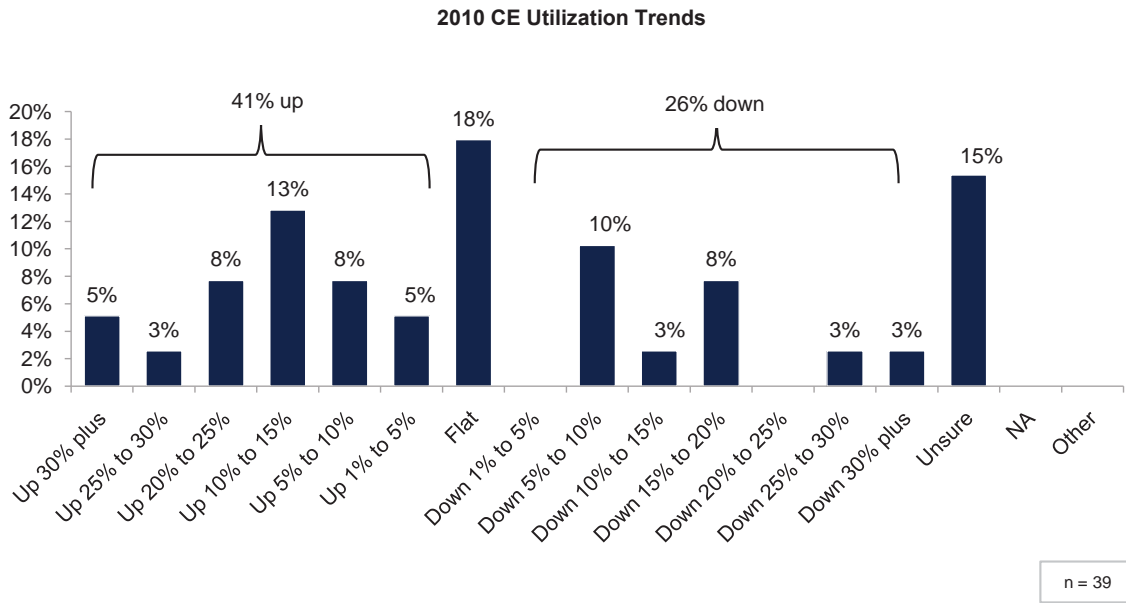
Most users process less than 800 Kb per day (21% said they process less than 50 Kb), with only 7% processing more than 1,000 Kb per day, which suggests most users are not using machines at full capacity. ABI's 3730xl, for example, can process 1,550 Kb per day using its StdSeq run module, whereas ABI's 3730 can process 775 Kb per day via StdSeq. These two machines represented 59% of total machines identified by respondents.



**CE Capacity Trends for 2010 and 2011 Mixed, but Skewed to the Positive**

Forty-one percent of respondents increased their CE reagent/consumable utilization in 2010, while 26% decreased their reagent usage and 18% saw no change in utilization. Responses were similar for 2011; 36% expect CE utilization to be up, 26% flat, and 24% down. We did not specifically ask respondents why they expected an increase in utilization in the survey; however, in our channel checks, lab managers overwhelmingly cited increased funding as the primary driver for the improved outlook next year.

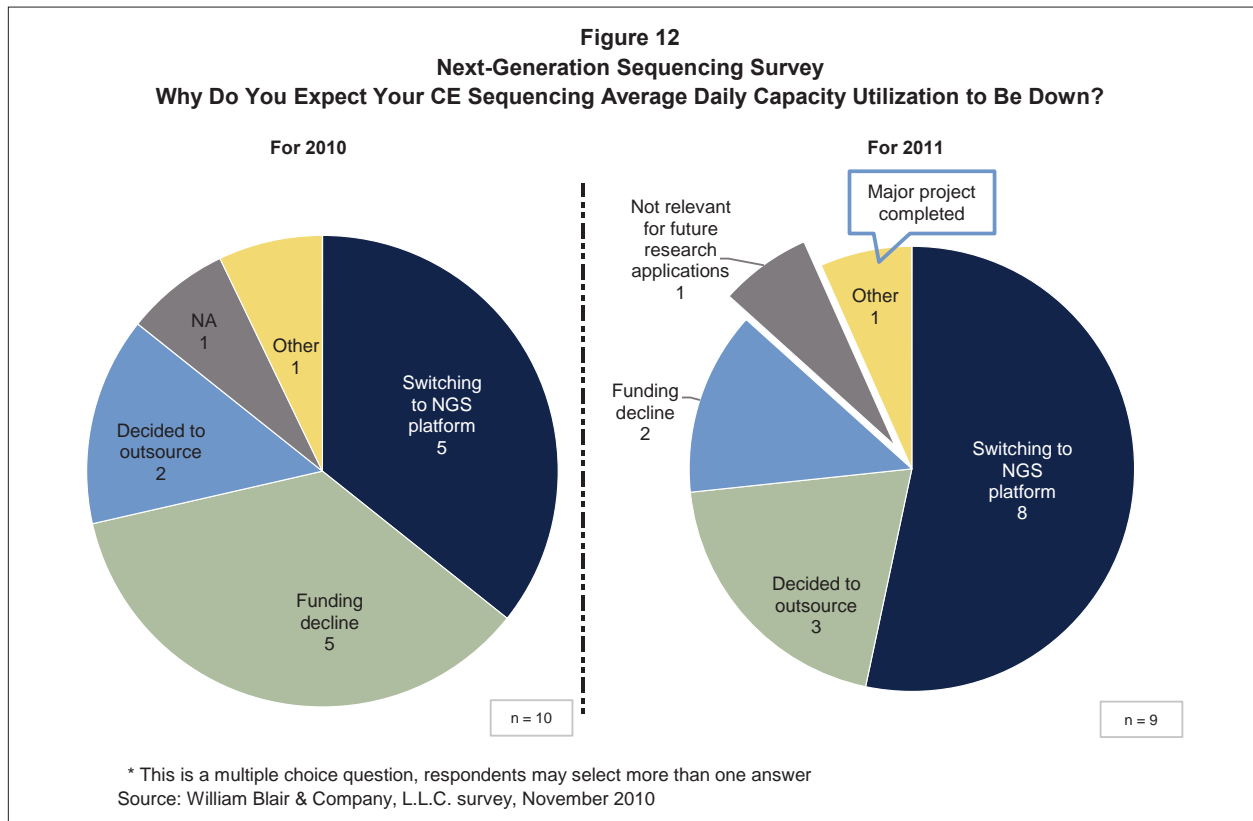
**Figure 11**  
Estimated CE Utilization in 2010 and 2011



