High-yield, Scalable Library Preparation with the NEBNext® Ultra™ II FS DNA Library Prep Kit

Improving performance, ease of use and reliability of enzymatic DNA fragmentation

Introduction

The continued expansion of the use of next gen sequencing depends in large part on overcoming the limitations and bottlenecks associated with high-quality library preparation. The requirement for numerous steps and expensive equipment can result in sample loss, errors and limited throughput. To address these issues, we have built upon our NEBNext Ultra II DNA library prep workflow to create a kit that includes a fragmentation system: the NEBNext Ultra II FS DNA Library Prep Kit. This kit integrates a new enzymatic DNA fragmentation reagent into the library prep workflow, such that fragmentation is combined with end repair and dA-tailing. The combination of these reactions eliminates the need for equipment to shear DNA mechanically and also reduces the number of sample transfers and losses. Subsequently, adaptor ligation is also carried out in the same vial, after which a single cleanup step is performed. For low input samples, PCR amplification is performed prior to sequencing.

Importantly, the enzymatic shearing of DNA with the FS kit does not introduce bias into the library, and the kit is suitable for input DNA from the full range of GC content. The reduced sample loss and increased efficiencies of the workflow enable use of lower input amounts, with a range of 100 pg – 0.5 µg, and insert sizes of 100 bp to 1kb can be generated.

Here we demonstrate the utility of the NEBNext Ultra II FS DNA Library Prep Kit for DNA fragmentation and library construction from a variety of sample types and for a number of applications.

Workflow

The NEBNext Ultra II FS DNA Library Prep Kit protocol, including fragmentation, is fast (~ 2.5 hours) and simple, and can accommodate 100 pg to 0.5 µg of input DNA (Figure 1). Fragmentation, End Repair and dA-Tailing reagents are combined, and there is no clean-up before adaptor ligation. The same fragmentation protocol is followed for all input amounts and for all GC contents. The kit also includes options for PCR-free workflows. The protocol is compatible with adaptors and primers from the NEBNext product line ("NEBNext Oligos") or from other sources.

NEBNext Ultra II FS DNA Library Prep Kit for Illumina® (NEB #E7805) kit components:

- NEBNext Ultra II FS Enzyme Mix
- NEBNext Ultra II FS Reaction Buffer
- NEBNext Ultra II Ligation Master Mix
- NEBNext Ligation Enhancer
- NEBNext Ultra II Q5 Master Mix
- TE Buffer (1X)

NEBNext Ultra II FS DNA Library Prep with Sample Purification Beads (NEB #E6177) kit components:

- NEBNext Ultra II FS Enzyme Mix
- NEBNext Ultra II FS Reaction Buffer
- NEBNext Ultra II Ligation Master Mix
- NEBNext Ligation Enhancer
- NEBNext Ultra II Q5 Master Mix
- TE Buffer (1X)
- NEBNext Sample Purification Beads

FIGURE 1:
NEBNext Ultra II FS DNA workflow

	Fragmentation/ End Repair/ dA-Tailing	Adaptor Ligation	Clean Up/ Size Selection	Amplification	Clean Up	Total Workflow
Hands-On	2 min.	1 min.	5 min.	0–1 min.	0–5 min.	**8–14 min.**
Total	37–62 min.	16–31 min.	27–37 min.	0–34 min.	0–27 min.	**1.3–3.2 hr.**

Increased Library Yields

The use of enzymatic fragmentation can result in higher library yields than workflows incorporating mechanical shearing of DNA, due to both reductions in sample loss and decreased DNA damage. The NEBNext Ultra II FS kit further increases library yields through the integration of the fragmentation reagent with end repair and dA-tailing reagents (thereby minimizing loss during transfer steps), by not requiring a clean-up step before adaptor ligation, and through the high reaction efficiencies of each step in the workflow.

Achieving sufficient library yields for high quality sequencing from very low input amounts can be especially challenging with mechanical shearing of DNA, a situation compounded by the preference to amplify libraries using as few PCR cycles as possible. The NEBNext Ultra II FS kit overcomes this low-input challenge, and users can now obtain higher library yields with input amounts as low as 100 pg of human genomic DNA, as shown in Figures 2 and 3.

FIGURE 2: **NEBNext Ultra II FS DNA produces the highest yields, from a range of input amounts**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts and numbers of PCR cycles shown. For NEBNext Ultra II FS, a 20-minute fragmentation time was used. For Kapa™ HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, and a 20-minute fragmentation time was used. Illumina® recommends 50 ng input for Nextera®, and not an input range; therefore, only 50 ng was used in this experiment. "Covaris®" libraries were prepared by shearing each input amount in 1X TE Buffer to an insert size of ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Error bars indicate standard deviation for an average of 3–6 replicates performed by 2 independent users.

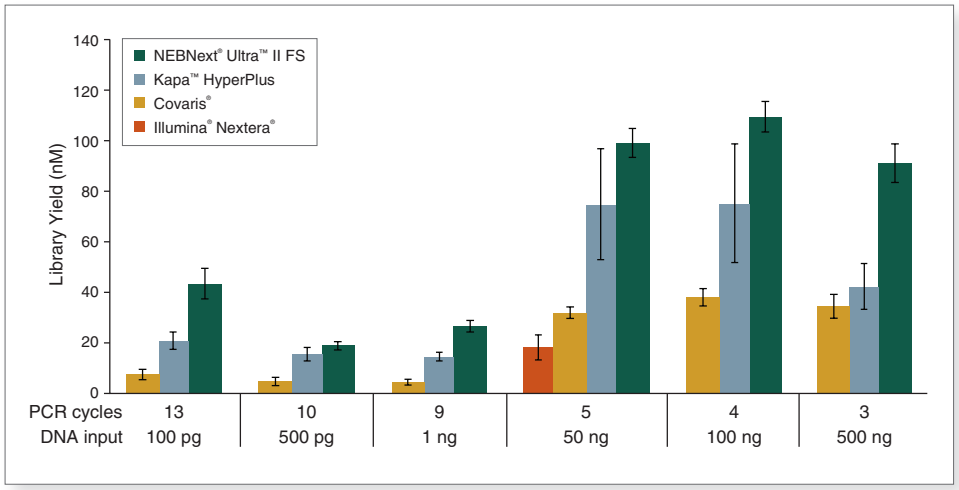
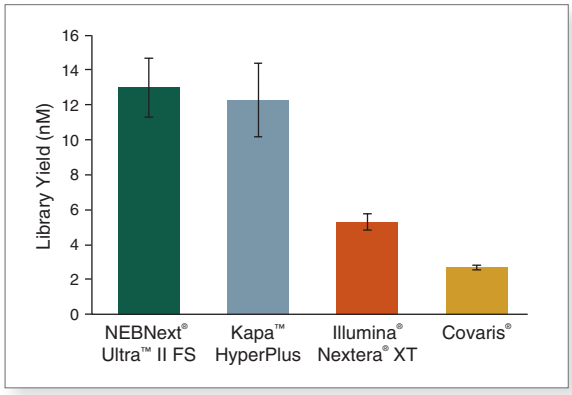


