Affymetrix®
Revolutionize life

DMET™ Plus Solution

Translating pharmacogenetics

Treat everyone as an individual

DMET™ Plus Solution

Translating pharmacogenetics into practice

Understanding the common variation in genes encoding for drug metabolism enzymes and drug transporters has the potential to significantly impact clinical research by predicting the impact of an individual's genetic variation on metabolic capacity. This understanding takes us one step closer towards the vision of personalized medicine by helping to avoid adverse drug responses, increasing treatment efficacy and providing both improved healthcare outcomes as well as substantial economic benefits.

DMET (**D**rug **M**etabolizing **E**nzymes and **T**ransporters) Plus Solution

Enables the cost-effective measurement of existing and new metabolic pathway involvement – by providing broad coverage of relevant pharmacogenetic markers (1,936 genetic variants across 231 relevant genes) *in one assay*

Provides high confidence in results – outstanding assay performance of >99% average sample call rate and >99.8% average sample reproducibility enables the accurate generation of haplotypes and supports longitudinal and other clinical research studies

Supports the rapid and comprehensive interpretation of genotyping data – the DMET™ Console Software tool translates genotyping data through to star allele classification and to predicted metabolizer status, allowing the rapid implementation of genetic understanding in clinical research

Applications:

- **Pharmacology research** – discovery and application of novel biomarkers resulting from pharmacogenetic associations
- **Translational clinical research** – longitudinal clinical research studies designed to generate comprehensive metabolic profiles
- **Pre-clinical research and development** – approximately 30% of drug candidates fail during development due to poor pharmacokinetics and toxicity, which can be strongly influenced by genetically determined variation in drug-metabolizing genes and transporter genes
- **Industry sponsored clinical research trials** – building databases of known genotypes to show effects of known metabolic pathways in intermediate and poor metabolizers and to confirm metabolic pathway involvement in newly discovered drug metabolism associations

The DMET Plus Solution:

- **Assay** – Molecular Inversion Probe (MIP) panel amplifies the precise target DNA of interest
- **Array** – allele-specific oligonucleotide array provides a single color readout on the GeneChip® Scanner 3000 or GeneChip® Scanner 3000Dx v.2, installed in over 2,000 labs globally
- **Analysis software** – DMET Console Software provides both the flexibility for user-defined reporting as well as the most comprehensive translation from genotypic data to star allele classification to predicted metabolizer status for the most clinically relevant genes