Source: William Blair & Company, L.L.C. survey, November 2010

**Some Transitioning to NGS Platforms Is Still Taking Place**

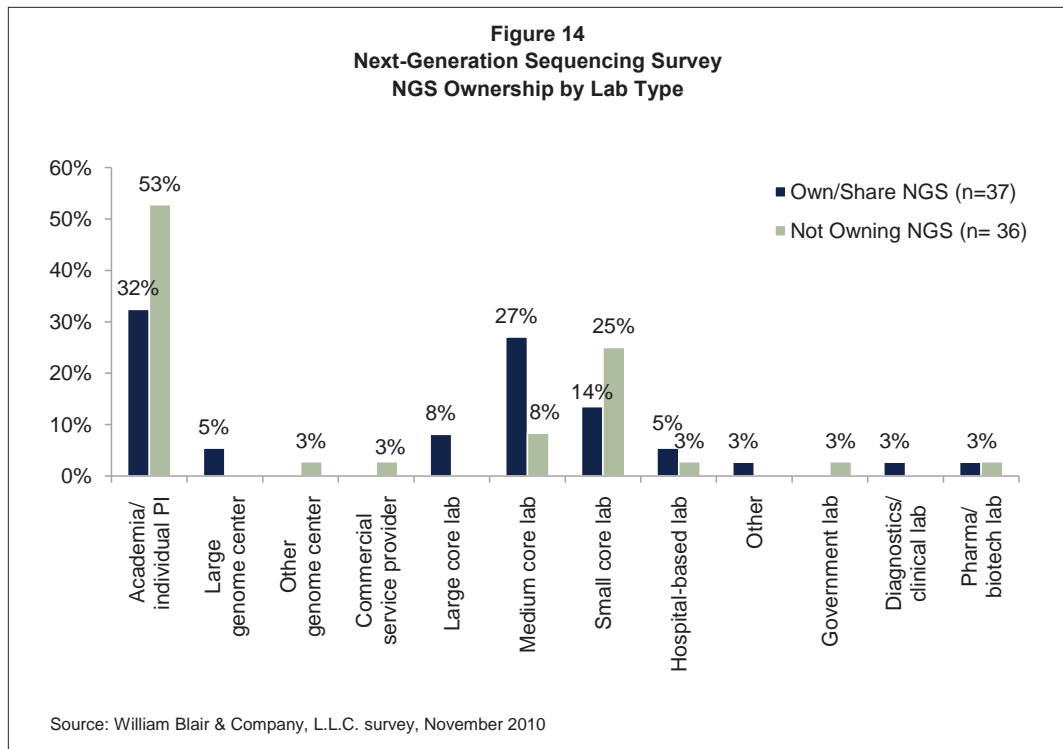
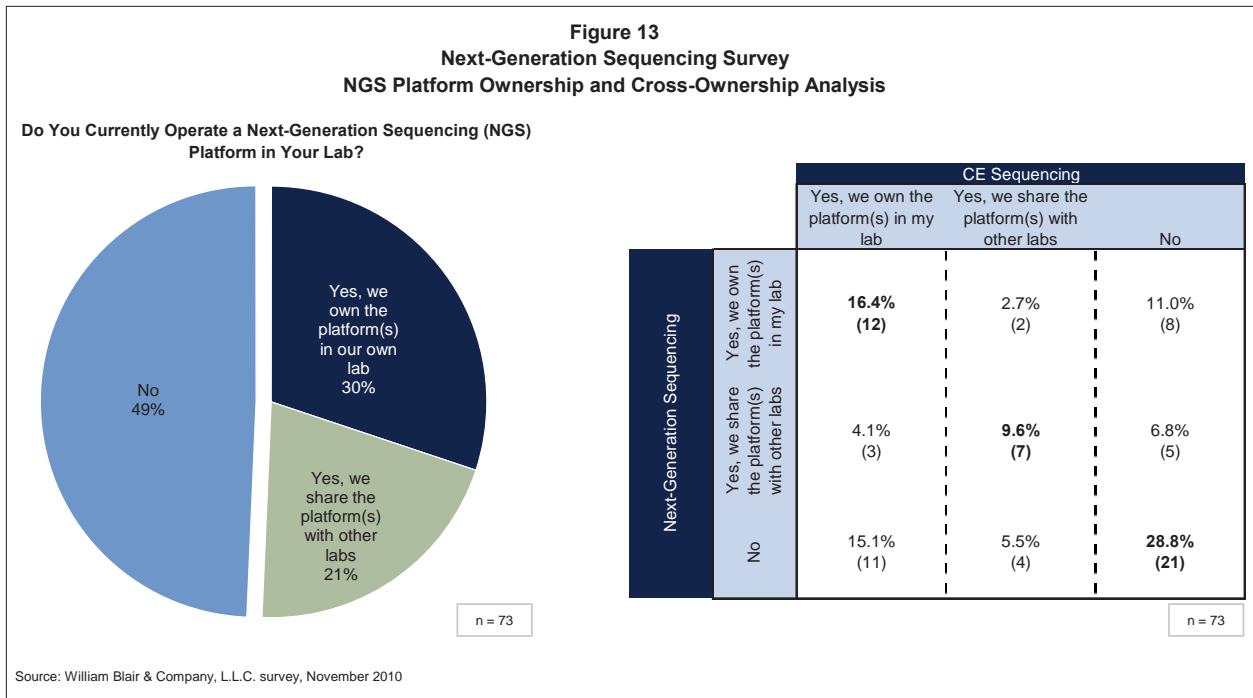
For respondents who experienced a decline in CE utilization in 2010 or expected a decline in 2011, the primary reason given was a decision to move to an NGS platform, particularly in 2011 (5 respondents in 2010 and 8 in 2011). While the sample size is small in this case (10 respondents indicated they expect their CE utilization to be down in 2010 and 9 in 2011), we believe this suggests there is still a conversion from CE to NGS under way. Respondents also cited a decision to outsource and funding declines as key drivers of the CE-based sequencing utilization decline. In our view, this points to the dynamic of the PI/smaller lab community, which is highly dependent on government funding and uses sequencing on a project-by-project basis.



**Part III. Next-Generation Sequencing User Experience and Trend Analysis**

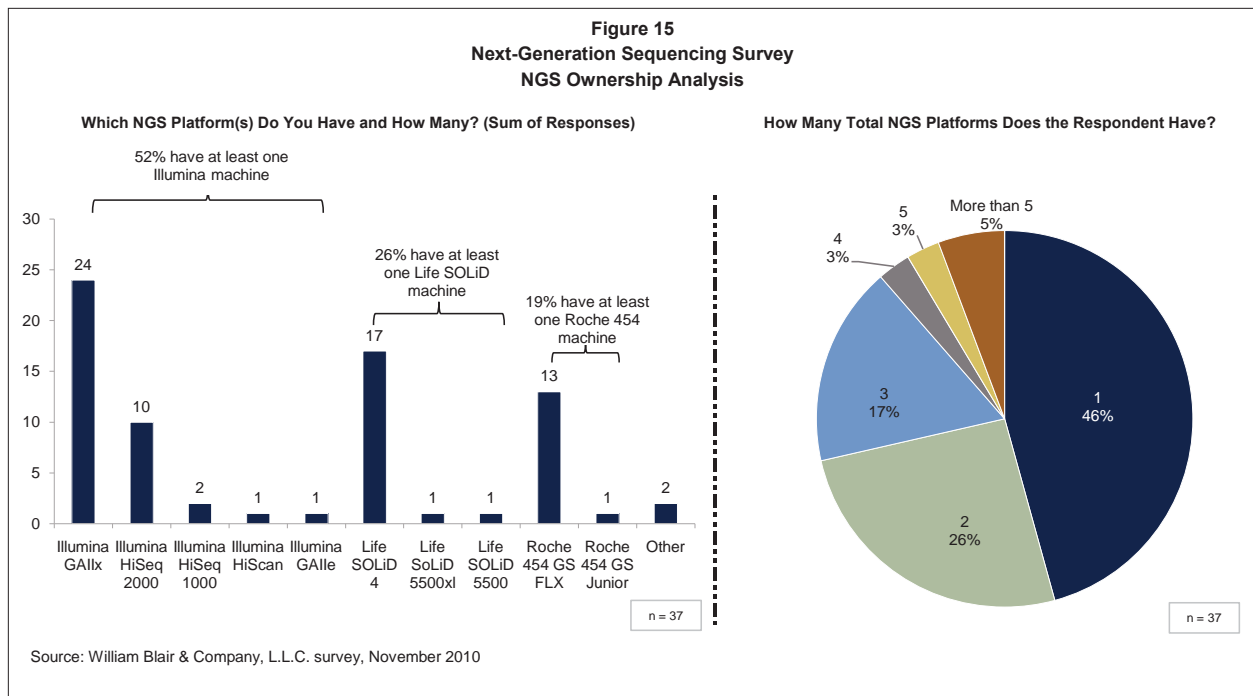
To assess potential NGS instrumentation and consumable utilization trends for 2011, we asked respondents to provide insight into which NGS platforms they maintained in their labs; what instruments they are likely to purchase, if any, in 2011 and longer term; and, if they own or share an NGS platform, how they expect capacity and consumable utilization to trend over the next year.