FIGURE 3: **NEBNext Ultra II FS DNA produces the highest yields from 1 ng of microbial DNA**

Libraries were prepared from 1 ng of a mix of genomic DNA from *Escherichia coli* (K12 MG1655), *Haemophilus influenzae* and *Rhodopseudomonas palustris*, using 9 PCR cycles for consistency across samples. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. For Kapa HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, followed by a 25-minute fragmentation. "Covaris" libraries were prepared by shearing 1 ng of DNA in 1X TE Buffer to an insert size of ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Error bars indicate standard deviation for an average of 2 libraries.



Robustness of DNA Fragmentation

Consistent and reliable fragmentation of DNA is critical for an enzymatic method to be adopted. Fragmentation using the NEBNext Ultra II FS kit is time-dependent, with fragmentation times amenable for manual or automated library preparation (Figure 4). Importantly, the final library size reflects the initial fragmented DNA, demonstrating that sufficient fragments of the desired size were produced during the fragmentation step (Figures 5, 6).

Since in practice the exact quantity of DNA in a sample, and the exact GC content, may be unknown, it can be challenging when different fragmentation protocols are required for different input amounts and GC contents. Additionally, the ability to use input DNA in a range of buffers greatly simplifies the very start of the workflow, especially in situations where the input DNA buffer composition may be unknown or uncertain. The Ultra II FS kit addresses all of these issues by requiring a single fragmentation protocol for the full range of input amounts (100 pg – 0.5 µg) (Figure 7) and for the full range of GC content (see next section). Additionally, DNA can be in water, Tris, 0.1X TE or 1X TE (Figure 8). Performance is consistent and reliable, as exemplified by the experiment shown in Figure 9 in which three first-time users obtained consistent results using the Ultra II FS kit.

FIGURE 4: **NEBNext Ultra II FS DNA enables time-dependent DNA fragmentation**

100 ng of Human NA19240 genomic DNA was incubated with the NEBNext Ultra II FS Enzyme Mix and Reaction Buffer for 5, 10, 15, 20, 25, 30 and 40 minutes at 37˚C, followed by 65˚C for 30 minutes for fragmentation, end repair and dA-tailing. After clean-up using NEBNext Sample Purification Beads, size was assessed using the Agilent® Bioanalyzer®.

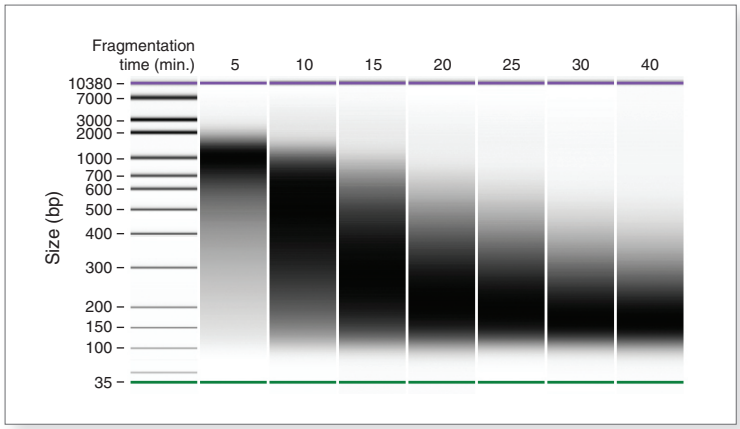


FIGURE 5: **NEBNext Ultra II FS DNA shows expected final library sizes with human DNA**

Libraries were constructed using the NEBNext Ultra II FS kit,100 ng of Human NA19240 genomic DNA, fragmentation times of 5, 10, 15, 20, 25, 30 and 40 minutes, and 4 PCR cycles. Size selection was not performed. After clean-up using NEBNext Sample Purification Beads, library size was assessed using the Agilent Bioanalyzer.

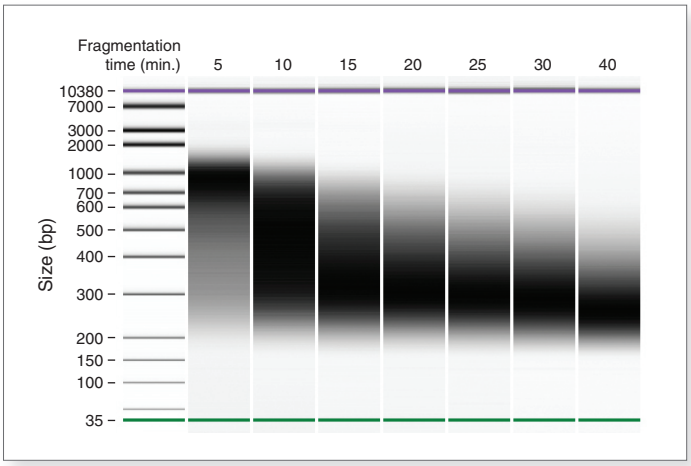


FIGURE 6: **NEBNext Ultra II FS DNA shows expected final library insert with microbial DNA**

Libraries were prepared from 1 ng of a mix of genomic DNA from *Escherichia coli* (K12 MG1655), *Haemophilus influenzae* and *Rhodopseudomonas palustris*, using 9 PCR cycles for consistency across samples. Fragmentation conditions targeting ~200 bp inserts were used, which would generate ~320 bp libraries, indicated by the horizontal gray line. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. For Kapa HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, followed by a 25-minute fragmentation. "Covaris" libraries were prepared by shearing 1 ng of DNA in 1X TE Buffer to an insert size of ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Average library size was measured using the Agilent Bioanalyzer. Error bars indicate standard deviation for an average of 2 libraries.

