MONOGRAM BIOSCIENCES

CAPABILITIES FOR SUPPORTING CLINICAL TRIALS | 2016

Monogram BIOSCIENCES
LabCorp Specialty Testing Group

MONOGRAM BIOSCIENCES OVERVIEW

Monogram was founded in November 1995 and acquired by LabCorp in August 2009

Monogram is a member of LabCorp's Specialty Testing Group with a focus on Virology, Infectious Disease and Oncology

- HIV – Leader in drug resistance testing
- HCV – Comprehensive portfolio
- Respiratory viruses – Novel services
- Oncology- Assay development

Established Clinical Reference Laboratory

- Fully CLIA/CAP accredited
- Testing for clinical patient management and drug/vaccine development

Monogram has supported development of many clinically available HIV antiretroviral therapy

Monogram's assays for clinical trials are offered through Covance Clinical Trials and directly with Monogram

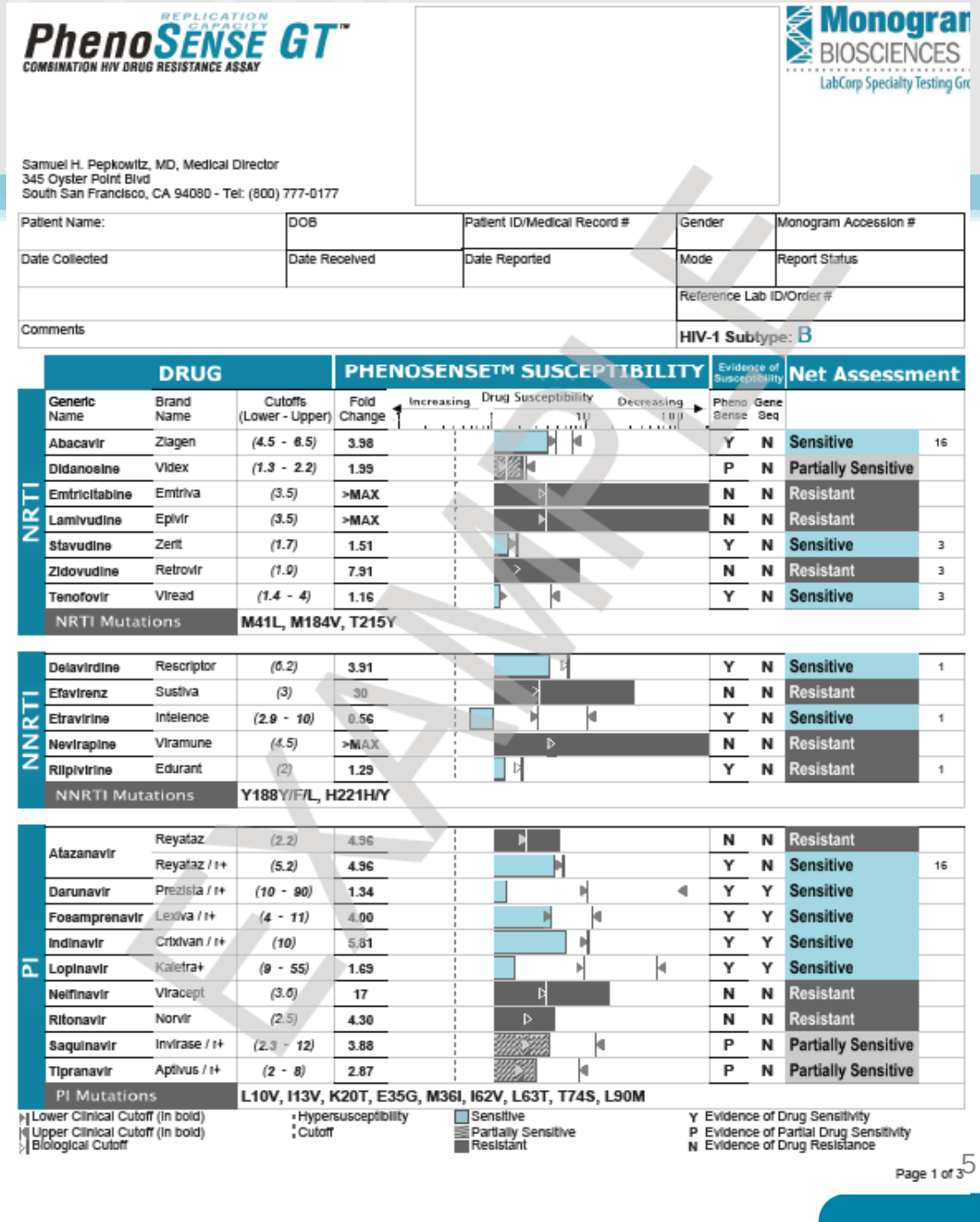
Assays For Infectious Disease

MONOGRAM HIV ASSAYS AND SERVICES

FOR CLINICAL RESEARCH AND DEVELOPMENT

- Protease/Reverse Transcriptase Inhibitor Resistance Assays
  - PhenoSense® (phenotype; infectivity assay)
  - GenoSure® MG (genotype; DNA sequencing assay)
  - PhenoSense® GT≤ (combination phenotype/genotype)
- GenoSure Archive® – DNA resistance testing for patients with undetectable VL
- Entry Inhibitor Susceptibility Assays (inhibitors of attachment, co-receptor engagement and membrane fusion)
- Trofile®, Trofile® DNA (co-receptor tropism determination)
- Integrase Inhibitor Resistance Assays (phenotype; genotype)
- GenoSure PRIme® (combination PR/RT, INI genotype)
- Assembly Inhibitor Resistance Assays (phenotype; genotype)
- Replication Capacity Assays (viral “fitness”) for HIV
- Subtype/clade determinations (A, B, C, D, F, AE, AG, BF, etc.)
- Neutralizing Antibody Assay for HIV
- Quasispecies characterization (clonal analysis)
- Next Generation Sequencing (minor variant characterization)
- HIV Curative Strategy assays
- PhenoScreen® Novel Drug Testing (lead compound characterization)
- Other supportive assays – Viral Load (Roche COBAS®, Abbott RealTi*me*), RVP