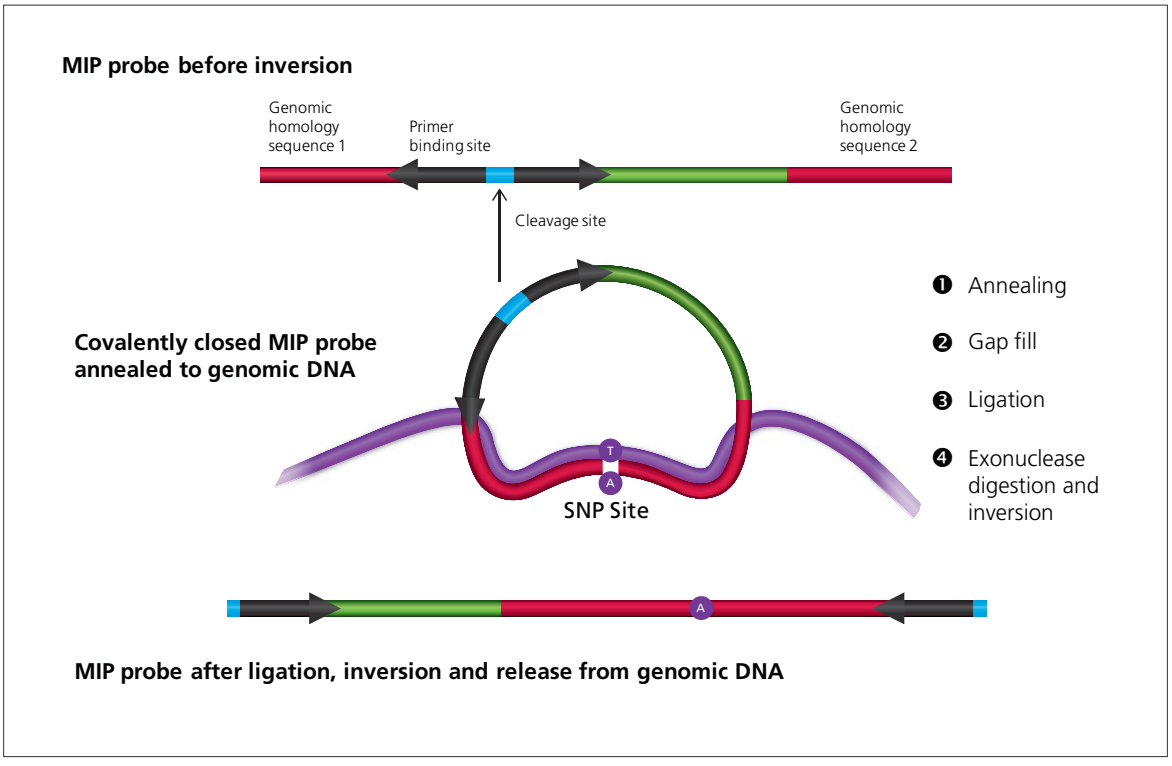
Outstanding data quality

Performance specifications*	
Average sample call rate	≥99%
Average sample concordance to reference	≥99.5%
Average sample reproducibility	≥99.8%
Average sample pass rate	>95%

*During the development of the DMET™ Plus Panel, an average sample pass rate in excess of 95 percent was observed, based on the performance of more than 3,500 samples processed by six sites (three external and three internal). Markers have been evaluated across a minimum of 1,200 individuals including 597 individuals from the extended HapMap population data.

Enabled by a product design that confers high specificity:

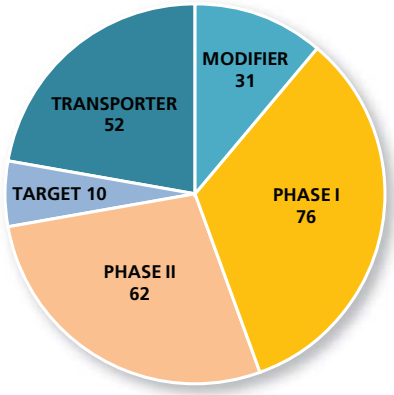
- **Initial multiplexed PCR** step to remove pseudogene bias (especially important for CYP2D6) prior to Molecular Inversion Probe (MIP) amplification, ensuring the highly specific detection of causative variation
- **MIP amplification** confers multiple levels of enzyme-mediated specificity—polymerization/gap-fill, ligation and exonuclease digestion; exonuclease digestion reduces background from residual probes and gDNA prior to amplification
- **Multiple array capture probes** with a unique probe tiling strategy enable highly accurate detection—even in the presence of known neighboring SNPs



Comprehensive and relevant genetic content

- **1,936** SNP, copy number, and indel markers across 231 genes including many genetic variants that cannot easily be detected by other technologies (e.g. SNPs and indels with secondary polymorphisms in close proximity, triallelic markers, and variants from multi-gene families)
- **100%** coverage of PharmaADME "Core ADME Genes" (32 genes) and 95% coverage of PharmaADME "Core Markers" (185 variants)
- Extensive coverage beyond PharmaADME core content to cover common and functional variants associated with hepatic detoxification for processing xenobiotics and environmental toxins including:
  - Markers associated with newly described adverse drug events e.g., CYP3A4_-392A>G
  - Structural variants in transporter genes – an important pharmaceutical target e.g., ABCG2_c.421C>A(Q141K)
  - Enrichment for mutations in ADME regulatory genes e.g., PPARD_c.-101-25241A>G
  - Inclusion of many population specific markers e.g., VKORC1_c.-1639G>A