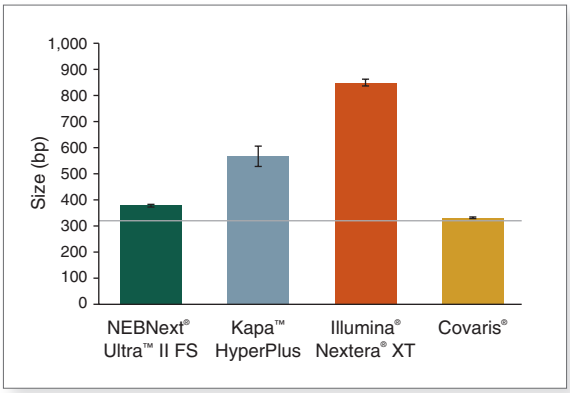


FIGURE 7: **Consistent and Reliable Library Preparation with NEBNext Ultra II FS DNA**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts shown. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. For Kapa HyperPlus, input DNA was cleaned up with 3X beads prior to library construction, as recommended, and a 20-minute fragmentation time. Library size was assessed using the Agilent Bioanalyzer. Low input (1 ng and below) libraries were loaded on the Bioanalyzer without a dilution. High input libraries were loaded with a 1:5 dilution in 0.1X TE.

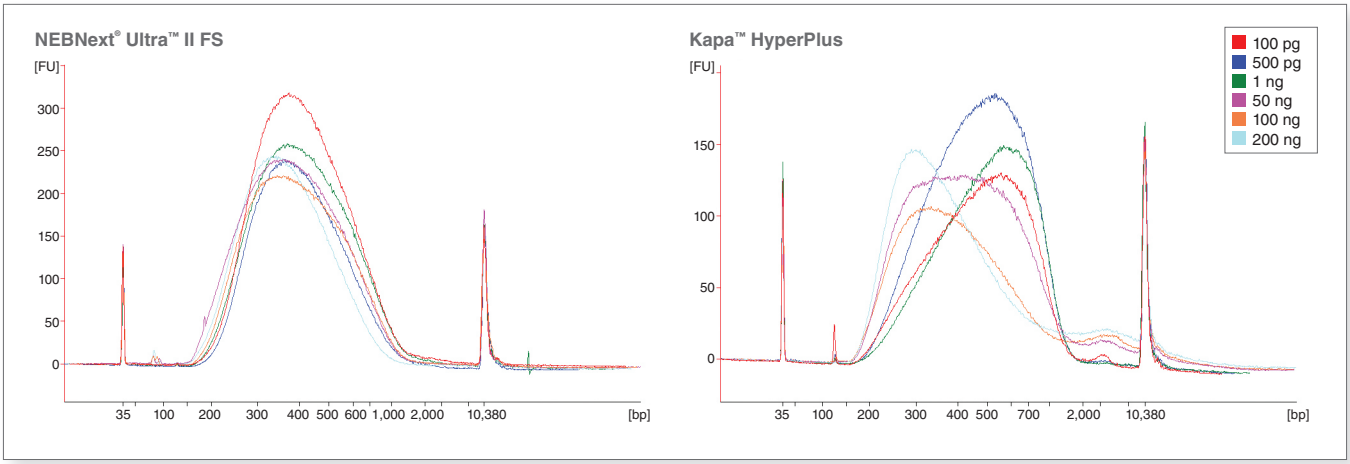


FIGURE 8: **NEBNext Ultra II FS DNA provides consistent fragmentation of DNA in water, Tris or TE**

Libraries were made using 100 ng Human NA19240 genomic DNA using the NEBNext Ultra II FS kit or the Kapa HyperPlus Kit. Fragmentation conditions targeting ~200 bp inserts were used, which would generate ~320 bp libraries. For the NEBNext Ultra II FS kit, input DNA was in H_2O, Tris, 0.1X TE or 1X TE. For the Kapa HyperPlus kit, libraries were made using the recommended dilution of the supplied Conditioning Solution (CS), or using DNA in Tris, 0.1X TE or 1X TE, in the absence of either Conditioning Solution or 3X bead clean up. Library size distribution was assessed using the Agilent Bioanalyzer. Fragmentation is consistent for the NEBNext Ultra II FS kit for DNA in H2O, Tris, 0.1X TE or 1X TE.