PHENOSENSE GT
REPORT FORM



REPLICATION CAPACITY
PhenoSense GT™
COMBINATION HIV DRUG RESISTANCE ASSAY

Monogram BIOSCIENCES
LabCorp Specialty Testing Gro

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South San Francisco, CA 94080 - Tel: (800) 777-0177

Patient Name:	DOB	Patient ID/Medical Record #	Gender	Monogram Accession #
Date Collected	Date Received	Date Reported	Mode	Report Status
			Reference Lab ID/Order #	
Comments			HIV-1 Subtype: B	

	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing ← Drug Susceptibility → Decreasing (1.0 10.0)	Pheno Sense	Gene Seq	Evidence of Susceptibility	Net Assessment	
DRUG				PHENOSENSE™ SUSCEPTIBILITY						
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	3.98		Y	N		Sensitive	16
	Didanosine	Videx	(1.3 - 2.2)	1.99		P	N		Partially Sensitive	
	Emtricitabine	Emtriva	(3.5)	>MAX		N	N		Resistant	
	Lamivudine	Epivir	(3.5)	>MAX		N	N		Resistant	
	Stavudine	Zerit	(1.7)	1.51		Y	N		Sensitive	3
	Zidovudine	Retrovir	(1.9)	7.91		N	N		Resistant	3
	Tenofovir	Viread	(1.4 - 4)	1.16		Y	N		Sensitive	3
	NRTI Mutations		M41L, M184V, T215Y							
NNRTI	Delavirdine	Rescriptor	(6.2)	3.91		Y	N		Sensitive	1
	Efavirenz	Sustiva	(3)	30		N	N		Resistant	
	Etravirine	Intelence	(2.9 - 10)	0.56		Y	N		Sensitive	1
	Nevirapine	Viramune	(4.5)	>MAX		N	N		Resistant	
	Rilpivirine	Edurant	(2)	1.29		Y	N		Resistant	1
	NNRTI Mutations		Y188Y/F/L, H221H/Y							
PI	Atazanavir	Reyataz	(2.2)	4.96		N	N		Resistant	
		Reyataz / r+	(5.2)	4.96		Y	N		Sensitive	16
	Darunavir	Prezista / r+	(10 - 90)	1.34		Y	Y		Sensitive	
	Fosamprenavir	Lexiva / r+	(4 - 11)	4.00		Y	Y		Sensitive	
	Indinavir	Crixivan / r+	(10)	5.81		Y	Y		Sensitive	
	Lopinavir	Kaletra+	(9 - 55)	1.69		Y	Y		Sensitive	
	Nelfinavir	Viracept	(3.6)	17		N	N		Resistant	
	Ritonavir	Norvir	(2.5)	4.30		N	N		Resistant	
	Saquinavir	Invirase / r+	(2.3 - 12)	3.88		P	N		Partially Sensitive	
	Tipranavir	Aptivus / r+	(2 - 8)	2.87		P	N		Partially Sensitive	
	PI Mutations		L10V, I13V, K20T, E35G, M36I, I62V, L63T, T74S, L90M							

