华大基因 BGI | Premier Scientific Partner

Biomarker Validation

Trans-omics Solutions for Pharmaceutical Research

Contact Us

Offices & Locations

China (Mainland)
BGI-Shenzhen, Beishan Industrial Zone, Yantian District, Shenzhen, 518083, China
Tel: 400-706-6615
+86-755-25281960
Email: bgi-PGx@genomics.cn
www.genomics.cn

Asia Pacific (Hong Kong)
BGI Hong Kong Co. Limited, 16th Dai Fu Street, Tai Po Industrial Estate, Tai Po, Hong Kong
Tel: +852-3610 3510
Email: bgihk.enquiry@genomics.cn
www.bgisequence.com

North America (Boston)
BGI Americas Corporation, One Broadway, 14th Floor, Cambridge, MA 02142, USA
Tel: +1-617-500-2741
Email: info@bgiamericas.com
www.bgiamericas.com
www.bgisequence.com

Europe (Copenhagen)
BGI Europe Corporation, Ole Maaløes Vej 3, DK-2200 Copenhagen N, Denmark
Tel: +45-7026-0806
Email: BGIEurope@genomics.cn
www.bgisequence.com

Preface

New paradigms for drug discovery call for a significant increase in the number of new drug targets in the pipeline in conjunction with a considerable reduction in the cost of drug discovery. It is difficult for large pharmaceutical companies' R&D budgets to increase sharply in order to sustain a corresponding increase in the pipeline. The solution is to significantly reduce the cost of drug discovery by reducing failure rates.

Biomarker validation is one of the most important steps in pharmaceutical R&D. Many industry experts believe that without additional well-validated targets, pharmaceutical companies are likely unable to maintain current levels of profitability. Thus, biomarker validation technologies are indispensable tools for pharmaceutical R&D.

Based on our high-throughput sequencing platforms and rich experience in genomics, BGI provides a variety of target validation solutions at trans-omics level, aiding to decipher the significance of DNA, RNA or protein molecules involved in disease process. These include SNP (single nucleotide polymorphism), SV (structural variation), CNV (copy number variation), quantitative mRNA, microRNA and protein validations, through multiple options: Sequenom MassARRAY SNP Genotpying, Custom Genotyping BeadChip, Custom Target Region Sequencing, PCR Sanger Sequencing, Real-Time Quantitative PCR and Target Protein Quantification.

BGI keeps up with the latest trend and advance in various pharmacogenomics technologies, and we are more than happy to provide cost-effective and ultrafast-turnaround service in conducting biomarker validation.

CONTENT

Platforms for DNA Biomarker Validation

BGI now provides four platforms to validate DNA biomarkers. Detection types of each platform and suggestions for platform selection are shown as follows:

Comparison of different DNA biomarker validation platforms

Platforms	Detection Types
Sequenom MassARRAY System	SNP
Custom Genotyping BeadChip	SNP, CNV
Custom Target Region Sequencing	SNP, SV
PCR Sanger Sequencing	SNP, SV

Recommended platforms according to different research projects

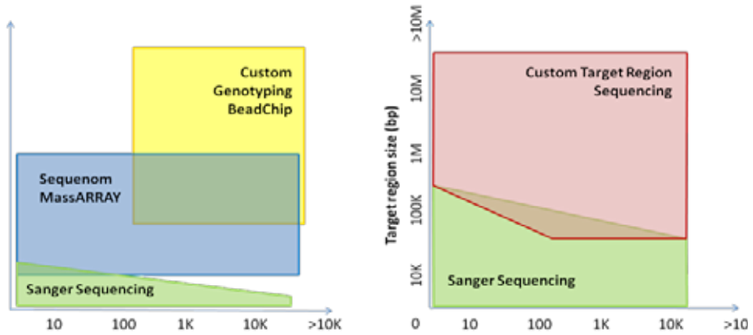


Figure on the left shows the recommended platforms according to SNP numbers and sample numbers. Sanger Sequencing (in green) is suitable for low-throughput SNPs (~10 SNPs), while Sequenom MassARRAY (in blue) for middle-throughput SNPs (~10 to ~1K SNPs) , and Custom Genotyping BeadChip (in yellow) for mid- to high-throughput SNPs (~100 to ~100K SNPs).

