M E M O R A N D U M

27 August 2019

STRICTLY CONFIDENTIAL
CONTAINS BUSINESS SECRETS

VIA E-MAIL (ILLUMINA_PACBIO@CMA.GOV.UK)

TO: Competition and Markets Authority

FROM: [CONFIDENTIAL]

RE: **Illumina, Inc.'s proposed acquisition of Pacific Biosciences of California, Inc. – [CONFIDENTIAL]**

Following the publication of the CMA's decision to refer the proposed Illumina/PacBio merger for a Phase 2 investigation ('the CMA's reference decision'), Illumina and PacBio's response to that decision, and the CMA's Issues Statement, [CONFIDENTIAL] provides below its views on the key points under investigation. Where possible, [CONFIDENTIAL] has provided further evidence to supplement the submissions it made during the first stage of the CMA's investigation.

1. One market for DNA sequencing

a. Long read is a substitute for short read

[CONFIDENTIAL] takes issue with Illumina and PacBio's ('the Parties') mischaracterisation of the market in their response to the CMA's reference decision. Contrary to the Parties' statement that "*there is no overlap*" between long read and short read, the market has evolved in such a way that there is already today substantial overlap between short read and long read sequencing and this overlap across applications increases as the cost of long read continues to drop. [CONFIDENTIAL] supports the CMA's proposed market definition including "*all DNA sequencing systems on a worldwide basis*" while noting that Chinese competitors, namely BGI, have difficulty entering and expanding in international markets. In particular [CONFIDENTIAL] would like to reinforce the following points:

i. As explained in [CONFIDENTIAL], from a technical perspective, technologies which are capable of reading short lengths of DNA can be substituted by long read technologies for all applications. Indeed, there are many use cases for which customers are already using the advantages brought by long-read technologies as a substitute for short-read: whole genome sequencing and assembly (including study of genome-wide variants), targeted sequencing, RNA sequencing, metagenomics, epigenetics, variants analysis (including SVs and SNPs/SNVs). We attach by way of example, a link to research published by PacBio demonstrating that SV calling in a melanoma cell line has higher precision and recall values using PacBio reads (96.3% precision and 95.99%

recall, vs. the GIAB HG002 benchmark), compared to Illumina short reads (85.35% precision, 55.88% recall). We also attach a link to a publication on the use of long read sequencing in SNVs. This publication describes the Longshot tool used for SNV calling which was tested on PacBio and nanopore long read human genome sequencing. Amongst other things, the article confirms that long sequencing reads were able to span 99.4% of the genome with at least 30 depth of coverage, whereas Illumina reads covered 96.3% of the genome with 30x sequencing depth.[1]

ii. As regards costs, PacBio's sequencing instruments have become more cost-effective over time, the pricing gap between the Parties has begun to close, and costs of PacBio long read are expected, absent the merger, to continue to drop. For example, the attached PacBio promotional material is promoting faster and significantly cheaper RNA sequencing with PacBio's Iso-seq protocol run on Sequel II.[2] In the attached overview of current sequencing technologies, which was published in April 2019, just after the launch of Sequel II, the author notes that the cost of PacBio's technology "*has DRAMATICALLY decreased in the last two years, making it pretty competitive.*"[3] The recent article from PacBio's David Rank, referred to below, also notes improved cost and throughput of Sequel II. In addition, [CONFIDENTIAL] notes that most of Illumina's arguments comparing its costs to PacBio, are based on their highest throughput box, NovaSeq, and disregard the fact that PacBio's technology is already cheaper in terms of cost/base and cost/run than a number of other Illumina platforms from which Illumina derives a significant part of its total revenue.

iii. Also, contrary to what the Parties claim in their response to the CMA's reference decision, accuracy of long read is improving and in some cases is better than accuracy from Illumina technology (see below reference to PacBio's performance in sequencing the Human Genome which notes a very high level of accuracy).

These factors mean that today, PacBio's technology imposes a competitive constraint on Illumina and as costs associated with long-read technologies are expected to continue to drop (in the absence of the merger), the lines between long read and short read sequencing are becoming increasingly blurred.

We attach a recent article from David R. Rank, Scientific Fellow at PacBio, entitled "*Highly-Accurate, Long-Read DNA Sequencing Improves Analysis of a Human Genome*." In this article, Mr. Rank notes both the increased accuracy of long-read (in comparison to Illumina) and improved costs and throughput with Sequel II, making it accessible to individual labs, a trend which he expects will continue.[4]

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[1] See for example a recent study from PacBio on SVs: https://www.pacb.com/wp-content/uploads/Wenger-AACR-2019-Structural-variant-detection-with-long-read-sequencing-reveals-driver-and-passenger-mutations-in-a-melanoma-cell-line-1.pdf. See also for SNVs: https://www.biorxiv.org/content/biorxiv/early/2019/03/01/564443.full.pdf.