Lower Clinical Cutoff (In bold)
Upper Clinical Cutoff (In bold)
Biological Cutoff
Hypersusceptibility
Cutoff
Sensitive
Partially Sensitive
Resistant
Y Evidence of Drug Sensitivity
P Evidence of Partial Drug Sensitivity
N Evidence of Drug Resistance

Page 1 of 3

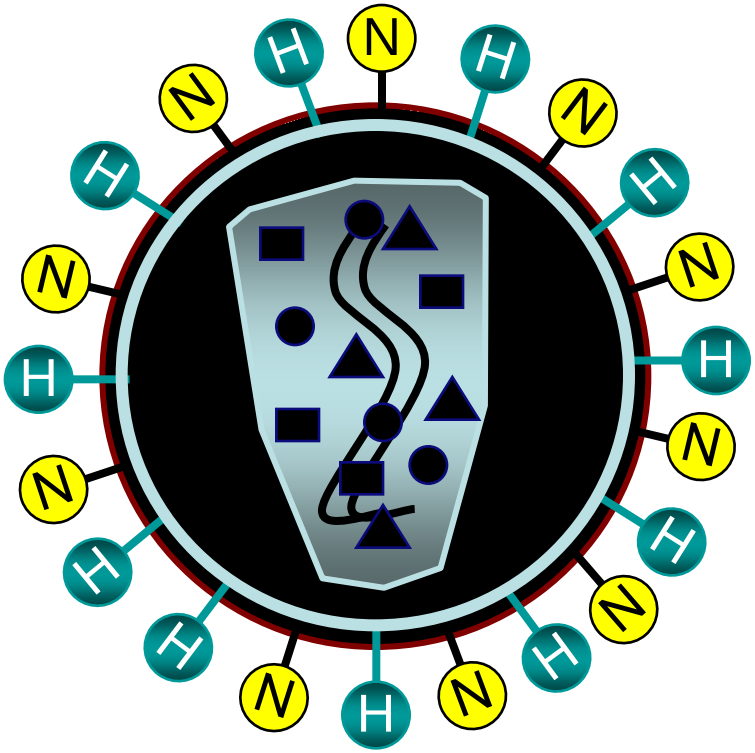
MONOGRAM BIOSCIENCES

RESPIRATORY VIRUS TESTING CAPABILITIES

- **GenMarkDx® Respiratory Virus Panel (RVP)**
  - Validated in multiple sample types for up to 14 virus targets
  - Can test for 10, 14 or 19 virus panels
  - Includes subtyping of Influenza and RSV
- **Cell-Based Neutralizing Antibodies Assay**
  - High throughput
  - Influenza A and B, RSV A and B
- **Sequencing (NGS)**
  - RSV
  - Influenza
  - HRV
- **qRT/PCR**
  - Qualitative/Quantitative qRT/PCR assays (i.e. for RSV): for specific viruses, please contact Monogram for more information
- **Phenotyping**
  - RSV, Influenza A and B
  - High throughput characterization of new and existing anti-viral compounds against a panel of clinical isolates and reference strain