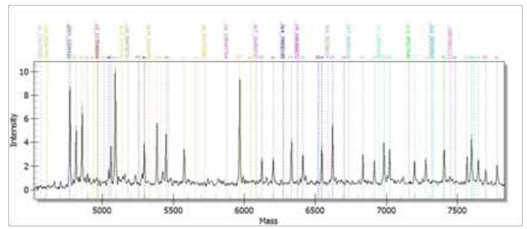
Figure on the right shows the recommended platforms according to different target region sizes. Sanger Sequencing (in green) is suitable for validation of small target regions (less than ~50 Kb), while Custom Target Region Sequencing (in red) for large target regions (larger than ~300 Kb). In the overlapped region (~50 Kb to ~300 Kb), unless sample numbers are very small, Custom Target Region Sequencing is recommended for most situations.

Sequenom MassARRAY SNP Genotpying

Introduction

Sequenom MassARRAY system provides unparalleled specificity and sensitivity using **MALDI-TOF mass spectrometry**. Combining benefits of the new iPLEX™ Gold assay, the leading technology for SNP Genotyping, MassARRAY system performs with the **highest levels of accuracy** for SNP validation.

MS spectrum:

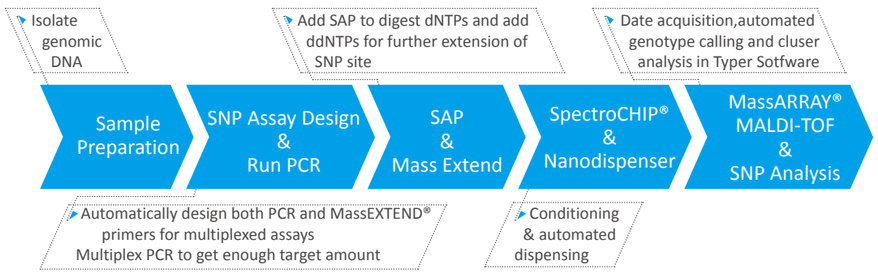


- Fully automated data acquisition and analysis

Technological advantages

- Greater than **99.7% accuracy**
- Easy discover of **unexpected events** such as **tri-allelic SNPs, PCR failure**, *etc.*
- Run more than **3,000 samples per workday**
- Ideal for analyzing **tens to hundreds of SNPs in hundreds to thousands of samples**

Workflow



Our experience

BGI has wide experience for Sequenom MassARRAY genotyping. So far, BGI has genotyped more than 45,000 samples by Sequenom MassARRAY platform with over half of them being clinical samples.

Custom Genotyping BeadChip

Introduction

Custom Genotyping BeadChips can meet the customers' needs, allowing flexible selection of the ideal solution for their loci multiplexing and sample throughput requirements. Loci of interest for researches can be easily designed on a BeadChip and then be genotyped.

BGI has BeadArray and iScan instruments with full automation for high throughput production runs of customized genotyping arrays using GoldenGate and Infinium assays.