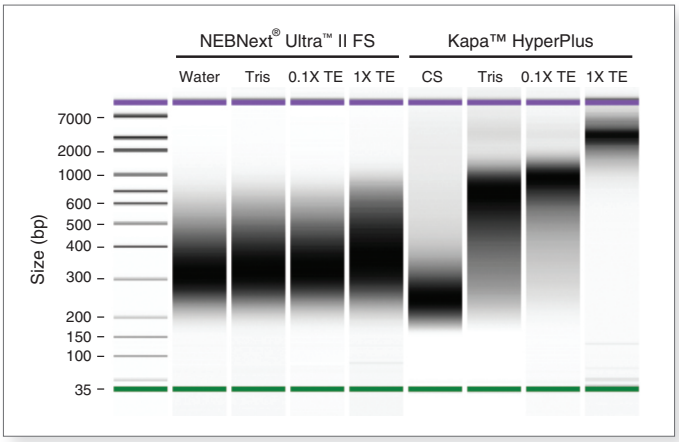
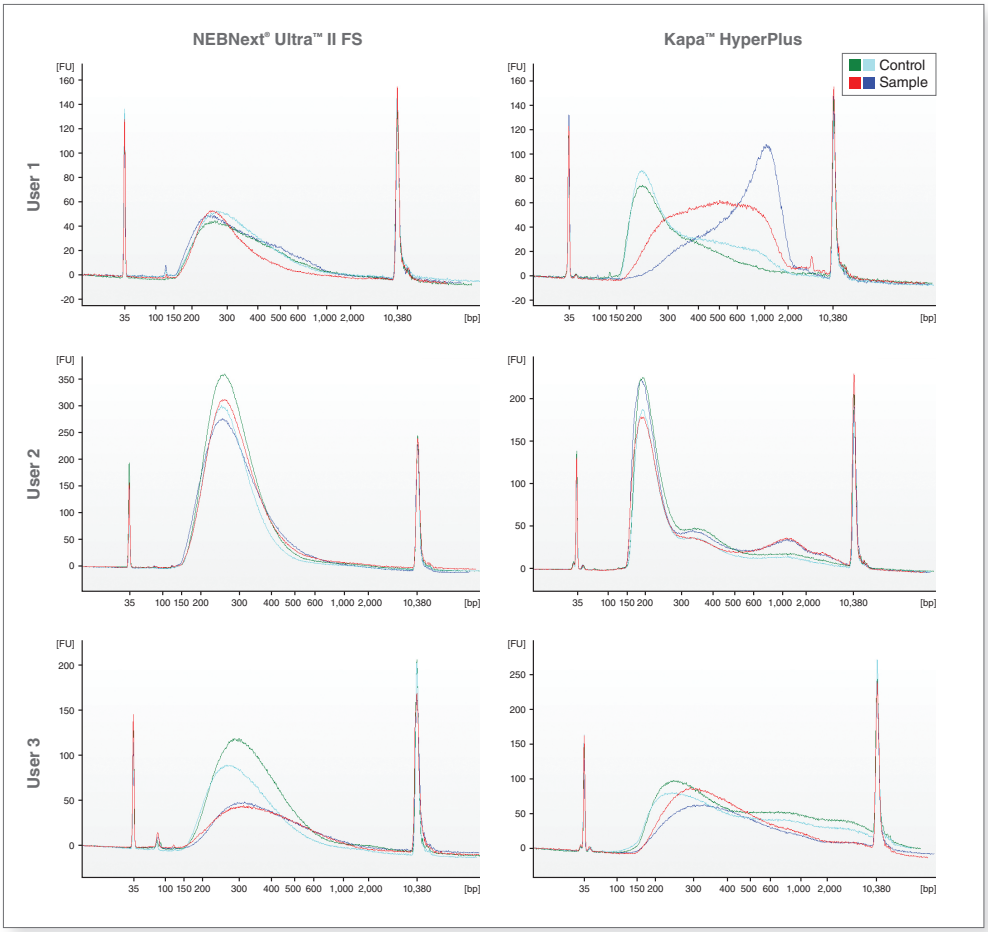


FIGURE 9: **Consistent and Reliable Library Preparation with NEBNext Ultra II FS DNA**

Eight libraries were constructed by each of three different users, with 100 ng DNA. Each user made 2 libraries with NA19240 Human gDNA ("control") and 2 libraries with a test sample of their choice, using both the NEBNext Ultra II FS kit and the Kapa HyperPlus kit. Manufacturers recommendations were followed for each kit. An equivalent volume of each final library was run on the Agilent Bioanalyzer to assess library quality and yield. The NEBNext Ultra II FS kit produced consistent fragmentation and performance, regardless of user or sample.



Uniform GC Coverage

While sufficient yield of a library is required for successful sequencing, the quality of a library is also critical, regardless of the input amount or GC content of the sample DNA. A high-quality library will have uniform representation of the original sample, including even coverage across the GC spectrum.

For enzymatic DNA fragmentation methods, randomness with regard to GC content can be of concern, and ensuring uniform GC coverage in libraries produced with the NEBNext Ultra II FS kit was of great importance. As is shown below, the Ultra II FS kit shows not only consistent uniformity of GC coverage at the full range of input amounts (Figure 10), but uniformity of GC coverage superior to mechanical shearing workflows and alternative enzymatic shearing methods (Figures 11, 12).

FIGURE 10: **NEBNext Ultra II FS DNA provides uniform GC coverage with human DNA over a broad range of input amounts**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts and number of PCR cycles shown. For NEBNext Ultra II FS, a 20-minute fragmentation time was used. For Kapa HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, and a 20-minute fragmentation time was used. Libraries were sequenced (2 x 76 bp) on an Illumina MiSeq®. Reads were mapped to the hg19 reference genome using Bowtie 2.2.4 and GC coverage information was calculated using Picard's CollectGCBiasMetrics (v1.117). Expected normalized coverage of 1.0 is indicated by the horizontal grey line, the number of 100 bp regions at each GC% is indicated by the vertical grey bars, and the colored lines represent the normalized coverage for each library.