DMET™ Plus coverage = 231 genes

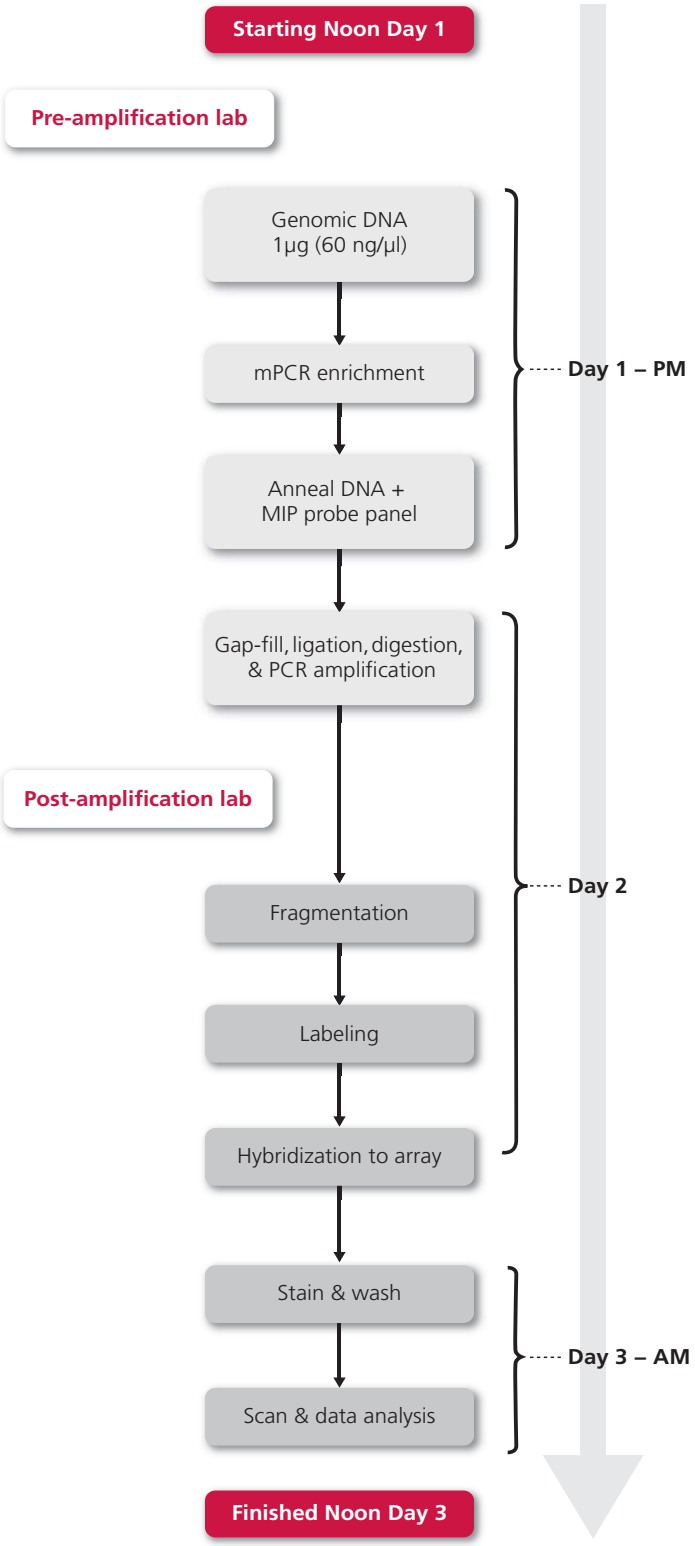


Genes represented by DMET™ Plus Panel								
ABCB1	ALDH2	COMT	CYP4F3	EPHX2	MAOA	RPL13	SLC22A14	TBXAS1 *
ABCB4	ALDH3A1	CROT	CYP4F8	FAAH	MAOB	RXRA	SLC25A27	TPMT *p
ABCB7	ALDH3A2	CYP1A1 *	CYP4F11	FMO1	MAT1A	SERPINA7	SLC28A1	TPSG1
ABCB11	AOX1	CYP1A2 *p	CYP4F12	FMO2 *	METTL1	SLC5A6	SLC28A2	TYMS
ABCC1	APOA2	CYP1B1 *	CYP4Z1	FMO3	NAT1 *p	SLC6A6	SLC28A3	UGT1A1 *p
ABCC2	ARNT	CYP2A6 *p	CYP7A1	FMO4	NAT2 *p	SLC7A5	SLC29A1	UGT1A3 *
ABCC3	ARSA	CYP2A7	CYP7B1	FMO5	NNMT	SLC7A7	SLC29A2	UGT1A4 *
ABCC4	ATP7A	CYP2A13*	CYP8B1	FMO6	NQO1	SLC7A8	SLCO1A2	UGT1A5
ABCC5	ATP7B	CYP2B6 *p	CYP11A1	G6PD	NR1I2	SLC10A1	SLCO1B1*p	UGT1A6 *
ABCC6	CA5P	CYP2B7P1	CYP11B1	GSTA1	NR1I3	SLC10A2	SLCO1B3	UGT1A7 *
ABCC8	CBR1	CYP2C8 *p	CYP11B2	GSTA2	NR3C1	SLC13A1	SLCO2B1*	UGT1A8 *
ABCC9	CBR3	CYP2C9 *p	CYP17A1	GSTA3	ORM1	SLC15A1	SLCO3A1	UGT1A9 *
ABCG1	CDA *	CYP2C18	CYP19A1*	GSTA4	ORM2	SLC15A2*	SLCO4A1	UGT1A10*