Among our survey respondents, just over 50% own or share at least one next-generation sequencer in their labs. The respondents who own or share both platforms vary in size, including core labs (49), academic/individual PI labs (32), large genome centers (5), hospital-based labs (5), and diagnostics/clinical labs (3). As expected, large core labs and genome centers are more likely to own (rather than share) an NGS platform.



**Responses Support NGS Market Share Estimates; Illumina the Most Widely Adopted**

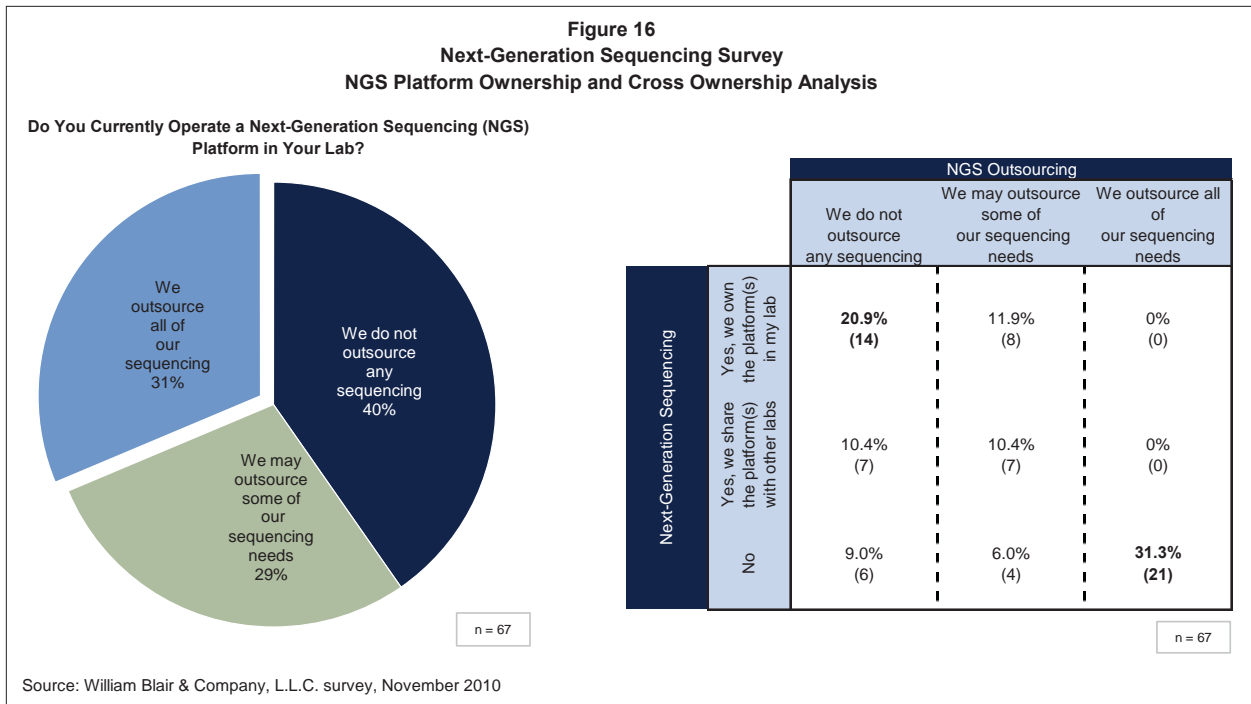
Illumina is the most widely adopted next-generation platform (we estimate the company has 60% of the NGS market) and, as expected, represented the most widely owned NGS platform in our survey. Of the 73 NGS platforms identified, 52% were Illumina machines (mostly GAIIX platforms), 26% were Life SOLiD machines, and 19% were Roche 454 platforms. Not surprisingly, given the weight of respondents toward small/midsize core and academic labs, the overwhelming majority own or share three NGS machines or fewer, with most respondents (46%) owning one machine.



**Many Labs Outsource NGS Needs, Even Those That Own an Instrument**

The respondents who do not own or share an NGS platform are more likely to outsource their NGS needs; however, those who own platforms also outsource sequencing in some cases (12%). While we did not ask this specific question in the survey, our channel checks suggest users who outsource next-generation sequencing may choose to do so because of capacity issues (e.g., an unexpected project arises) or because a different platform is desirable for a specific project. In terms of where samples are sent, researchers use a range of sources: core labs (46%), for-profit service providers (30%), and nonprofit service providers (24%).

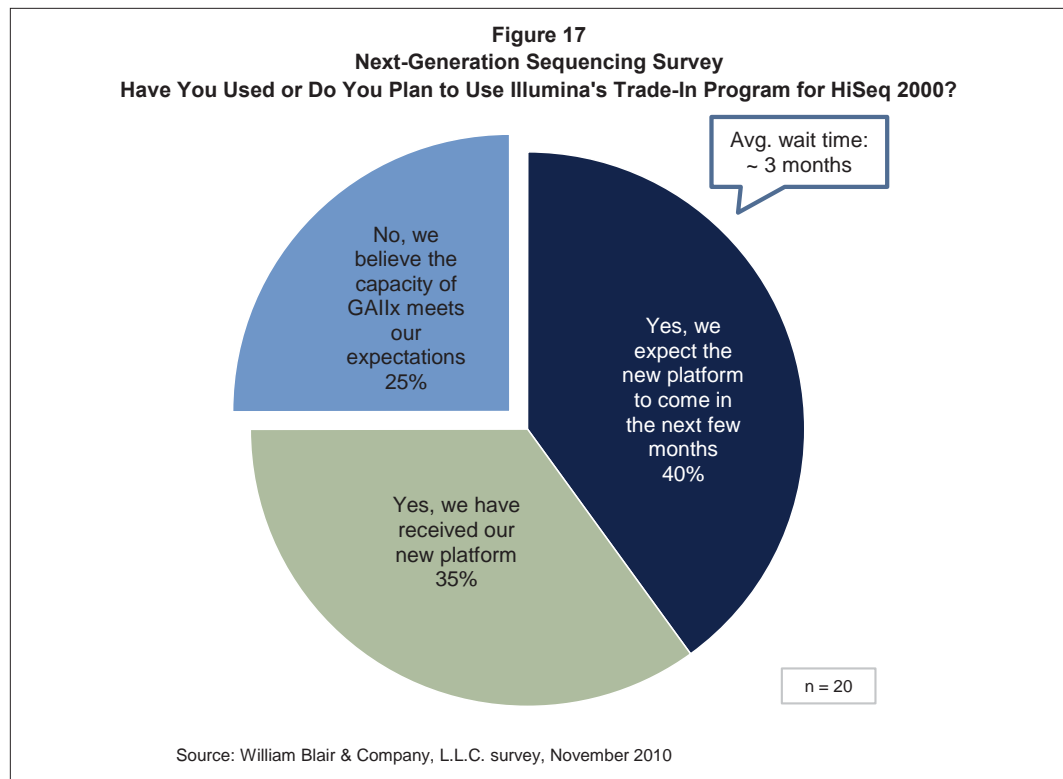
While the purpose of this specific survey was not to assess outsourcing trends, our channel checks suggest for-profit sequencing service providers have been gaining traction as a result of the following: 1) capacity constraints at large genome centers (such as the Broad Institute, the Dana-Farber/Harvard Cancer Center, the Genome Center at Washington University, etc.), 2) not-for-profit service providers may not be allowed to accept sequencing projects from non-academic organizations, and 3) some for-profit service providers have begun to provide more sample prep and data analytics support (such as Complete Genomics and Cofactor Genomics) or have a fleet of experienced bioinformaticians (such as the National Center for Genome Resources).