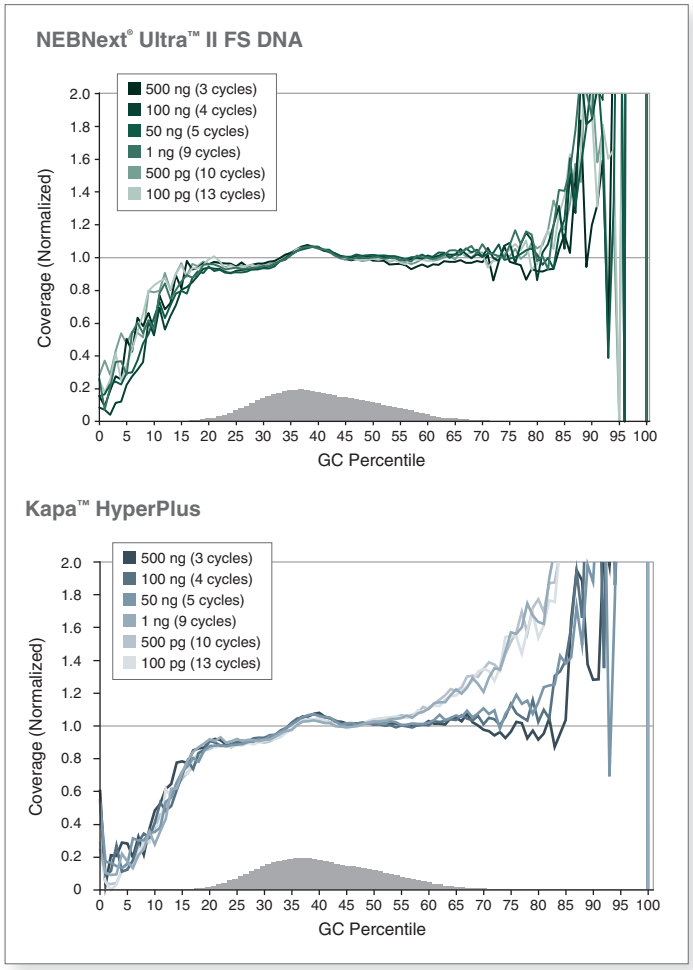


FIGURE 11: **NEBNext Ultra II FS DNA provides superior GC coverage**

Libraries were prepared from 50 ng Human NA19240 genomic DNA using the library prep kits shown and 5 PCR cycles. For NEBNext Ultra II FS, a 20-minute fragmentation time was used. For Kapa HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, and a 20-minute fragmentation time was used. "Covaris" libraries were prepared by shearing input DNA in 1X TE Buffer to an insert size of ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Libraries were sequenced on an Illumina MiSeq (2 x 76 bp). Reads were mapped to the hg19 reference genome using Bowtie 2.2.4 and GC coverage information was calculated using Picard's CollectGCBiasMetrics (v1.117). Expected normalized coverage of 1.0 is indicated by the horizontal grey line, the number of 100 bp regions at each GC% is indicated by the vertical grey bars, and the colored lines represent the normalized coverage for each library.

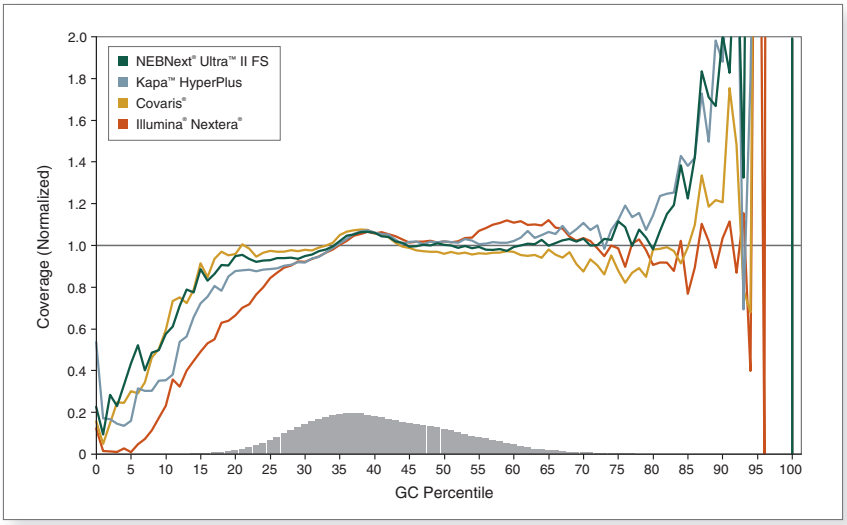
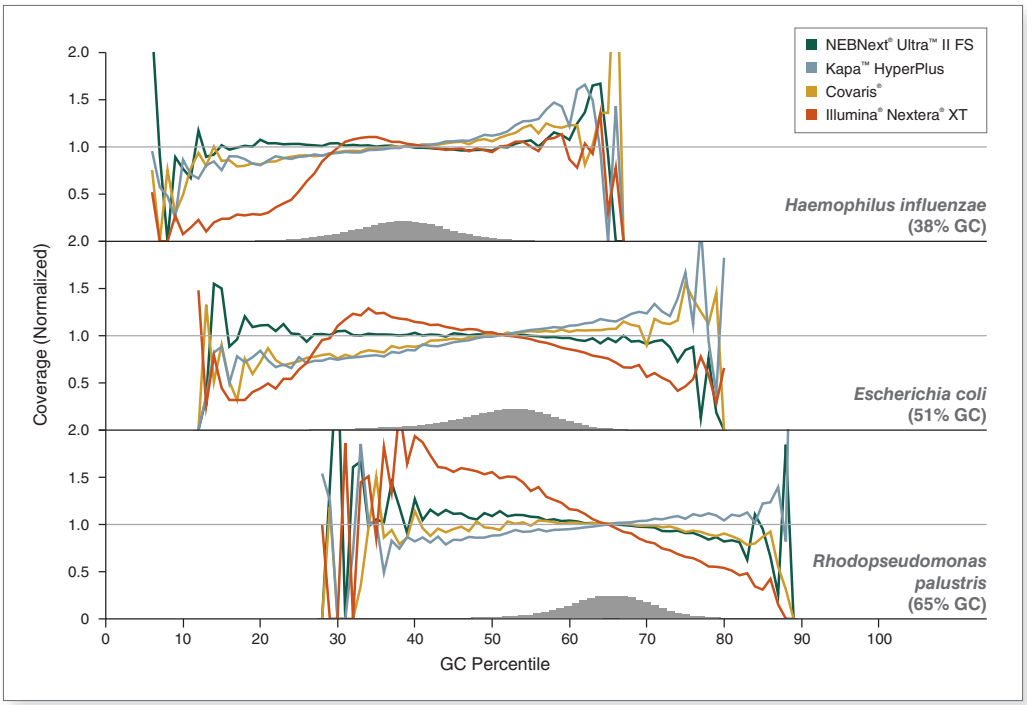


FIGURE 12: **NEBNext Ultra II FS DNA provides uniform GC coverage for microbial genomic DNA over a broad range of GC composition**

Libraries were prepared using 1 ng of a mix of genomic DNA samples from *Haemophilus influenzae*, *Escherichia coli* (K-12 MG1655), *Rhodopseudomonas palustris* and the library prep kits shown, with 9 PCR cycles for consistency across samples, and sequenced on an Illumina MiSeq. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. For Kapa HyperPlus libraries, input DNA was cleaned up with 3X beads prior to library construction, as recommended, followed by a 25-minute fragmentation time. "Covaris" libraries were prepared by shearing 1 ng of DNA in 1X TE Buffer to an insert size of ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Reads were mapped using Bowtie 2.2.4 and GC coverage information was calculated using Picard's CollectGCBiasMetrics (v1.117). Expected normalized coverage of 1.0 is indicated by the horizontal grey line, the number of 100 bp regions at each GC% is indicated by the vertical grey bars, and the colored lines represent the normalized coverage for each library.