[2] See https://www.pacb.com/blog/introducing-iso-seq-express/.

[3] See 'Comparison Table for the Technologies' referenced in https://ncgas.org/Blog_Posts/Third%20Generation%20Sequencing%20Update.php#Balance.

[4] See https://bioengineeringcommunity.nature.com/users/288939-david-r-rank/posts/52218-highly-accurate-long-read-dna-sequencing-improves-analysis-of-a-human-genome

b. Complementary use of long read and short read for certain applications

While today, customers are using long read and short read technologies in a complementary fashion for certain applications, [CONFIDENTIAL] believes that, given the inherent limitations of short read sequencing, customers will progressively switch to long read technologies for most applications. In fact, even within a specific experiment combining short reads with long reads, customers are tending to use long read for a bigger portion of the sequencing work. Where biologists are combining shorter reads – which currently have either a lower or higher cost per Gb depending on the Illumina system used – with technologies that provide longer reads that confer benefits in sequencing and assembling a whole genome – they may typically mix two or more technologies in a certain percentage, e.g. 20X coverage of the genome with short reads and 10X coverage with longer reads. As the performance of longer reads improves, these users may choose to increase the proportion of their experiment that is done with those technologies, and therefore there is a competitive element within a single experiment between two technologies.

In addition, based on [CONFIDENTIAL], some users suggest that even for some applications which might normally use both, PacBio's data is better on its own than combined with Illumina's.

Finally, [CONFIDENTIAL] considers that for the generation of a reference genome/*de novo* sequencing, it is unlikely that any platform can produce a perfect answer, and so combinations of methodology are likely to overcome any deficiencies in the other (when combined optimally). [CONFIDENTIAL] believes that customers such as the Earth Biogenome Project[5], and Genome in a bottle[6], would still continue to use a combination of both approaches to refine their results and get the best possible answer.

2. The merger would lead to higher prices and a reduction in innovation competition

The proposed merger will further strengthen the enormous leverage that Illumina can already exert on customers for sales of instruments, sequencing services and consumables by eliminating a direct current competitor and an important future competitive constraint, which third-parties active in DNA sequencing won't be able to replicate, leading to higher prices and a reduction in innovation.

a. Price competition

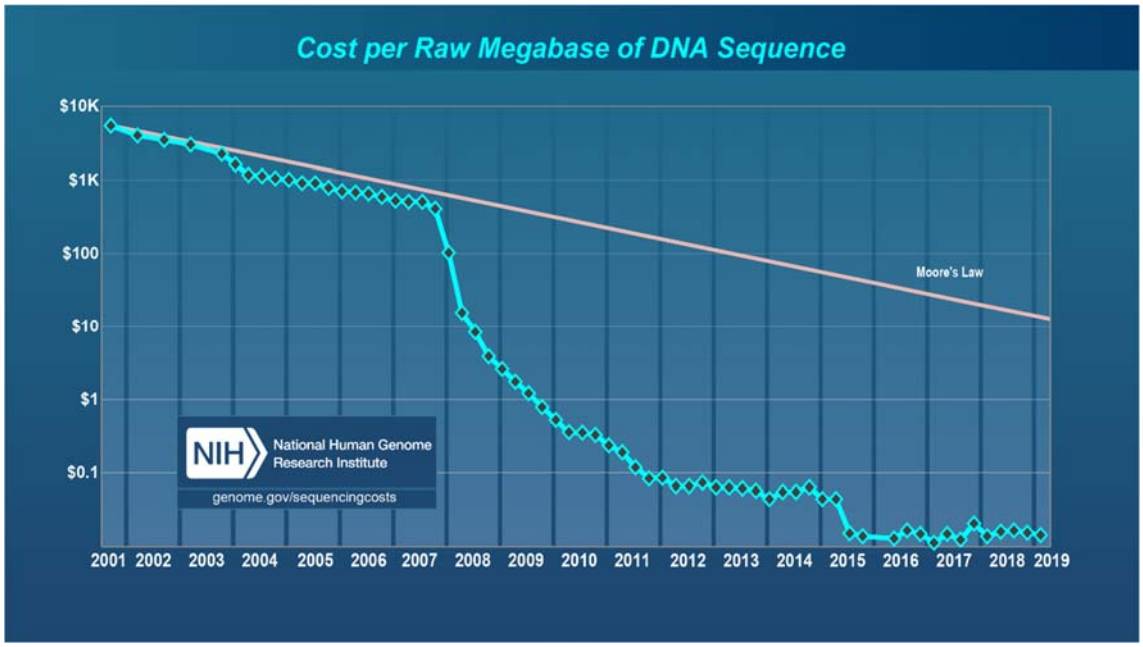
While the cost of sequencing went down between 2007, following Illumina's acquisition of Solexa, and 2012, this was not driven by Illumina as much as it was a response to competitive threats at the time. Once those competitive threats were removed, including with the discontinuation of ThermoFisher's SOLiD sequencer, prices flattened until 2015 which saw another drop in response to a new competitive threat, this time from BGI which subsequently also discontinued its product, leading again to a flattening of prices. The attached article published in 2014 and looking back at the previous decade in DNA sequencing, notes Illumina's dominance and that the fall in human genome sequencing costs below USD 5,000 was at the time "*driven by competition between companies such as Illumina and Complete*

