White Paper： NGS（Next Generation Sequencer） Application of nanoimprint lithography to chip mass production

1. Executive Summary

Nanoimprint technology was originally developed about 25 years ago as a fine pattern formation technology for semiconductors. In recent years, optical sensors for mobile devices, automatic driving, robotics, security, etc., and light guide plates for augmented reality (AR) glasses have become major applications, and the technology has been reconsidered for structure formation applications such as DOE and MLA at a level of few hundred nanometers to few micrometers. The application of NGS discussed here is not for optical components, but for nanoimprint technology as the one for mass-producing substrates with a fine hole structure in the reading area of DNA testing chips.

2. Introduction

Next-generation sequencers (NGS), which were introduced in the United States in the mid-2000s, are devices that can read gene sequences at high speed. The number of DNA fragments that can be read simultaneously in NGS is greater than in conventional DNA sequencers, making it possible to analyze genomes (genetic information) at an overwhelmingly low cost and in a short time. The NGS equipment market is expected to quadruple over the next 10 years, starting in 2016 (according to SEED Planning data). The current NGS market has been led in development by Illumina, the largest DNA sequencer company in the US. The development of sequencers for the "new next generation" is also gaining momentum, especially in the US and China. In contrast to next-generation sequencers, which generally amplify DNA and read out the base sequence by optically detecting fluorescent labels, this new method does not amplify DNA but electrically reads out the base sequence one molecule at a time. In principle, it can read out nucleotide sequences faster and at a lower cost than current next-generation sequencers.

What can be done with NGS?

First, it can be used to determine nucleotide sequences. For example, genome sequencing and comprehensive sequencing of transcripts (mRNA). The high performance and low cost of next generation sequencers has brought them to a level that most people can afford. Another thing that can be done is to know the quantity. Next-generation sequencers are able to determine the nucleotide sequence of a variety of DNA in a mixed state. This is because the machine is able to separate the diverse DNA into individual molecules. Therefore, the DNA that was more abundant in the DNA used for input will result in more output, and the DNA that was less abundant will result in less output. As a result, it is also possible to know the frequency of nucleotide sequences. This feature has led to the development of a variety of applications. For example, the gene expression levels can be measured.
Metagenomics, which is the sequencing of the genomes of organisms in soil and water, can also be used to determine what kinds of organisms were present in the soil and to what extent.

In addition, by examining where transcription factors, such as the Yamanaka 4 factor (famous for iPS cells), bind to genomic DNA, we can determine what genes are involved in the regulation of gene expression. Other methods have also been developed to predict the evolution of organisms over time based on the diversity and frequency of SNPs in the genome.

NGS is having a particularly large impact in the field of cancer medicine, where next-generation sequencers are being used to comprehensively analyze cancer gene information, leading to the development of drugs that target key genetic abnormalities (molecular targeted drugs). There is a growing movement to introduce this into daily practice rather than research.

3. Thesis Questions

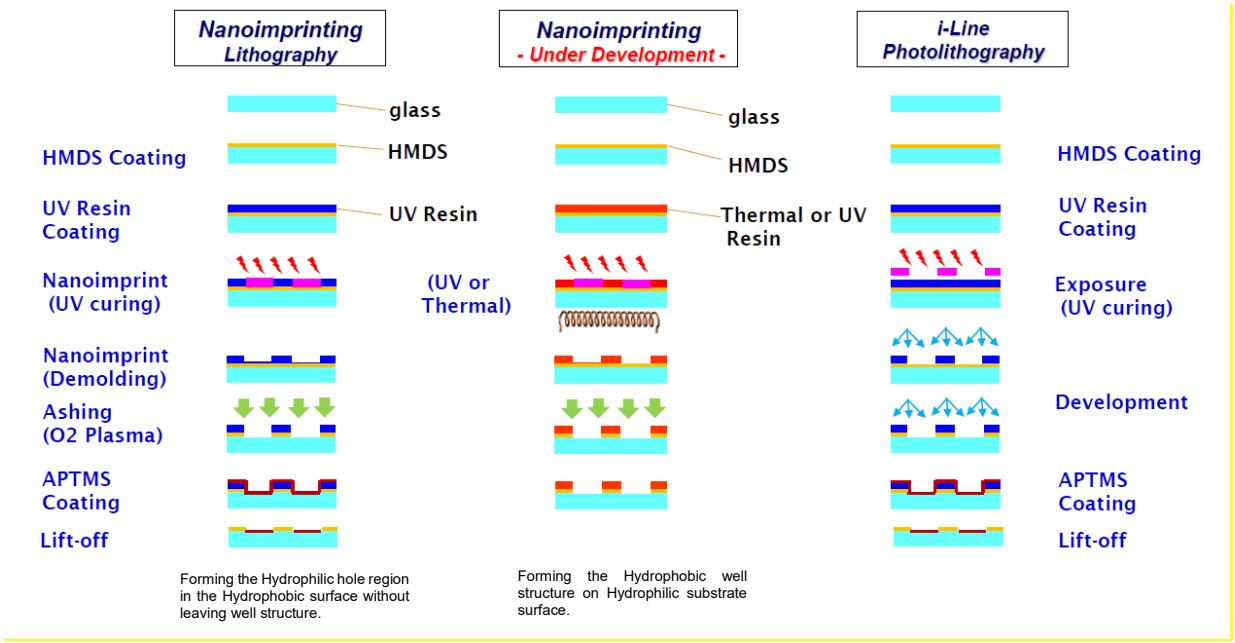
In the NGS industry, sequencing became possible at a cost of about US$1,000 a few years ago now, but there is a need for further cost reduction, faster processing, and accuracy. In this context, the cost of sequencing equipment as well as the cost of testing per specimen, i.e., the cost of chips, can be reduced, thereby expanding the range of applications of NGS, including clinical applications, and the market is expected to grow.

4. Solutions

NGS devices and their dedicated chips, which are still in the development stage, have their own unique well structure. The hole structure has usually a diameter of 0.5 to 1um, and the inside of the hole is hydrophilic, while the rest of the hole is hydrophobic, allowing DNA or polymerase to be added to the hydrophilic part, and DNA input solution to selectively adhere to the hole part. Usually, it is possible to create similar results using an i-line exposure system other than nanoimprint for a hole of this size, but nanoimprint is superior in two major ways. First, when a hole diameter smaller than 0.5um is required, where there are complexities to mold using an i-line lithography system, in the case of nanoimprint, it can be done as long as the mold can be created using an excimer laser source used for semiconductor lithography. Second, the process is simple, making it easy to achieve mass production effect while reducing its cost.

5. Products Info

As a mass production process for NGS chips, SCIVAX has developed a material and process to create a hydrophilic APTMS hole region surrounded by a hydrophobic HMDS region on a glass wafer and has launched a mass production line. (The process on the left in the figure below) In addition, for more advanced NGS customers, we are developing a process to form hydrophobic well 3D hole structures on glass wafers using a resin that has no effect on autofluorescence.



6. Conclusion

As described above, nanoimprint technology has been recognized as an essential mass production technology for the technical and business development of NGS, and SCIVAX has launched a foundry service for mass production of NGS chips using the most suitable equipment, materials and processes developed in-house.