Library Quality

As noted above, an ideal library will represent completely and proportionally the sequence of the sample DNA, regardless of the input amount and GC content of the sample DNA.

Especially when input amounts for a library are low, there is a risk that the resulting library will lack this diversity, and that some sequences will be over- or under-represented. This could be due to preferential amplification of some sequences during PCR of the final library, or non-random DNA fragmentation at the beginning of the library prep process. Comparison of the level of sequence coverage, in 10 kb intervals, achieved for libraries with different input amounts is a useful measure of the diversity of a library. This is especially useful when the comparison is with a PCR-free library made with a higher input amount, as such a library is typically not affected by the factors that lead to bias in libraries. Here we show good correlation of a PCR-free library prepared with 100 ng of Covaris-sheared human genomic DNA, and amplified libraries prepared with 1 ng of Covaris-sheared DNA or with the NEBNext Ultra II FS kit (Figure 13). Another way to measure library quality is to determine the depth of coverage of randomly-sampled 75 bp sequence reads. Figure 14 shows this data for libraries prepared using the Ultra II FS kit or using mechanically-sheared DNA, for higher (100 ng) and lower (1 ng) input amounts, without and with PCR, respectively. The Ultra II FS library coverage is more consistent with the "gold standard" PCR-free libraries. These library quality differences are also reflected in the sequencing metrics shown in Table 1.

FIGURE 13: **Read depth analysis shows consistently high correlation for NEBNext Ultra II FS DNA libraries at low input amounts**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts shown, with 9 PCR cycles, for consistency across samples for the 1 ng libraries, and without amplification for the 100 ng Covaris library. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. "Covaris" libraries were prepared by shearing each input amount in 1X TE Buffer to ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Libraries were sequenced on an Illumina HiSeq® 2500 (2 x 75 bp). 723M reads were randomly sampled (seqtk) and aligned to the GRCh38 full reference genome using bwa (0.7.15). Adaptors were trimmed prior to alignment using trimadap (r9). Duplicates were marked using samblaster (0.1.24). The GRCh38 reference genome was divided into 10 kb windows and the number of reads per 10 kb window was calculated. Results are similar for 1 ng NEBNext Ultra II FS and Covaris libraries compared with a 100 ng input PCR-free Covaris library.

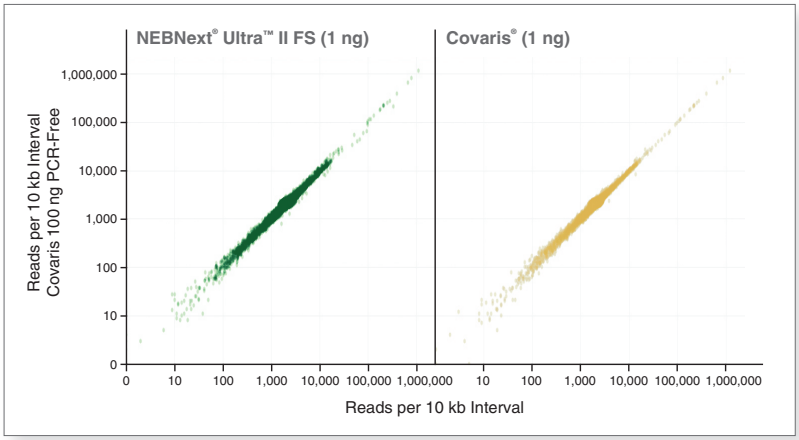


FIGURE 14: **NEBNext Ultra II FS DNA produces uniform coverage even at low input amounts**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts shown, with 9 PCR cycles for the 1 ng libraries, and no amplification for the 100 ng libraries. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. "Covaris" libraries were prepared by shearing each input amount in 1X TE Buffer to ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Libraries were sequenced on an Illumina HiSeq 2500 (2 x 75 bp). 723M 75 bp reads were randomly sampled (seqtk) and aligned to the GRCh38 full reference genome using bwa (0.7.15). Adaptors were trimmed prior to alignment using trimadap (r9). Duplicates were marked using samblaster (0.1.24). Ultra II FS provides more uniform coverage depth, with fewer regions of excess coverage.

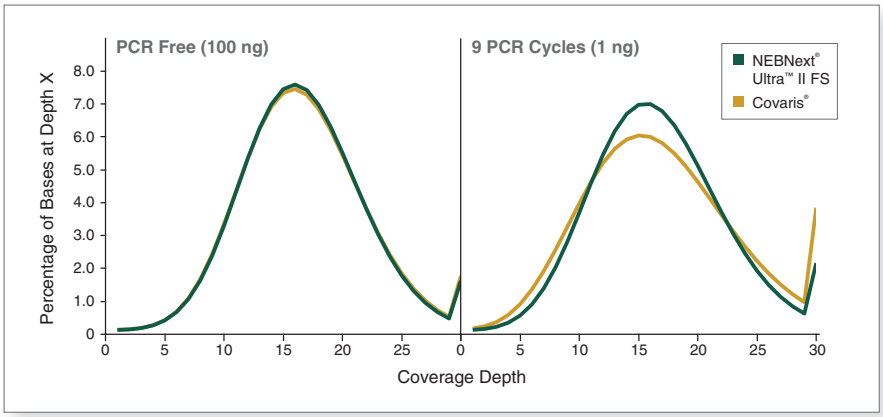


TABLE 1: **NEBNext Ultra II FS enables high quality sequence data even at low input amounts**