[5] See https://www.earthbiogenome.org/
[6] See https://www.nist.gov/programs-projects/genome-bottle

Genomics."[7] Illumina's past behaviour supports [CONFIDENTIAL] concerns that the proposed merger is designed to eliminate a substantial competitive threat and, among other things, to maintain higher prices than those which would have prevailed in the absence of the merger.

As can been seen from the graphs below, sequencing costs which, given its dominant position, are essentially set by Illumina, have not fallen since 2015, following the launch of Illumina's HiSeq X10.

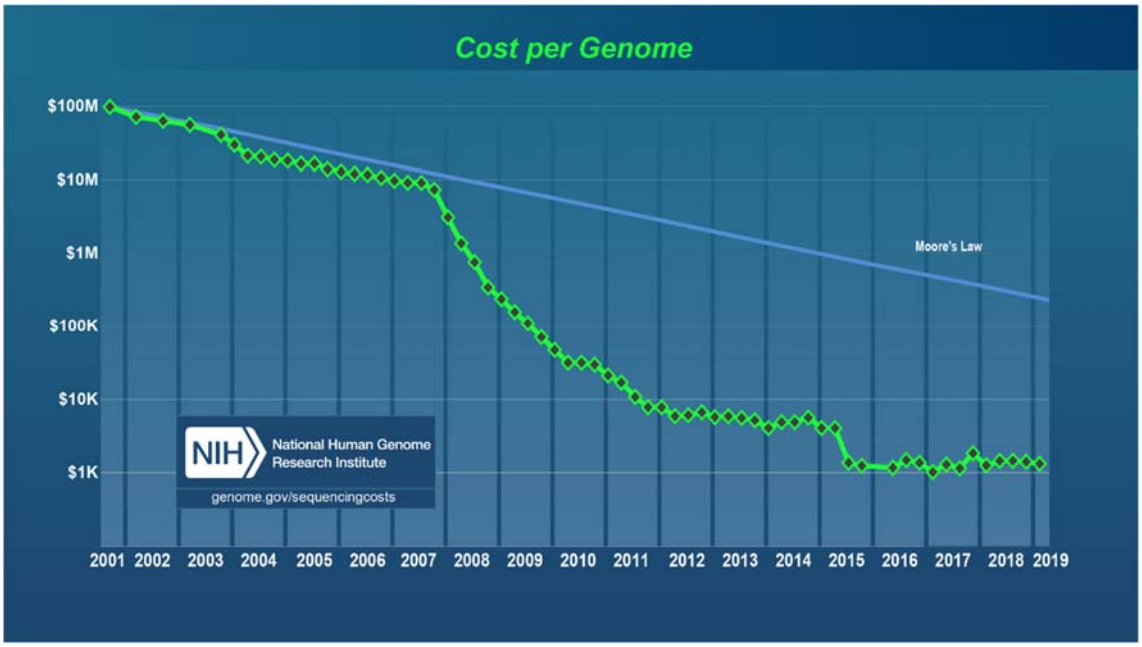
Chart 1: Sequencing costs per Mb[8]



Source: National Human Genome Research Institute (NHGRI) data (Sept. 2001- Feb. 2019)

Chart 2: Sequencing costs per genome[9]

[7] See Annex 1.
[8] See underlying data available at https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data. Note that the 2019 data was collected in February and therefore does not reflect the recent launch of PacBio's Sequel II.
[9] See underlying data available at https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data. Note that the 2019 data was collected in February and therefore does not reflect the recent launch of PacBio's Sequel II.