ABCG2	CES2	CYP2C19*p	CYP20A1	GSTA5	PGAP3	SLC16A1	SLCO5A1	UGT2A1
ABP1	CHST1	CYP2D6 *p	CYP21A2	GSTM1 *p	PNMT	SLC19A1	SPG7	UGT2B4
ADH1A	CHST2	CYP2E1 *p	CYP24A1	GSTM2	PON1	SLC22A1	SPN	UGT2B7 *p
ADH1B	CHST3	CYP2F1 *	CYP26A1	GSTM3	PON2	SLC22A2*	SULT1A1*	UGT2B11
ADH1C	CHST4	CYP2J2 *	CYP26C1	GSTM4	PON3	SLC22A3	SULT1A2	UGT2B15*
ADH4	CHST5	CYP2S1 *	CYP27A1	GSTM5	POR	SLC22A4	SULT1A3	UGT2B17*
ADH5	CHST6	CYP3A4 *p	CYP27B1	GSTO1	PPARD	SLC22A5	SULT1B1	UGT2B28
ADH6	CHST7	CYP3A5 *p	CYP39A1	GSTP1 *p	PPARG	SLC22A6	SULT1C2	UGT8
ADH7	CHST8	CYP3A7 *p	CYP46A1	GSTT1 *	PPP1R9A	SLC22A7	SULT1C4	VKORC1 *p
AHR	CHST9	CYP3A43*	CYP51A1	GSTT2	PRSS53	SLC22A8	SULT1E1	XDH
AKAP9	CHST10	CYP4A11	DCK	GSTZ1	PTGIS *	SLC22A11	SULT2A1	
ALB	CHST11	CYP4B1 *	DPYD *	HMGCR	QPRT	SLC22A12	SULT2B1	
ALDH1A1	CHST13	CYP4F2 *	EPHX1	HNMT	RALBP1	SLC22A13	SULT4A1	

* = translated to star allele classification p = translated to predicted phenotype/metabolizer status