DNA input	Library Method	% Aligned	% Aligned in Pairs	% Proper Pairs	% Unique
100 ng	Ultra II FS	98	97	96	93
	Covaris	97	98	97	93
1 ng	Ultra II FS	98	97	94	80
	Covaris	98	98	97	68

% Aligned = Number of reads aligned / total reads
% Aligned in Pairs = Number of reads aligned in pairs / total reads
% Proper Pairs = Number of reads marked by BWA (0.7.15) as "proper pairs" during alignment (reads are in correct orientation and expected insert size)
% Unique = number of reads not marked as duplicate by samblaster / total reads

PCR-Free Libraries

Construction of a library using a PCR-free workflow removes the risk of incorporation of bias during library amplification. However, the input amounts required to produce sufficient amounts of a high-diversity library without an amplification step are necessarily higher, and this can be limiting. With the NEBNext Ultra II FS protocol, by performing fragmentation, end repair and dA-tailing in the same reaction vial, sample loss due to transfer or clean-up steps after DNA fragmentation are eliminated, and yields are higher.

Additionally, the use of Ultra II FS enzymatic DNA fragmentation rather than mechanical shearing reduces DNA damage, and consequently increases library yields, making the omission of the PCR step now feasible for lower nanogram level input amounts (Figures 15, 16).

FIGURE 15: **NEBNext Ultra II FS DNA produces higher yields of PCR-free libraries**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts shown, without amplification. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. "Covaris" libraries were prepared by shearing each input amount in 1X TE Buffer to ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Library yields were determined by qPCR using the NEBNext Library Quant Kit for Illumina (NEB #E7630). Error bars indicate standard deviation for an average of 2 libraries.

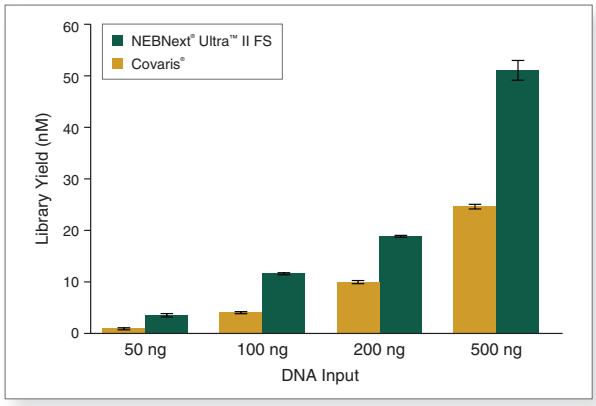
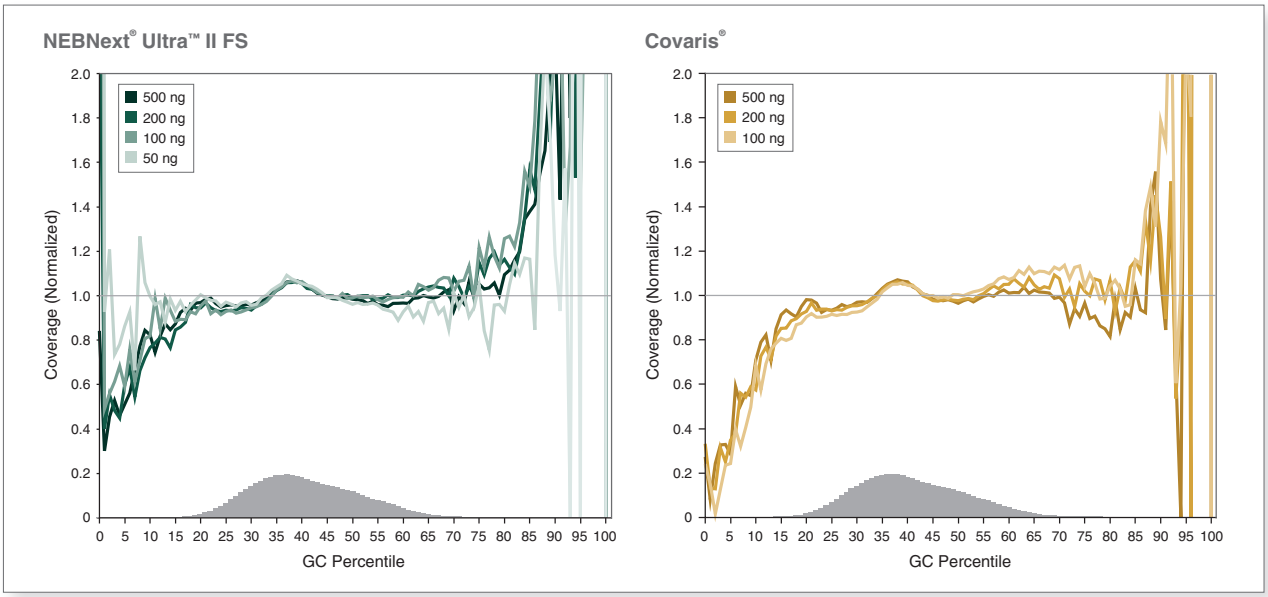


FIGURE 16: **NEBNext Ultra II FS DNA generates PCR-free libraries with uniform GC coverage, across a range of input amounts**

Libraries were prepared from Human NA19240 genomic DNA using the input amounts shown, and without amplification. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. "Covaris" libraries were prepared by shearing each input amount in 1X TE Buffer to ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Libraries were sequenced on an Illumina MiSeq (2 x 76 bp). Reads were mapped to hg19 using Bowtie 2.2.4 and GC coverage information was calculated using Picard's CollectGCBiasMetrics (v1.117). Expected normalized coverage of 1.0 is indicated by the horizontal grey line, the number of 100 bp regions at each GC% is indicated by the vertical grey bars, and the colored lines represent the normalized coverage for each library. Ultra II FS produced libraries with similar GC coverage to Covaris-sheared libraries, even with an order of magnitude difference in input.



Variant Detection

Enzymatic DNA fragmentation enables increased library yields in comparison to mechanical shearing methods, in part due to the reduced DNA damage that occurs during shearing (1,2). Additionally, sequence markers indicative of oxidative damage to DNA have been found in libraries constructed with mechanically-sheared DNA, that are absent in libraries constructed using the NEBNext Ultra II FS kit (Figure 17), and greater differences are seen with lower input amounts. This highlights the higher quality of libraries constructed with the Ultra II FS kit compared to Covaris-sheared DNA libraries, especially at low input amounts.