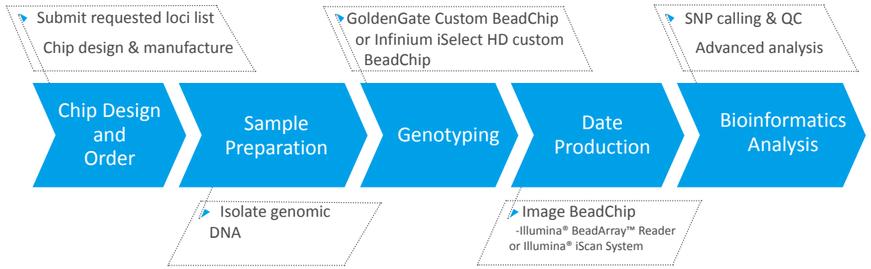
Custom Genotyping Assay Details

	GoldenGate	Infinium iSelect HD
Marker Density	96-3K	3K–90K
Chip Format	32 samples	24 samples

Technological advantages

- **Industry-Leading Data Quality**
  Accurate and reproducible data with proven assays
- **Flexible Content**
  Custom assays in wide range of multiplex levels for any SNP and any genome
- **Broad Range of Throughput Capabilities**
  Multi-sample formats and automation-compatible, rapid scanning technology

Workflow



Demo cases

Projects	Chip type	Samples	Appplications
The Sino-Danish Diabetes Disease Project	iSelect (Custom 20K)	17,000	GWAS analysis
The China-Japan Friendship Hospital Diabetes Project	GoldenGate 96 plex	11,000	GWAS validation

Custom Target Region Sequencing

Introduction

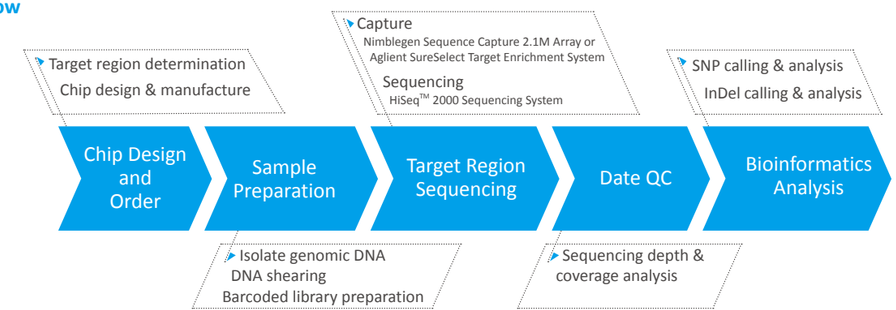
Custom Target Region Sequencing (TRS) is a state-of-the-art technology for target region validation, combining the flexible selectivity of region capture platform with high-throughput and resolution of NGS. TRS is recommended for **validating large target regions in many samples and,** at the same time, for achieving unparalleled efficiency in sequencing a statistically relevant number of samples.

By screening **relevant regions** with **large sample size**, real causative genes and the pathogenic mechanism of a particular disease could be revealed.

Technological advantages

- Focusing on genetic mutations on regions of interest: range from **tens of Kbs to several Mbs**
- Deep investigation on specific regions: coverage can reach **hundreds- or even thousands- fold**
- High throughput: suitable for **large number of samples**

Workflow



PCR Sanger Sequencing

Introduction

Sanger sequencing is the **gold standard** in genetic analysis. With standout long read length, Sanger sequencing is widely used for SNP and SV (structure variation) validation in specific regions.