Comprehensive interpretation analysis

DMET™ Plus Workflow – 48 hrs to results



DMET™ Console Software offers:

- **Single-sample genotyping** – pre-defined marker boundaries allow samples to be processed in batches of any size with no impact on reported genotypes
- **Easy-to-view data** – cluster visualization for SNP and copy number markers
- **Customized content data reports** – user-defined marker lists for initial genotyping as well as final reports
- **Translation of genotypes** into gene-level diplotypes using star allele nomenclature and then into a metabolizer status bin that indicates the relative level of metabolic activity, for example, the metabolic status bin that describes ultra-rapid metabolizers (UM), extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM)

DMET™ Plus marker summary

Example translation for UGT2B7 gene

Reference Information

UGT2B7		Allele Names					
cDNA Position	Change	*1a	*1g	*2c	*2a	*2e	*3
-327G>A	Promoter	G	G	A	G	G	G
-161C>T	Promoter	C	C	T	C	C	C
211G>T	A71S	G	G	G	G	G	T
735A>G	T245T	A	G	A	A	A	A
801T>A	P267P	T	T	A	T	A	T
802C>T	H268Y	C	C	T	T	T	C
1062C>T	Y354Y						
		Allele Activity					
		→	→	↑	↑	?	→

Translation Workflow

Step 1 - Genotypes

sample 1	sample 2	sample 3
G/G	A/A	G/A
C/C	T/T	C/T
G/G	G/G	G/G
A/G	A/A	A/G
T/T	A/A	T/A
C/C	T/T	C/T

Step 2 - Haplotypes (star allele classification)

*1a/*1g	*2c/*2c	*1g/*2c

Step 3 - Allele Activity

→ / →	↑ / ↑	→ / ↑

Step 4 - Predicted Phenotype

Extensive Metabolizer	Ultrarapid Metabolizer	Extensive or Ultrarapid Metabolizer

The GeneChip® System 3000 Instrumentation Platform

Flexible, proven, powerful

This industry-recognized instrumentation combined with innovative assays provide a fully integrated system for all your genetic analysis needs. The DMET™ Plus Solution may be run on either the GeneChip® System 3000 or the GeneChip® System 3000Dx v.2.

The GeneChip® System (GCS) 3000Dx v.2 is FDA-cleared and includes the GeneChip® Scanner 3000Dx v.2 with AutoLoaderDx, GeneChip® Fluidics Station 450Dx v.2, and Workstation with Affymetrix Molecular Diagnostic Software (AMDS). The GeneChip® Hybridization Oven 645 is also required. **With this complete platform, you have everything you need for hybridizing, washing, staining, and scanning of microarrays.**

GeneChip® System 3000Dx v.2 assay menu		
Application area	RUO*	IVD**
3' IVT expression analysis	√	√
Whole-transcript expression analysis	√	√
Genotyping/copy number	√	
Cytogenetic analysis	√	
Drug metabolism/pharmacogenomics	√	√
miRNA gene regulation	√	
Targeted resequencing	√	
Custom assays	√	√

* "Research Use Only" (RUO) array requires an array-specific Assay Software Module (ASM). A custom ASM can be developed for any GeneChip® Array.
** FDA-cleared, IVD or CE-marked test developed by a third-party company on the Affymetrix® GCS 3000Dx platform.

Ordering information

Part number	Description
901268	**DMET™ Plus Premier Pack** Contains sufficient reagents and arrays for 48 reactions (45 samples and 3 controls)
901495	**DMET™ Plus Starter Pack** Contains sufficient reagents and arrays for 8 reactions (7 samples and 1 control)

World-class support

Affymetrix offers an expanding portfolio of customer support and services—from training and instrument maintenance to consulting and compliance—led by our world-class team of multilingual technical experts, field application scientists (FAS), and regional field service engineers (FSE). For more information please visit www.affymetrix.com/service.

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P/N CL01351 Rev. 1