Additionally, the high quality of Ultra II FS-generated libraries enabled detection of known mutations at expected frequencies (Figure 18).

1. Costello, M., et al. (2013) *Nucleic Acids Res.* 41, e67.
2. Chen, L., et al. (2017) *Science.* 355, 752–756.

FIGURE 17: **NEBNext Ultra II FS DNA libraries show reduced markers of oxidative damage compared to libraries produced by mechanical shearing**

Libraries were prepared from 1 ng and 100 ng Human NA19240 genomic DNA, using 9 and 4 PCR cycles, respectively. NEBNext Ultra II FS libraries were prepared using a 20-minute fragmentation time. "Covaris" libraries were prepared by shearing each input amount in 1X TE Buffer to ~200 bp using a Covaris instrument, followed by library construction using the NEBNext Ultra II DNA Library Prep Kit (NEB #E7645). Libraries were sequenced on an Illumina HiSeq 2500 (2 x 75 bp). 723M reads were randomly sampled (seqtk) and aligned to the GRCh38 full reference genome using bwa (0.7.15). Adaptors were trimmed prior to alignment using trimadap (r9). Duplicates were marked using samblaster (0.1.24). Variants were called on chromosome 1 using freebayes (1.0.2.29) with frequency based options requiring at least 10 reads per site. More variants are observed for C>A and G>T transversions compared with all other variants for PCR-amplified Covaris libraries. These variants indicative of oxidative damage are not pronounced in NEBNext Ultra II FS libraries.

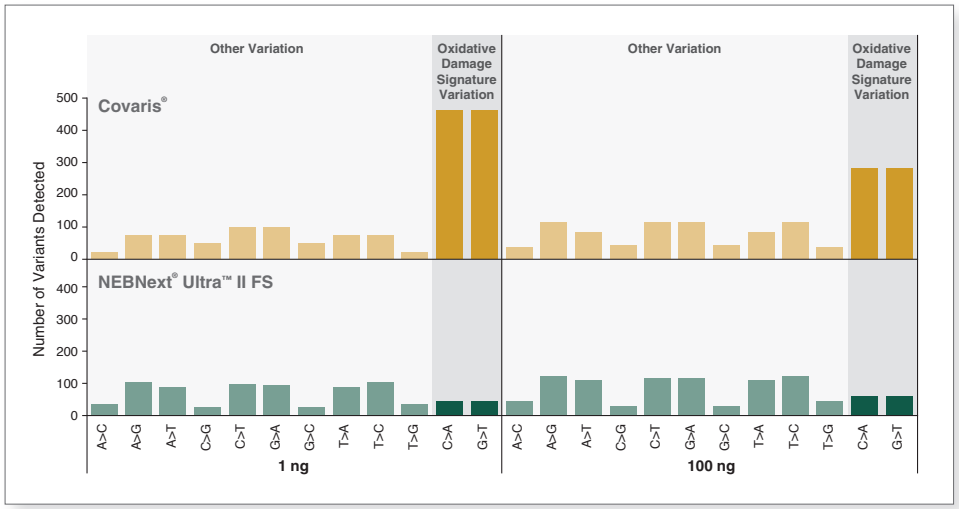
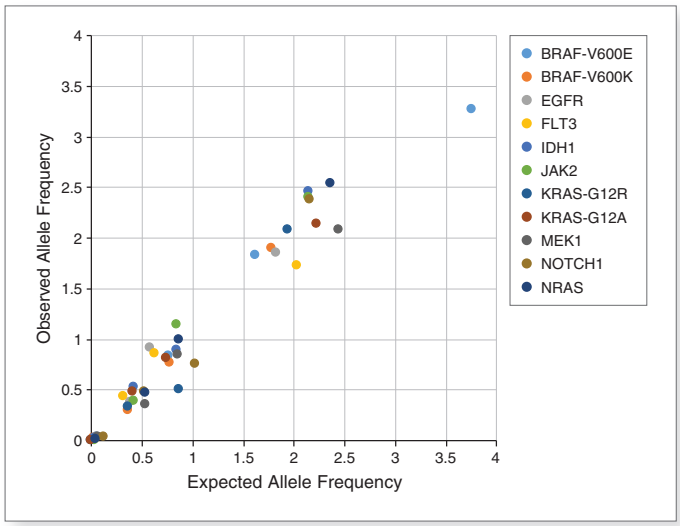


FIGURE 18: **NEBNext Ultra II FS DNA enables accurate variant detection**

Tru-Q 1 (5% Tier) Reference Standard (Horizon® HD728) was spiked into wild type human DNA (NA19240) at varying expected allele frequencies. 100 ng of the DNA mix was used to generate NEBNext Ultra II FS libraries, followed by target enrichment using the ClearSeq® Comprehensive Cancer XT panel (Agilent #5190-8011). Droplet digital PCR (Bio-Rad® QX200) was used to detect 11 of the known Tru-Q 1 mutations in the input DNA sample as well as the Ultra II FS libraries. All 11 mutations were detected at expected frequencies.



Conclusion

The NEBNext Ultra II FS DNA Library Prep Kit for Illumina provides a simple and reliable solution for DNA fragmentation integrated with library construction. The kit enables production of high quality libraries from a broad range of input amounts and GC contents with a single fragmentation protocol, greatly simplifying the scalability of library construction:

- Perform fragmentation, end repair and dA-tailing with a single enzyme mix
- Obtain robust fragmentation with a single protocol, regardless of DNA input amount or GC content
- Generate high quality libraries from 100 pg–0.5 µg input DNA
- Use with DNA in standard buffers (TE, Tris-HCl) and water
- Save time with a streamlined workflow: ~ 2.5 hours, with < 15 minutes hands-on time
- Experience reliable fragmentation, even with very low input amounts
- Generate high yields with increased reaction efficiencies and minimized sample loss
- Vary incubation time to generate a wide range of insert sizes

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