PSEUDOTYPING HIV-1 CORES
WITH INFLUENZA HA/NA PROTEINS

Patient HIV-1 *env*



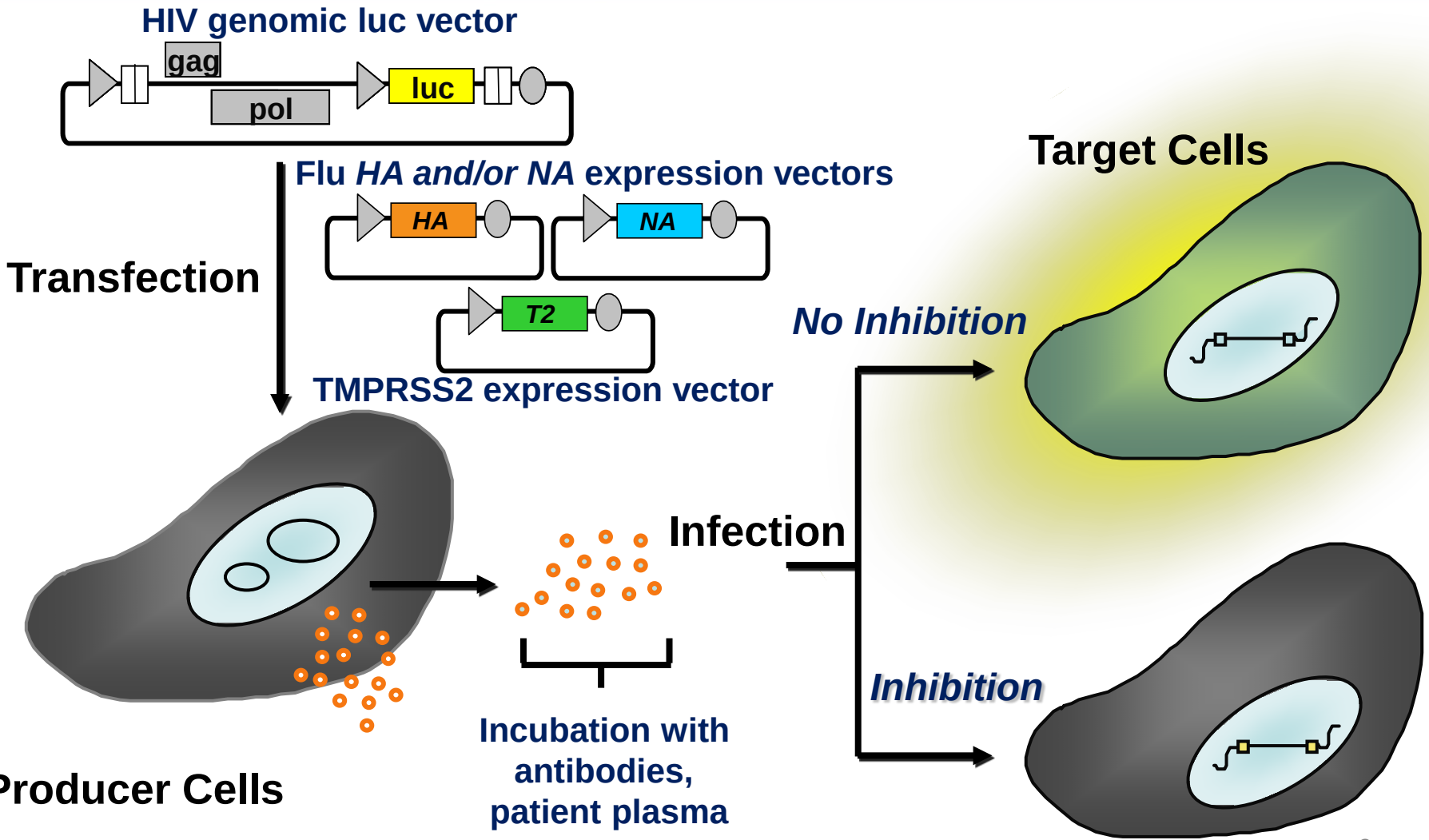
Influenza HA and NA

MONOGRAM NEUTRALIZATION ASSAY
FOR INFLUENZA

- **Recombinant pseudovirion, single cycle assay; patented technology**
- **Pseudovirion library: >60 HA and >50 NA expression vectors**
  - Clinical HA and/or NA sequences
  - Cultured and well-characterized isolates
  - Synthetic gene sequences
- **Inter-assay variation: IC_{50} ≤2.5-fold**
- **~10-100x more sensitive than HAI and micro-neut assays**
- **Automated processes**
  - HA and NA cloning and vector construction
  - Cell assay throughput and reproducibility
- **Assay throughput**
  - Currently 1000 titrations (IC_{50}) per day (100 sera x 10 viruses)

INFLUENZA A/B

nAb ASSAY



TMPRSS2: human airway trypsin-like serine protease

SEQUENCE-BASED HCV RESISTANCE ASSAYS

BY SUBTYPE

ASSAY DEVELOPMENT STATUS

Genotype/ Subtype	NS3/4A	NS5A	NS5B	Platform
GT1a,1b	CLIA/CAP*	CLIA/CAP*	CLIA/CAP*	Sanger/NGS
	Development (DEV)			NGS
GT2a,2b	CLIA/CAP	CLIA/CAP	RUO	Sanger/NGS (CLIA/CAP - Sanger)
GT3	RUO	CLIA/CAP*	RUO	Sanger and/or NGS
GT4	RUO	RUO	RUO	Sanger and/or NGS
GT6	RUO	RUO	DEV	NGS