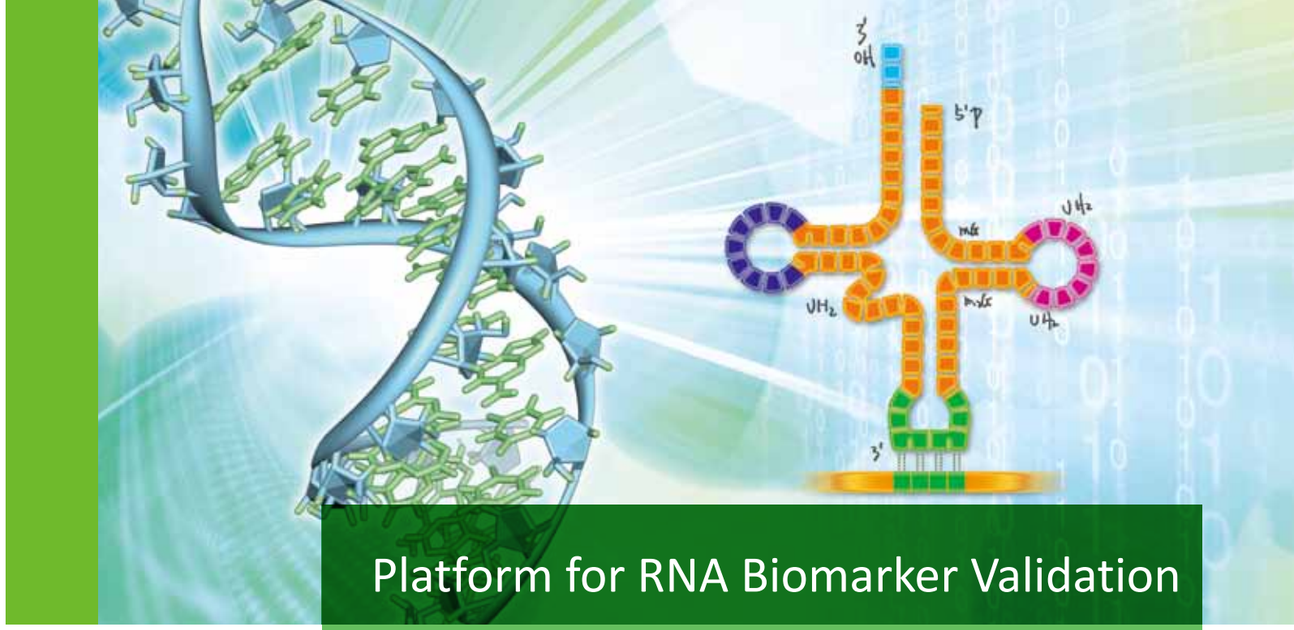
BGI performs PCR Sanger sequencing using ABI 3730xl DNA Analyzers.

Technological advantages

- **Gold standard method** for DNA sequencing
- **Standout long read length**: 800 bp / 1000 bp (Average / Maximum)
- Suitable for lower sample throughput
- Throughput: 12,000 reactions per workday

Workflow

Sample Preparation → Primer Design & Run PCR → Sanger Sequencing → Date Production & Analysis



Platform for RNA Biomarker Validation

Real-Time Quantitative PCR

Introduction

Real-Time Quantitative PCR (qPCR) is considered the gold standard for accurate, sensitive and fast quantification of nucleic acid sequences with extremely low cost. qPCR has been widely applied in many aspects of RNA validation: absolute quantification, relative quantification, transcriptional SNP validation, microRNA research, *etc*.