Source: NHGRI data (Sept. 2001- Feb. 2019)

Note the following observations made by Dr Rob Carlson back in 2014 regarding Illumina's influence on pricing and the lack of competition leading to higher prices than would otherwise have prevailed:

> *"Illumina's instruments are now responsible for such a high percentage of sequencing output that the company is effectively setting prices for the entire industry. Illumina is being pushed by competition to increase performance, but this does not necessarily translate into lower prices. It doesn't behove Illumina to drop prices at this point, and we won't see any substantial decrease until a serious competitor shows up and starts threatening Illumina's market share. The absence of real competition is the primary reason sequencing prices have flattened out over the last couple of data points.*"[10]

More recently (July 2019) another expert in the field notes the lack of competition as the reason why WGS costs have flattened since 2015.[11]

[CONFIDENTIAL]. In fact, the lack of any further significant price reductions between 2012-2015 coincides with the period following the discontinuation of the SOLiD sequencer line by ThermoFisher, which used to impose some form of competitive constraint over the already dominant Illumina. Moreover, the drop in price recorded in 2015 results from Illumina's launch of HiSeq X10, a launch which we believe was to respond to BGI's launch of *Revolocity*, around the same time. While *Revolocity* could have imposed some competitive constraint on

[10] https://synbiobeta.com/time-new-dna-synthesis-sequencing-cost-curves-rob-carlson/
[11] See a recent Twitter thread from Yaniv Erlich available at: https://twitter.com/erlichya/status/1156621496963534848?s=20

Illumina, BGI did not succeed in successfully commercialising *Revolocity* and decided to discontinue this product line shortly after its launch.[12]

As explained in [CONFIDENTIAL], PacBio's Sequel II was positioned to be a significant and disruptive threat to Illumina's dominant position. Indeed, [CONFIDENTIAL]. This threat would be removed by the proposed merger to the detriment of consumers in the UK and globally.

b. Innovation competition

As explained in [CONFIDENTIAL], [CONFIDENTIAL] believes that there is a high likelihood that post-merger Illumina would not drive innovation with respect to long read sequencing as quickly or aggressively as PacBio would have, absent the merger.

Illumina has a history of slowing down innovation, or even discontinuing entire business lines, following acquisitions of competing technologies. We provide below a few examples from Illumina's acquisitions of Avantome, Helixis, and Moleculo.

- Avantome was a company working on developing a low-cost, long read sequencing technology, which was acquired by Illumina in 2008.[13] Avantome's plan was to remove the need for expensive optics in sequencers, thus reducing the costs of sequencing instruments. It appears however that the development of the Avantome technology was paused, or at least extremely slowed down, following the acquisition, until the launch 10 years later of Illumina's iSeq (priced at about USD 19,500). The iSeq seems to be the result of the Avantome R&D process and one can't help but wonder the reasons for such a long development phase, especially in light of Illumina's substantial annual R&D spend amounting to approx. 20% of its annual revenues.[14] [CONFIDENTIAL].

- Helixis developed and manufactured a promising low cost, high performance real-time polymerase chain reaction (PCR) instrument to significantly reduce the price of a box for nucleic acid analysis, based on a technology developed at Caltech by Nobel Laureate David Baltimore.[15] Helixis was acquired by Illumina in 2010,[16] but the Helixis technology was never commercialised, which again seems surprising in light of Illumina's annual R&D spend.

- Moleculo was a company developing a synthetic long read (or 'linked long read') technology, which was acquired by Illumina in 2012.[17] While Illumina did release a commercial version of the Moleculo technology in 2014 (under the brand name *TruSeq Synthetic Long-Read*),[18] it decided to discontinue the line a few years later.[19]

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[12] See https://www.genomeweb.com/sequencing/bgi-halts-revolocity-launch-cuts-complete-genomics-staff-part-strategic-shift#.XV00hugzZPY
[13] See Illumina's 2009 Annual Report, p.3 available at https://www.sec.gov/Archives/edgar/data/1110803/000093639209000092/a51300e10vk.htm
[14] See Merger Notice, para. 287.
[15] See https://www.illuminaventures.com/our-portfolio
[16] See Illumina's 2011 Annual Report, p. 32, available at https://www.sec.gov/Archives/edgar/data/1110803/000095012311019925/a58258e10vk.htm
[17] See https://www.illumina.com/science/technology/next-generation-sequencing/long-read-sequencing.html
[18] See https://www.biocompare.com/Editorial-Articles/169003-Next-Gen-DNA-Sequencing-Fall-2014-Update/
[19] See https://www.illumina.com/science/technology/next-generation-sequencing/long-read-sequencing.html

c. Absence of meaningful competitive constraint post-merger

[CONFIDENTIAL] competitors would be able to constrain a merged Illumina/PacBio. [CONFIDENTIAL].