*Commercially available for clinical testing (NGS, 10% variant reporting threshold)

PHENOTYPIC HCV RESISTANCE ASSAYS
BY SUBTYPE

- For preclinical and clinical drug development, research studies, genotypic algorithm development
- Includes drug susceptibility and replication capacity assessment for plasma-derived sequences, virus panels including DAA-naïve and resistant samples, reference viruses and SDMs

ASSAY DEVELOPMENT STATUS

Genotype/ Subtype	NS3 protease	NS5A	NS5B
GT1a,1b	RUO	RUO	RUO
GT2a,2b	-	DEV	RUO
GT3	-	DEV	RUO
GT4	-	DEV	RUO

NEXT GENERATION SEQUENCING:
ILLUMINA MiSeq PERFORMANCE

- **Illumina® MiSeq® platform**
  - 2x300bp paired end reads (2x150bp also available)
  - 25 million paired end reads/run
  - 15 Gb of data/run
  - High quality sequence data
- **Nextera XT sample prep**
  - 1ng input DNA requirement
  - “If it can be amplified, it can be sequenced”
    - PCR amplicons >300bp (RT-PCR or PCR)
    - Plasmids
  - Barcode and multiplex up to 96 samples/run
- **Ultra deep sequencing**
  - Coverage >10,000X
  - Reliable detection of variants at ≥0.5%

NEXT GENERATION SEQUENCING ASSAYS

ON THE ILLUMINA MiSeq PLATFORM

Virus	Target	Length (bp)	Amp	NGS	Analysis
HCV GT1a/1b	NS3/4A protease	~2000	Yes	Yes	Yes
	NS5A	~1400	Yes	Yes	Yes
	NS5B polymerase	~1700	Yes	Yes	Yes
HCV GT2,3,4	NS3/4A protease	~2000	Yes	Yes	Yes
	NS5A	~1400	Yes	Yes	Yes
	NS5B polymerase	~1700	Yes	Yes	Yes
HIV-1 (all subtypes)	PR/RT*	~1600,~2100	Yes	Yes	Yes
	RH/integrase**	~1600	Yes		
	PR/RT/IN***	~3200	Yes	Yes	Yes
	Envelope	~2600	Yes	Yes	Yes
	Gag-protease	~1800	Yes	Yes	Yes
SIV	Envelope	~2600	Yes		

*protease/reverse transcriptase, **RNaseH/integrase, ***protease/reverse transcriptase/integrase

ADDITIONAL NEXT GENERATION SEQUENCING ASSAYS

BY VIRUS

Virus	Target	Length (bp)	Amp	NGS	Analysis
Influenza A&B	hemagglutinin	~1700	Yes		
	neuraminidase	~1400	Yes		
RSV	F protein	~2000	Yes	Yes	Yes
	G protein	~1000	Yes		
	SH protein	~500	Yes		
	L protein	~1600		Yes	
HBV	reverse transcriptase	~2500	Yes	Yes	DEV
HRV	VP1	~850	Yes	Yes	DEV
CMV					
Others?	amplification dependent				

NOTE: *Any region that can be successfully amplified (Amp) can be also be sequenced using the Illumina MiSeq platform (NGS), and can be analyzed using MGRM's proprietary NGS sequence analysis pipeline.*

ASSAYS FOR CANCER

VERATAG® TECHNOLOGY
FOR CANCER BIOMARKER INTERROGATION

- Monogram offers our proprietary VeraTag® technology to pharmaceutical partners and academic collaborators for drug development and clinical research
- Proximity binding-based assays that quantify protein expression, activation, and/or protein complex formation
- VeraTag assays provide sensitive and quantitative measurements of protein biomarkers in formalin-fixed paraffin-embedded (FFPE) samples.
- Biomarkers include:
  - cell-surface receptors
  - activated proteins including phospho-proteins
  - protein complexes (homo- and heterodimers, ligand-receptor, etc.)
  - Immune checkpoint proteins

HERMARK® BREAST CANCER ASSAY
(MEASURES HER2 TOTAL RECEPTOR)

- HERmark® refers specifically to a HER2 total VeraTag® assay that is CLIA-validated and used in the clinic for Breast Cancer classification
- Launched commercially by Monogram in 2008, HERmark is available through LabCorp, Integrated Oncology and direct from Monogram
- Clinical studies have demonstrated the utility of accurate and quantitative HER-2 protein expression determinations as an addition to IHC and FISH testing[1-5]
- HERmark is currently being used in a prospective clinical trial as a companion diagnostic