**Illumina’s Trade-In Program Appears on Track to Be Mostly Complete by First Quarter 2011**

When Illumina introduced the HiSeq in January 2010, the company offered a trade-in program for researchers that had ordered or received a Genome Analyzer in fourth quarter 2009 (where they received a credit for the full cost of the Genome Analyzer toward the HiSeq) or received an instrument before fourth quarter 2009 (where they received a \$150,000 credit). According to management’s comments, better-than-expected trade-in volume has partly driven the success of HiSeq 2000 market penetration, and the company expects to realize the full impact of the trade-in program by the first half of 2011. Although the GAllx-to-HiSeq trade-in program bodes well for future consumable sales (since the HiSeq is expected to use roughly double the amount of reagent that the GAllx used), the conversion will likely drive some margin compression in the nearer term.

Of the 20 respondents that own a GAllx, 15 (or 75%) indicated they expect to take advantage of Illumina’s HiSeq trade-in program. Seven respondents have received their platform(s) and eight expect to receive their machine in six months or less (with an average wait time of about three months). Some respondents indicated they expect to keep both platforms (GAllx and HiSeq), but have negotiated a better price on the HiSeq. Thus, our survey results seem to support the notion that the majority of the trade-in program should be complete by the first half of next year and most likely by the end of first quarter 2011.



### **NGS Capacity and Consumable Utilization Trends Appear Positive, Particularly for the HiSeq**

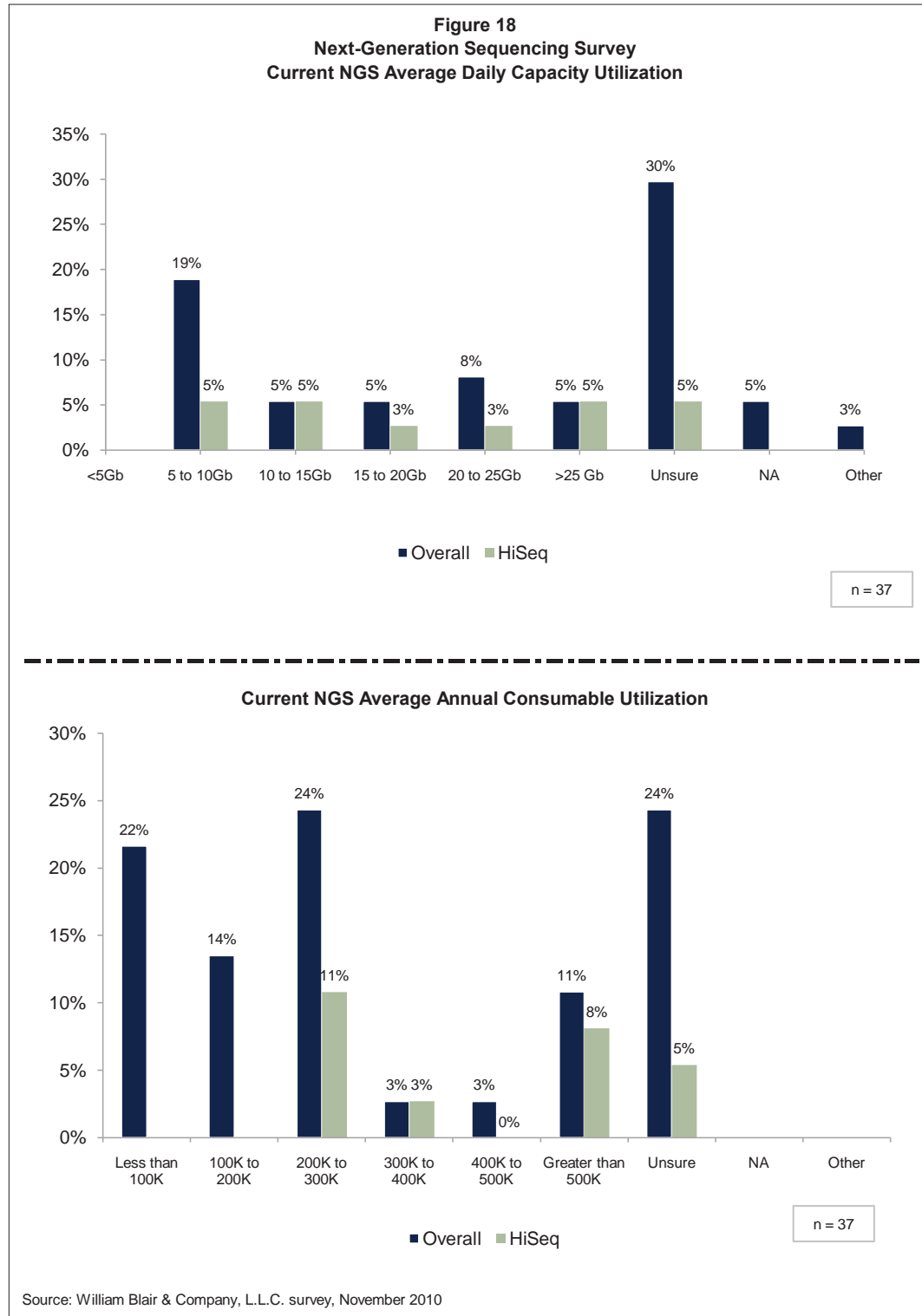
Average daily capacity utilization is highly correlated with lab size in our survey: the higher the volume, the larger the lab size. As illustrated in figure 18, capacity utilization for overall NGS and HiSeq users was fairly evenly distributed and ranged from 5 to 10 Gb per day to greater than 25 Gb per day.

Our survey included responses from 10 HiSeq users, which were more weighted toward smaller labs (medium core labs and academic/individual PIs). Many users own multiple NGS machines and thus it is difficult to assess specific per-machine HiSeq usage, and we admittedly have a small sample size to analyze. Most HiSeq users cited annual consumable usage of at least 200,000 to 300,000 or more; three HiSeq owners cited annual consumable usage of 500,000 or more—all respondents had one HiSeq in their lab.