As regards new entrants, they face a substantial uphill struggle in developing and commercializing a product and getting it to a stage where it could be competitive in terms of price, sequencing accuracy and throughput with the existing commercial products. It should be noted for example that when PacBio launched their product in 2010 it had read lengths of only 4000 bases and an error rate of ~15%.[20] It has taken them a further eight years of continuous R&D to achieve their current read lengths and sequencing accuracy and their pace of innovation is not slowing down, as shown by the recent launch of the Sequel II product. Similarly, Illumina products have vastly improved since 2010 due to the large amount of money invested in R&D. As the bar becomes increasingly high in terms of the existing commercial products, so does the barrier to entry for new entrants in terms of launching products that are able to successfully compete with these existing products.

As explained in [CONFIDENTIAL], entering the sequencing segment requires a substantial amount of money and time to develop a workable technology and to get it adopted by customers. Access to IP rights also constitutes a significant barrier to entry. It is difficult to evaluate whether companies which are currently undertaking R&D will eventually evolve to be serious competitors in the market. In fact, the only profitable sequencing technology available on the market today is Illumina's.

The CMA's Phase 1 decision mentions a few potential entrants including Roswell, Quantapore, GenapSys, Omniome, Roche, and NanoString. [CONFIDENTIAL] believes that none of these companies would pose any significant competitive constraint to a merged Illumina/PacBio in the short or medium term, if at all. While Roswell indicated in early 2018 that they were planning to test their technology with early-access customers by the end of the year, this plan does not seem to have materialized yet.[21] Likewise, Omniome's and Quantapore's products seem to be in the early phases of development, and none of them announced any early access program nor a date for commercial launch.

GenapSys' GENIUS sequencer and NanoString's Hyb & Seq platforms are still in development and currently tested by a handful of early access customers.[22] NanoString indicated that it doesn't expect to commercially launch its platform before 2021.[23]

Finally, Roche's product development seems to have been put on hold.

3. Foreclosure of [CONFIDENTIAL]

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[20] See Annex 1.
[21] See https://www.roswellbiotech.com/wp-content/uploads/2018/10/Roswell-Biotechnologies-Harnesses-Molecular-Electronics-for-Chip.pdf and https://www.roswellbiotech.com/wp-content/uploads/2019/01/Techstartups-Roswell-Biotechnologies-secures-32-million-Series.pdf
[22] See https://www.genapsys.com/geniusclub2/geniusclub.html
[23] See https://www.globenewswire.com/news-release/2019/02/27/1743215/0/en/NanoString-Showcases-GeoMx-and-Hyb-Seq-Platforms-at-2019-Advances-in-Genome-Biology-and-Technology-AGBT-Conference.html

As explained above [CONFIDENTIAL], the proposed transaction eliminates the strongest emerging competitor to the already dominant Illumina. It will be extremely difficult, if not impossible, for any current or future competitors to actually replace the competitive constraint that PacBio is placing and would increasingly place on Illumina but for the merger.

Given Illumina's market power, [CONFIDENTIAL] believes that the merged entity will also likely be incentivised to embark on a bundling strategy offering incentives or forcing customers to take PacBio in combination with Illumina products, in order to foreclose competitors and new entrants. Illumina has a track record of using its dominance to drive the market to a more centralized market including when it launched HiSeq X10, locking in the key opinion leader labs and getting customers to buy 10 instruments, ensuring that they were locked in for several years, foreclosing competitors from those opportunities.

Bundling of Illumina and PacBio products [CONFIDENTIAL].

Finally, [CONFIDENTIAL] the views expressed in the CMA's Phase 1 decision on the fact the proposed transaction will increase Illumina's ability to strategically block the entry and expansion of competitors and new entrants by increasing the scope and extending the lifetime of Illumina's patent portfolio. Illumina and PacBio both have a long track record in aggressive and strategic use of their IP rights to impede competition ([CONFIDENTIAL]). [CONFIDENTIAL].