1. Chumsri S, Weidler J, Ali S, et al. Prolonged Response to Trastuzumab in Patient With HER2-Nonamplified Breast Cancer With Elevated HER2 Dimerization Harboring ERBB2 S310F Mutation. (J Natl Compr Canc Netw 2015;13:1066–1070)
2. Yardley DA, Kaufman PA, Huang W, et al. Quantitative measurement of HER2 expression in breast cancers: comparison with 'real-world' routine HER2 testing in a multicenter collaborative biomarker study and correlation with overall survival. Breast Cancer Res. 2015;17:41. doi: 10.1186/s13058-015-0543-x.
3. Scaltriti M, Nuciforo P, Bradbury I et al. High HER2 Expression Correlates with Response to the Combination of Lapatinib and Trastuzumab. Clin Cancer Res. February 1, 2015 21; 569. DOI: 10.1158/1078-0432.CCR-14-1824. Epub 2014 Dec 2.
4. Duchnowska R, Biernat W, Szostakiewicz B, et al. Correlation between quantitative HER2 protein expression and risk of brain metastasis in HER2-positive advanced breast cancer patients receiving trastuzumab-containing therapy. The Oncologist. 2012;17(1):26-35. doi: 10.1634/theoncologist.2011-0212. Epub 2012 Jan 10 Oncologist. 2012;17(1):26-35.
5. Bates M, Sperinde J, Köstler WJ, et al. Identification of a sub-population of metastatic breast cancer patients with very high HER2 expression levels and possible resistance to trastuzumab. Ann Oncol 2011; 22(9): 2014-2020.

HERmark® BREAST CANCER ASSAY

VERATAG® ASSAYS

CUSTOM DEVELOPMENT THROUGH CLIA VALIDATION

Total Receptors
- HERmark HER2 (Tier 3)
- EGFR/HER1, p95HER2, and HER3 (Tier 2)
- cMET (Tier 1)

Receptor Dimers
- Homodimers: HER1:HER1 & HER2:HER2 (Tier 2)
- Heterodimers: HER1:HER2, HER1:HER3, HER2:HER3 (Tier 1)

Activation Markers
- phosphoHER1 & phosphoHER3 (Tier 1)
- HER3-PI3k complex (Tier 1)

Receptor Ligands and Complexes
- HGF Ligand (Tier 1)
- cMET-HGF complex (Tier 1)

Immune Markers
- CD3 (Tier 1)
- PD-L1 (In Development)
- PD1 (In Development)
- PD1/PDL1 Complex (In Development)

Tier 0 – Custom / Contract Assay Development

Tier 1 – Experimental Assay with Characterized Performance
Utilized for pre-clinical and other experimental analyses (e.g. MOA)

Tier 2 – RUO Analytically-Validated Assay
Utilized for retrospective clinical trial analyses

Tier 3 – Fully CLIA-Validated Assay
Utilized for prospective clinical trials where data contributes to treatment decisions

MONOGRAM'S COMMITMENT
TO QUALITY ASSURANCE

- **Major QA Systems and Processes**
  - Documentation – Controlled documents processing, MasterControl® Document Management System
  - Computer Validation/IT Change Control – Applications/software, Instruments, Customized Data (client) Deliverables
  - Sample/Records Management – Lab records review, Double Data Entry (accessioning TRF verification), Long Term Sample Storage (filing, retrieval and destruction), Sample Investigations
  - Clinical QA – Proficiency testing, Occurrence Management, Internal Audit program
- **Other QA systems**
  - Equipment Records Management, Calibration Review
  - Document Archiving, Employee Training Records
  - Inspection Preparedness/External Audit Hosting (partnership with the CRL)

CURRENT/FUTURE AREAS OF FOCUS
AT MONOGRAM

- **Antiviral Drug Development and Resistance**
  - Chronic Virus Infections (HIV-1, HCV, HBV, HDV, CMV)
  - Respiratory Virus Infections (RSV, HRV)
  - Hemorrhagic Virus Infections (Ebola, Dengue)
- **Viral Vaccine Development**
  - HIV-1, Influenza, RSV, Ebola, Dengue
- **HIV-1 Curative Strategies**
  - Molecular assays, Infectivity assays, Proteomic assays
- **Oncology Biomarker and Drug Development**
  - Receptor signaling, Immune checkpoints
  - Oncogene mutations, expression signatures