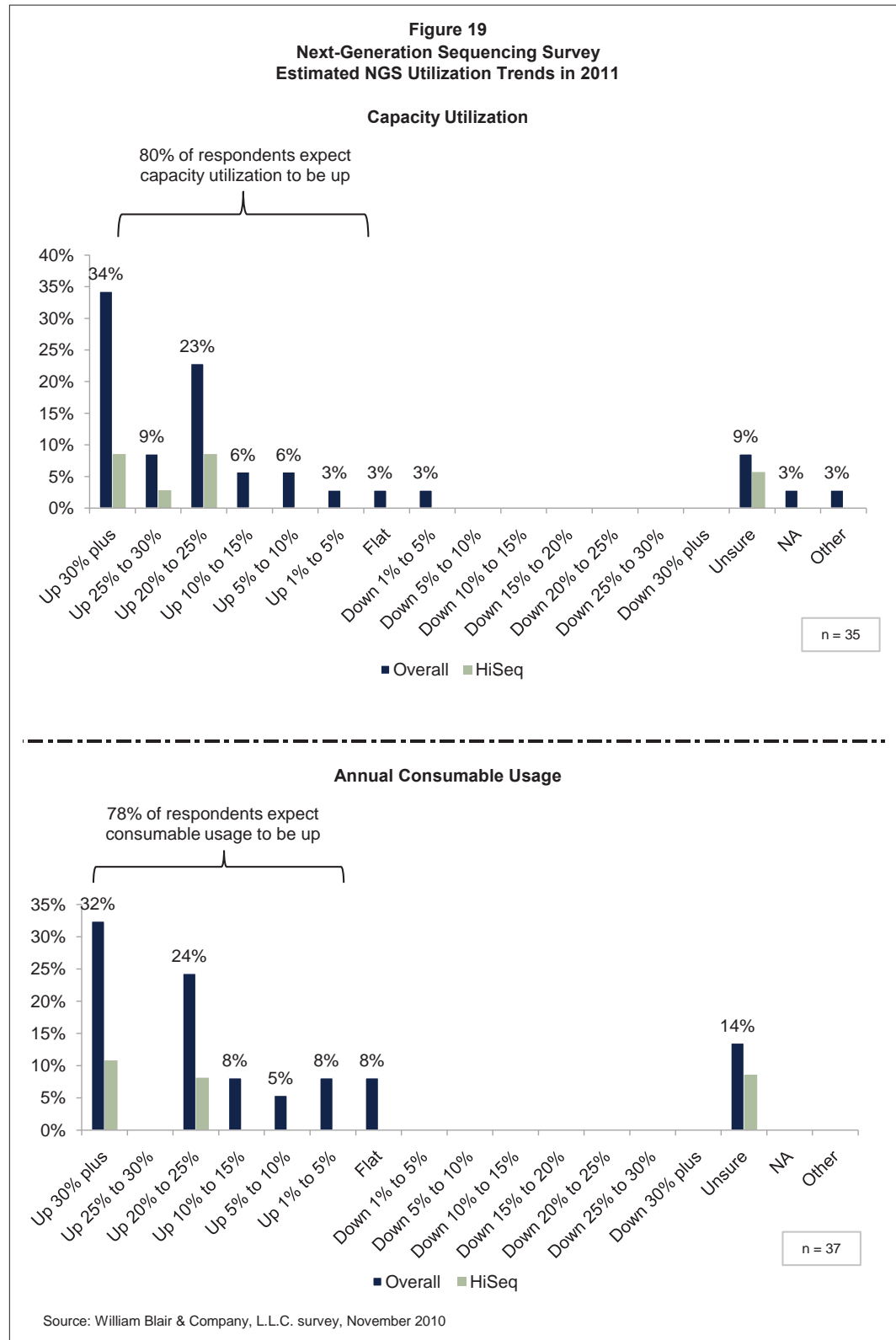
***NGS-related utilization and consumable usage trends appear positive for 2011 and particularly for the HiSeq (although it is early in the product life cycle).*** Of the 37 respondents with an NGS platform, 80% expect their NGS utilization to be up in 2011. Seventy-eight percent of respondents expect 2011 consumables spending to be up from 2010, with 32% pointing to growth in reagent usage of more than 30%.

Trends look even more positive for HiSeq users. As stated above, our survey included responses from 10 HiSeq owners, more weighted toward smaller labs and with many users owning multiple NGS machines. Still, survey responses and subsequent follow-up support the notion that HiSeq consumable usage should be at least roughly double that of the Genome Analyzer (or in the \$300,000 to \$400,000 range on average), as the average annual per HiSeq consumable usage for these specific HiSeq users appears to be around \$300,000. We have assumed average per HiSeq reagent usage of \$315,000 in 2011 and \$350,000 in 2012.

In our view, this bodes well for the overall average per HiSeq machine consumable usage considering most HiSeq instruments shipped to date reside in genome centers or large core labs, which should have much higher utilization rates (and thus reagent usage) than those in smaller labs. Given that researchers are just receiving HiSeq machines, we also expect some ramp-up time.



As illustrated in figure 19, the majority of NGS users (80% of 35 respondents) expect their NGS daily capacity to trend upward in 2011 and 78% (of 37 respondents) expect an increase in annual consumable utilization.

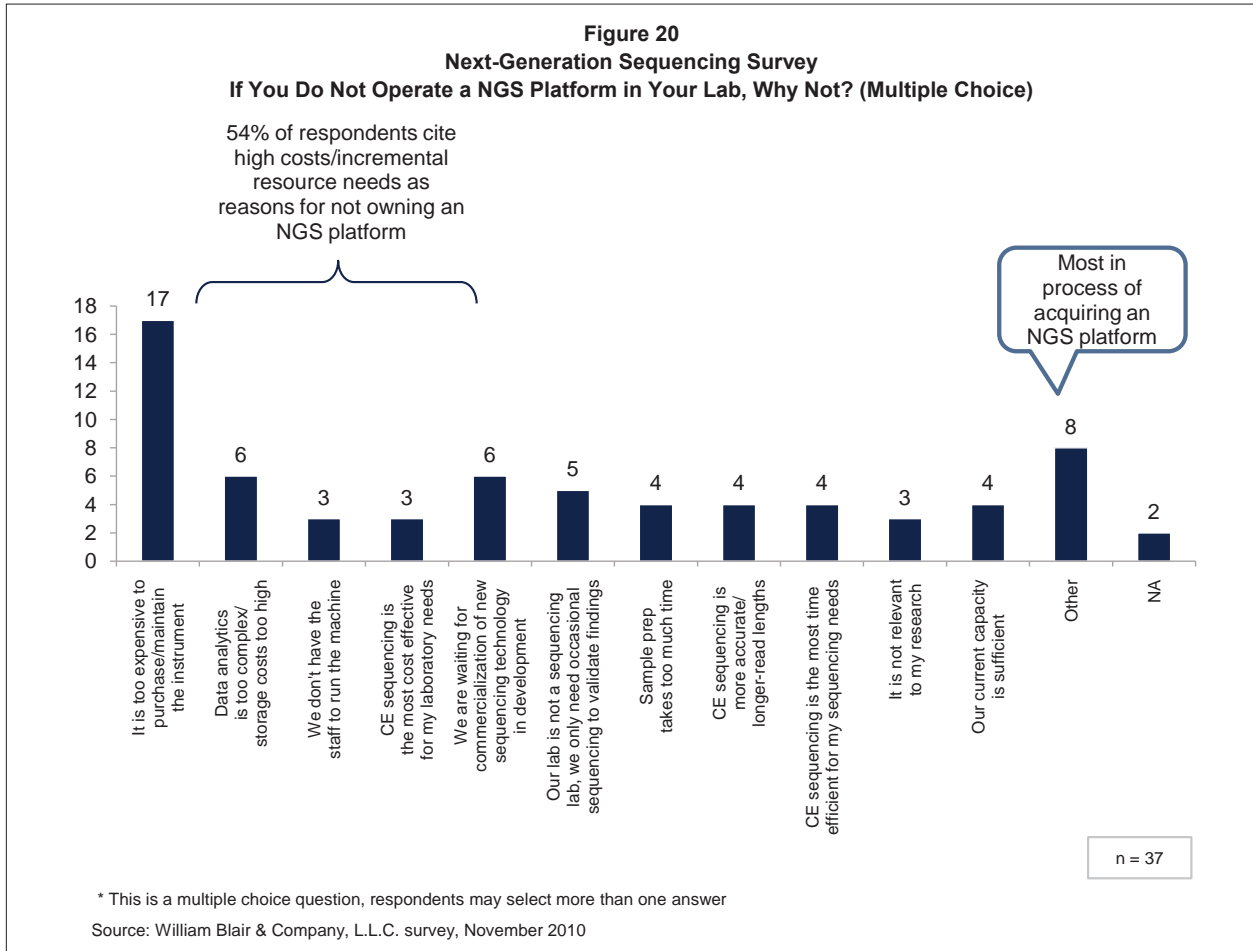


Trends look even more positive for HiSeq users, with the majority of respondents expecting capacity to be up 20% or more in 2011. In fact, *all users who expect consumables spending to increase more than 30% in 2011 operate at least one Illumina instrument.* Again, it is early in the product cycle for the HiSeq as users begin to implement and validate the systems; however, consumable utilization trends on the HiSeq thus far look encouraging.