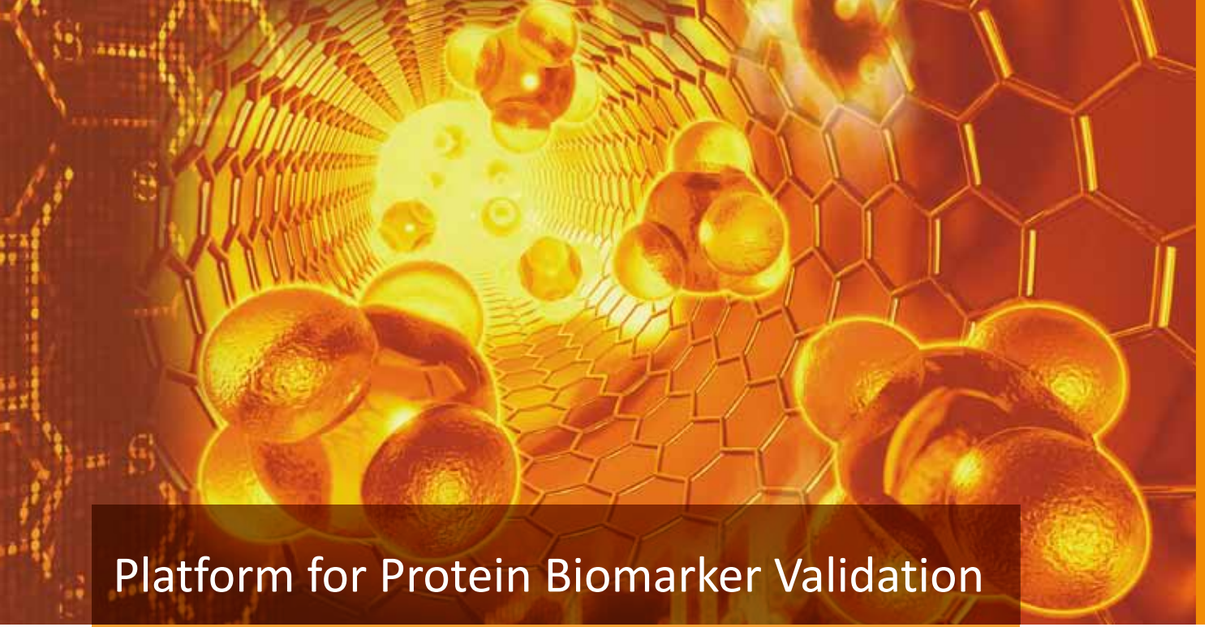
BGI provides Applied Biosystems StepOnePlus™ Real-Time PCR system for RNA biomarker validation.

Technological advantages

- **Gold standard method** for gene expression quantification
- Fast PCR reactions in less than 40 minutes

Workflow

Sample Preparation → Primer Design & Order → qPCR → Date Production & Analysis



Platform for Protein Biomarker Validation

Target Protein Quantification

Introduction

Multiple-reaction-monitoring (MRM) is a highly selective, sensitive, and robust assay to monitor the presence and amount of biomolecules. MRM also eliminates the long timeline, performs at lower cost and has a high success rate.

BGI provides **AB SCIEX QTRAP® 5500 LC/MS/MS System** platform, the most advanced technology (nanoLC-MRM/MS/MS or nanoLC-SRM/MS/MS) to verify candidate biomarkers by **target proteins relative quantification and absolute quantification**.

Performance Characteristics:
Mass Range: 5-1000 amu
Resolution: >12,000 FWHM (Trap)
Sensitivity:
Improved 9 times (MRM)
Improved 10-100 times (Trap)
Scanning speed:
Up to 2,400 amu/s (QQQ)
Up to 20,000 amu/s (Trap)
Polarity transition time: 50ms.

Technological advantages

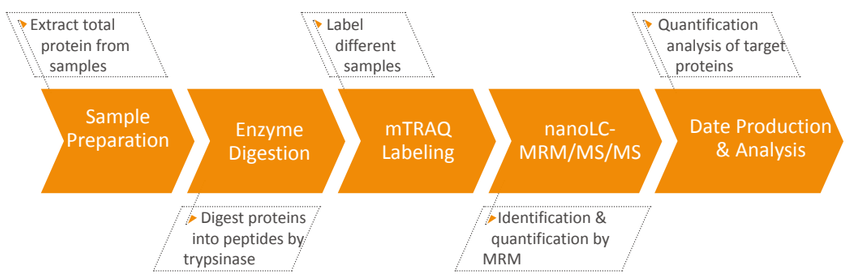
Highest Selectivity
- Antibodies independent: measure is not dependent on affinity reagents
- MRM can be developed and optimized for all novel candidates of interest

Unparalleled Sensitivity
- High specificity for targeted protein(s) including post-translational modifications and isoforms

Scalable Throughput
- MRM offers superior multiplexing capabilities, allowing simultaneous quantification of numerous proteins in parallel (Multiplexing of more than 80 proteins per assay)

Rapid Turnaround Time
- Assay development time is rapid compared to traditional techniques, often just 3-5 months rather than years.

Workflow



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