Our sensitivity analysis suggests that consumable utilization represents by far the greater upside opportunity (compared with machine sales), and thus, in our view, these results bode well for Illumina’s growth prospects in 2011. We estimate consumable upside could add \$0.10 to our adjusted 2011 EPS estimate of \$1.46 for Illumina (assuming an average annual consumable usage of \$400,000 per HiSeq at a gross margin of 65%).

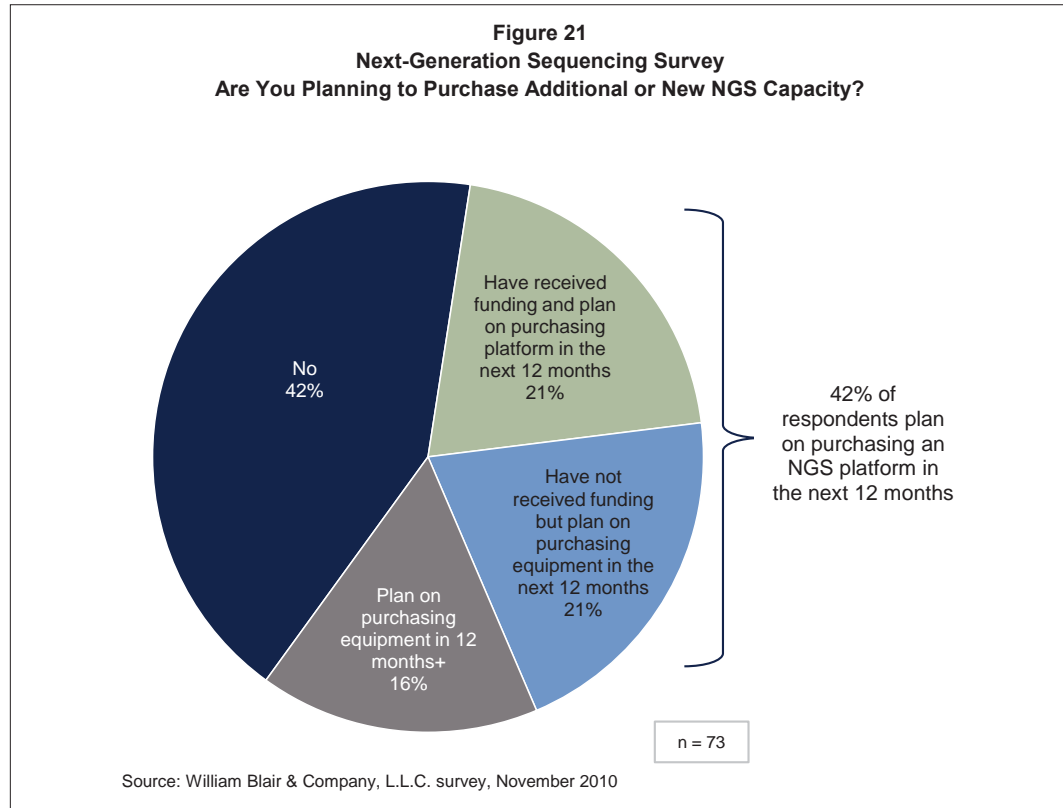
**Incremental Costs Are the Largest Barrier to Adoption of NGS Platforms**

Many respondents cited expenses as a reason not to purchase an NGS platform, including both the cost of maintaining the instrument (17 respondents) and incremental resource needs (12), which we believe points to the high elasticity of the demand curve. Interestingly, only a few users (6) indicated they were waiting for commercialization of new technology before purchasing a sequencing platform.



## Part IV. Next-Generation Sequencing Future Purchasing Trends

In addition to consumable utilization patterns, we also sought to determine future instrumentation purchasing trends. A total of 42% of respondents (30 respondents) plan to purchase an NGS platform in the next 12 months, half of whom have already secured funding for the purchase, while the other half are still waiting for the funding. In addition, 16% of respondents, though interested, intend to purchase an instrument in more than 12 months.



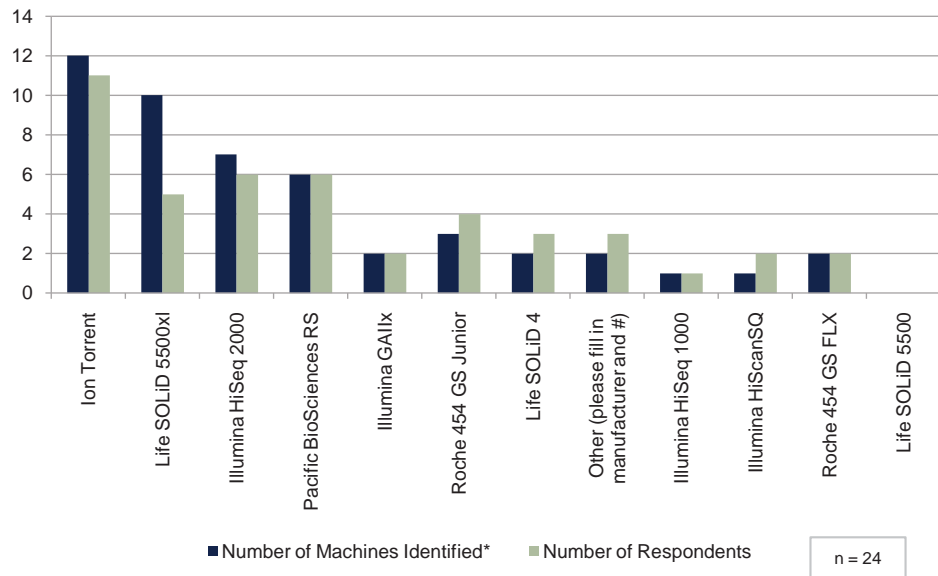
### Illumina's HiSeq and Life's 5500xl Are the Most Popular Platforms

In terms of NGS platform interest, Illumina's HiSeq and Life's 5500xl were clear winners. Of the 49 total NGS machines respondents plan to purchase in the next 12 months, 22% (or 11) are Illumina instruments, including 7 HiSeq 2000 machines, 1 HiSeq 1000, 1 HiScanSQ, and 2 GAllx platforms.

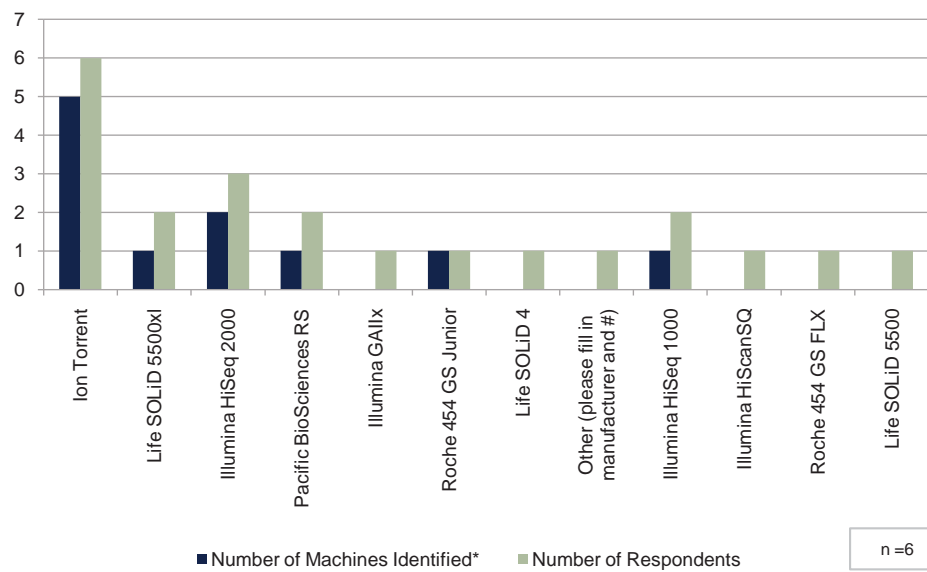
We suspect some of the 5500xl machines identified (20% of the total, or 10 machines) reflect SOLiD 4 upgrades. In early November, Life Technologies introduced a new platform, the 5500xl, which replaces the SOLiD 4 and is in lieu of a previously announced upgrade to the SOLiD 4 (the SOLiD 4hq). The 5500s will be available on a broader scale in first quarter 2011. Existing SOLiD 4 customers who had already purchased the HQ upgrade or planned to do so will receive the 5500xl instead and can keep their existing SOLiD 4 instrument for at least three months at no additional cost. Among the 10 5500xl instruments, we estimate 7 could be SOLiD 4 trade-ins (in other words, respondents currently own a SOLiD 4), with one large order from a research hospital lab.

**Figure 22**  
**Next-Generation Sequencing Survey**  
**NGS Platform Future Purchasing Trends**

**Future Sequencing Platforms (Next 12 Months)**



**Future Sequencing Platforms (More Than 12 Months)**



\* Respondents entered 0 if number of machines to be purchased is unknown

Note: Respondents could select more than one platform

Source: William Blair & Company, L.L.C. survey, November 2010

Table 1 outlines purchasing trends for the next 12 months in more detail. In terms of funding status, respondents selecting Illumina are more likely to have received funding already (six respondents) versus Ion Torrent (five respondents), PacBio RS (two respondents), Roche GS FLX (two respondents), and Life SOLiD 5500xl (two respondents).

The majority of respondents who expressed interest in Life's SOLiD 5500xl are still in the process of receiving funding approval, which makes sense given the introduction of the 5500 was only recently announced. In addition, all six of the respondents who indicated their intention to purchase a HiSeq 2000 in the next 12 months worked at academic/PI labs; this supports Illumina's management commentary that the company is gaining traction with the HiSeq outside the genome centers.

**Table 1**  
**Next-Generation Sequencing Survey**  
**Next-12-Month Purchasing Trends for Next-Generation Sequencers**

	Will Purchase in Next 12 Months, Have Received Funding		Will Purchase in Next 12 Months, Have Not Received Funding		Total Machines Identified
	Number of Respondents, Number of Machines Known	Number of Respondents, Number of Machines Unknown	Number of Respondents, Number of Machines Known	Number of Respondents, Number of Machines Unknown	
Illumina HiSeq 2000	6	1	1	0	7
Illumina HiSeq 1000	0	0	1	0	1
Illumina GAllx	0	0	2	0	2
Illumina HiScanSQ	0	1	1	0	1
Roche 454 GS FLX	2	0	0	0	2
Roche 454 GS Junior	0	0	4	0	4
Life SOLiD 5500xl	2	0	9	0	11
Life SOLiD 5500	0	0	0	0	0
Life SOLiD 4	0	0	2	0	2
Pacific BioSciences RS	2	0	4	0	6
Ion Torrent	5	0	7	0	12
Other (please fill in manufacturer and #)	0	0	2	0	2

Academic/  
PIs

2 of 7 potential GAllx upgrades

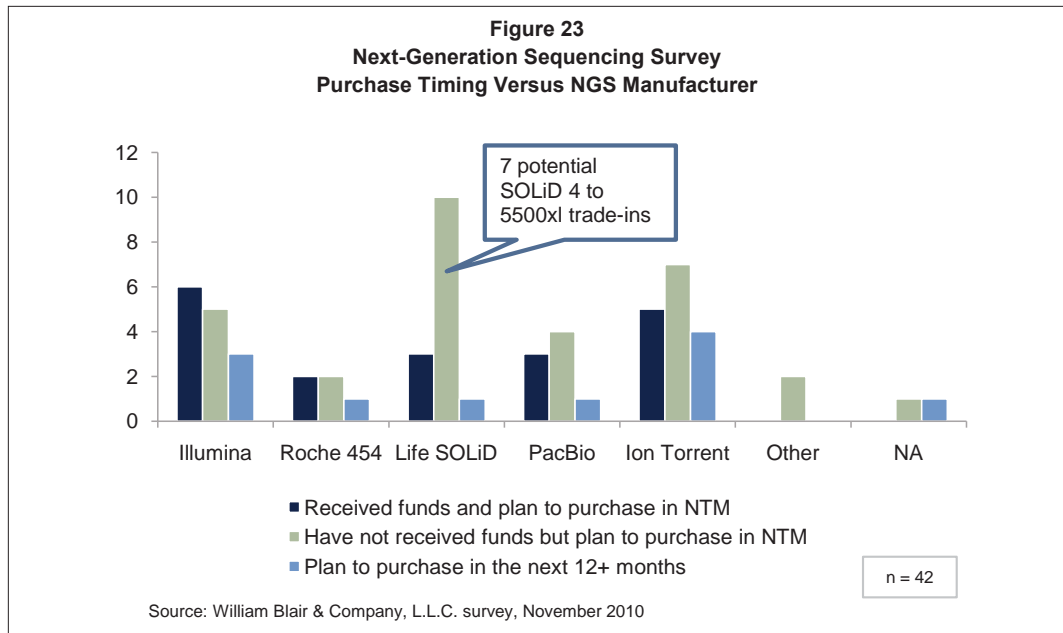
Early access programs ?

Early access programs ?

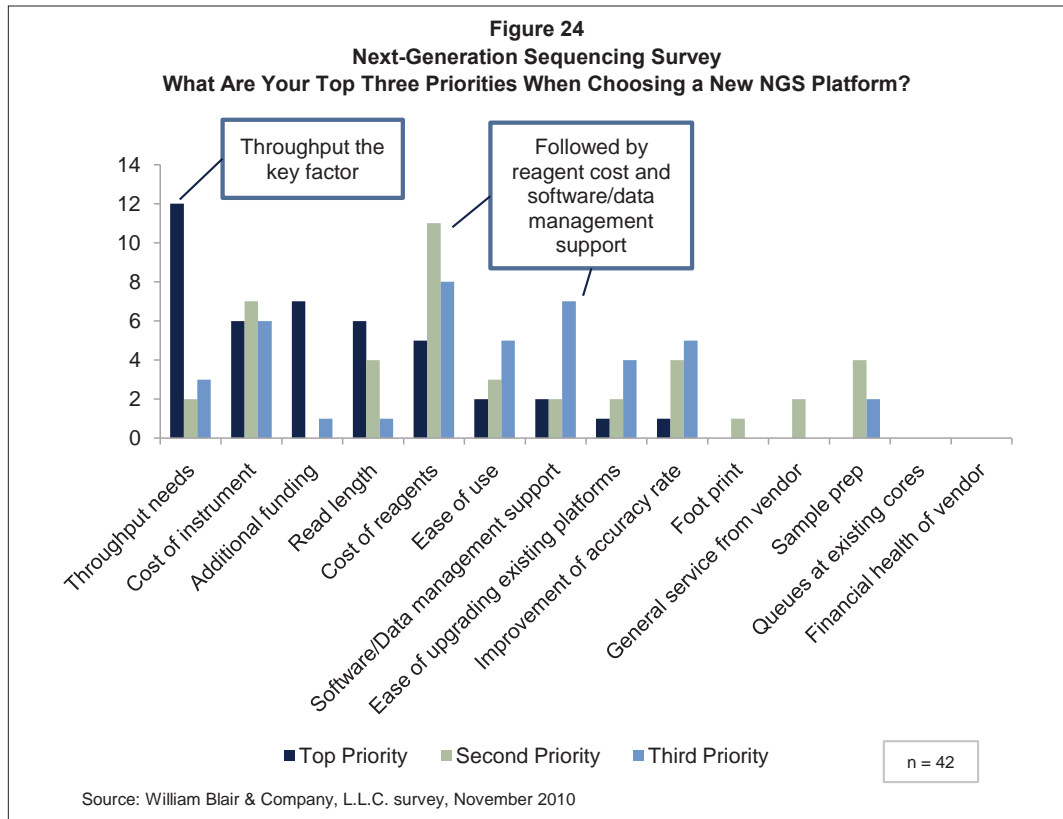
7 of 8 potential upgrades from SOLiD 4

n = 33

Source: William Blair & Company, L.L.C. survey, November 2010



**Throughput, Reagent Cost, and Data Support Are Key Factors in Purchasing Decisions**  
 We also asked respondents to rate their top three priorities when evaluating a new NGS platform. Respondents overwhelmingly agree that throughput is the most important factor at this stage. Cost of reagents was also a commonly cited factor, as well as data support. In our view, these results help explain the interest in the HiSeq (which offers the highest throughput at 200 Gb per run, versus the SOLiD 4 at up to 100 Gb per run) and in Life’s 5500xl, which will offer throughput close to the level of the HiSeq (at up to 180 Gb per run for microbeads). Interestingly, financial health of the vendor was not a factor at all, which bodes well for the some of the earlier-stage companies not backed by a more-established player.



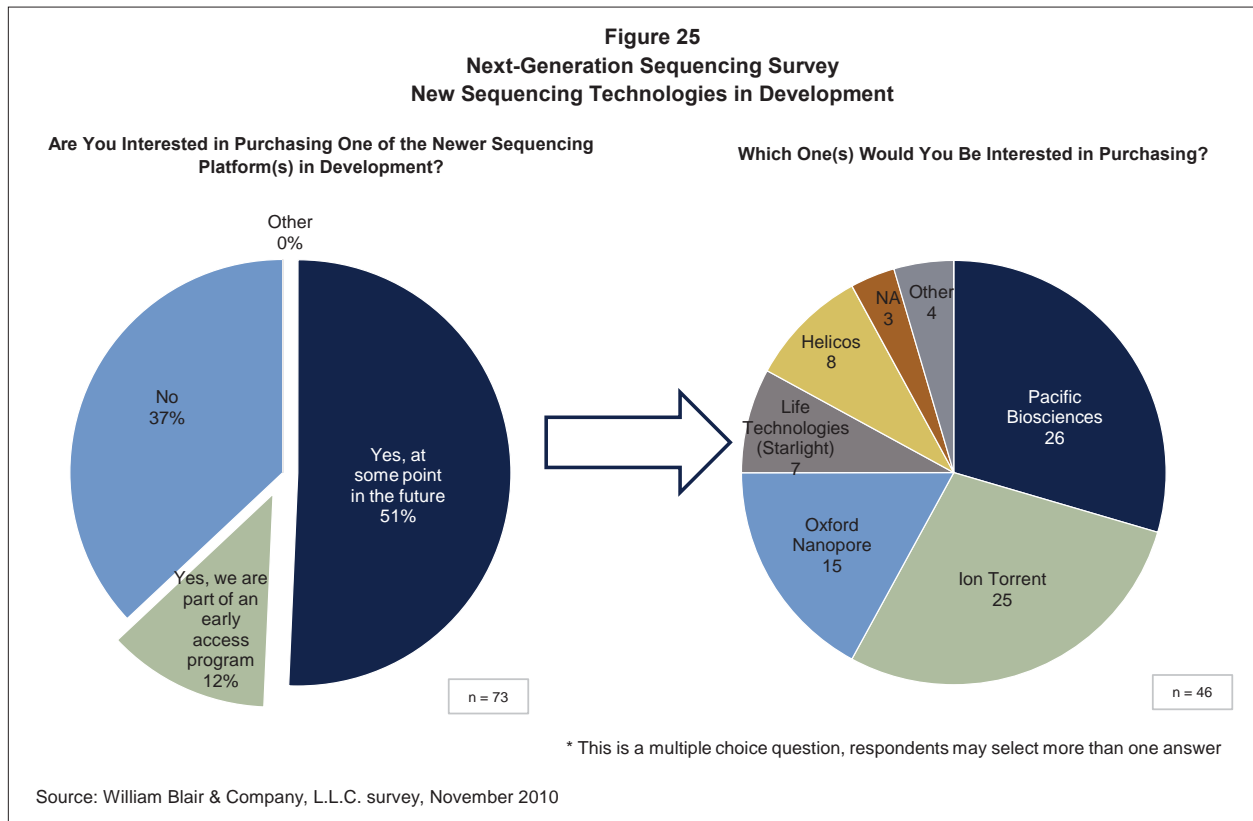
**Pacific Biosciences, Ion Torrent, and Oxford Nanopore Are Generating a Lot of Interest**

A number of third-generation vendors (including Pacific Biosciences, Life Technologies through Ion Torrent and Starlight, Halcyon, and Oxford Nanopore) have generated quite a bit of buzz at industry conferences, promising longer read lengths, higher quality, and higher throughput—all at a low cost. It is early in the life cycle of these companies and most do not have instruments available commercially, although Pacific Biosciences and Life Technologies (through Ion Torrent) have early access programs in place.

In early December, Life Technologies released initial specs for Ion Torrent's Personal Genome Machine (PGM); it will generate 100,000 single reads per run, at a read length of 100 to 200 base pairs and an accuracy rate of 99%, resulting in throughput starting at 10 Mb per run. The company has an early access program under way and began shipping machines worldwide in late 2010. The system costs \$49,500 (not including a \$16,500 data server).

Pacific Biosciences also recently released beta specs for its RS system (\$695,000 ASP). The company has shipped 11 instruments to early access customers, and beta instruments are generating read lengths of 700 to 750 bases and a raw accuracy of 80% to 85% and consensus accuracy of 99.99%. The company is targeting a commercial rollout in the first half of 2011.

The excitement around these platforms was reflected in our survey. Twelve percent of respondents (or 9 respondents) indicated they were part of an early access program and another 49% indicated they would be interested in one of the newer technologies at some point in the future. Respondents cited Pacific Biosciences (30%), Ion Torrent (28%), and Oxford Nanopore (17%) as platforms of interest.



The strong interest in Ion Torrent (Life's) PGM may have been driven by its recent launch. The PGM costs significantly less (at \$49,500) than other NGS platforms and has much shorter run times (an hour) but also lower throughput (starting at 10 Mb per run). In our view, the lower entry point enables more professionals (and not limited to the genomic research field)

to embrace the technology. Given its low throughput and fast run times, we believe it is more likely to be used for targeted resequencing and potentially microbial genome sequencing (rather than whole human genome sequencing), and thus will likely complement instead of cannibalize Illumina's market opportunity.

## Conclusion

In summary, our survey suggests that NGS instrument and consumable usage trends (as well as funding trends) appear positive for 2011, which bodes well for NGS manufacturers, given the high-margin, recurring nature of consumable-based revenue. Finally, future purchasing trends were positive for both Illumina platforms (representing 22% of future machines identified) and Life Technologies' 5500xl (20% of machines identified). Respondents also demonstrated significant interest in Life Technologies' Ion Torrent (representing 24% of identified machines), Pacific Biosciences' RS platform (12% of machines identified), and Oxford Nanopore.

Additional information is available upon request.

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DJIA: 11,722.89  
 S&P 500: 1,276.56  
 NASDAQ: 2,702.20

The prices of the common stock of other public companies mentioned in this report follow:

Complete Genomics, Inc.	\$8.04
Illumina, Inc. (Outperform)	\$66.00
Life Technologies Corporation	\$56.58
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